



Review Article

Perspectives on biological growth and remodeling

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ABSTRACT

The continuum mechanical treatment of biological growth and remodeling has attracted considerable attention over the past fifteen years. Many aspects of these problems are now well-understood, yet there remain areas in need of significant development from the standpoint of experiments, theory, and computation. In this perspective paper we review the state of the field and highlight open questions, challenges, and avenues for further development.

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Contents

1. Introduction	864
2. Kinematics	865
2.1. Volumetric and surface growth	865
2.2. Incompatible growth and remodeling	866
2.3. On reference configurations for growth	866
2.4. The mapping φ for a deformed, growing body	867
2.5. Resorption at a point	867
2.6. Physical and mathematical basis of the multiplicative decomposition	867
3. Constitutive relations for growth	868
3.1. Scalar and tensorial constitutive laws for F^g	868

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3.2.	Phenomenological evolution equations for F^g .	868
3.3.	Micromechanically motivated evolution equations for F^g —an example	869
4.	The role of mixture theory	869
4.1.	Constrained mixture theory.	870
4.2.	Thermodynamics and dissipation	870
5.	The cellular and sub-cellular scale for growth models.	870
6.	Morphogenesis.	872
7.	Plant growth	873
7.1.	The mechanics of growth at the cell level	873
7.2.	Tissue growth.	874
8.	Structural optimization and bone remodeling	874
9.	Some open problems in growth and remodeling	876
9.1.	Collagen fiber remodeling in arterial walls.	877
9.2.	Cerebral aneurysms	877
10.	Computational issues.	878
10.1.	Computational framework for multiplicative growth.	878
10.2.	Numerical algorithms	878
11.	Links to molecular mechanisms in the context of tumor growth	879
12.	Concluding remarks	880
	References	880

1. Introduction

Biological growth occupied the minds of students of evolutionary and organismic biology in the early twentieth century. Foremost among them were D'Arcy Thompson and Julian Huxley. Their classics, “On Growth and Form” (Thompson, 1917) and “Problems of Relative Growth” (Huxley, 1932), put forth the idea of growth as a change in form. The focus then was on the recurring observation that certain organisms and their sub-parts grew into well-defined geometric forms. As in other aspects of life science, however, the advent of molecular and cell biology subsequently over-shadowed this organism-level morphological view. The dominant view today is that molecular interactions drive biological processes. Perhaps as a natural outcome of this view, the contemporary classic “The Molecular Biology of the Cell” (Alberts et al., 2008) describes growth as an increase in mass driven primarily by the biochemistry. Both of these viewpoints—growth as changes in form or changes in mass—have found acceptance within the continuum mechanics community.

Early work by Skalak et al. (1982) introduced the kinematic treatment of continuum mechanics to describe surface growth (see also Cowin and Van Buskirk, 1979). It was followed by a more comprehensive discussion (Skalak et al., 1997) of growth velocities and velocities of generating cells that shape antlers, horns, tusks, and shells. Among continuum mechanicians there remain adherents to the view that the important effects of growth are explained by induced changes in form. The other opinion, that of growth as a change in mass, has drawn from the thermodynamics of open systems and more specifically in some cases, from the continuum theory of mixtures. It too has numerous adherents.

Modern continuum mechanical treatments of growth as a change in mass do not ignore the related change in form, however, as do some quarters of the mathematical biology community. How to translate gain and loss of mass into non-uniform changes in form is a central question for continuum mechanics. A common approach has been to treat local changes in mass via variations in concentrations, and to allow stress, or alternately the elastic part of the deformation gradient, to be driven by these variations in concentration. This approach is predicated upon a decomposition of the deformation gradient tensor into elastic and growth components, mathematically isomorphic to the multiplicative decomposition that is a cornerstone of finite strain plasticity. The coupled solution of balances of mass and linear momentum then governs changes in form: An increase in mass is accompanied by an increase in volume and *vice versa* for a decrease in mass. This simple approach (some would say simple-minded) successfully models residual stress in growing tissues. Indeed, a series of seminal studies by Fung and co-workers (Liu and Fung, 1988; Omens and Fung, 1990) on residual stress in arteries and the heart was interpreted in terms of continuum growth theories (and remodeling—see below). In the 1990s Fung also introduced the concept of a “mass–stress relation” for growth, a generalization to unmineralized tissues of a concept developed for mineralized tissue (bone) growth (Pauwels, 1980; Kummer, 1972; Firoozbakhsh and Cowin, 1981). Another general approach to modeling growth (and remodeling) has stemmed from Fung's suggestion, that is, by incorporating biologically driven mass density productions and survival functions within constitutive relations for stress response based on simple rule of mixture formulations (Humphrey and Rajagopal, 2002).

“Remodeling”, a term often used jointly with growth, has been employed to describe changes in properties, such as the anisotropy, stiffness and strength, that result from fine changes in microstructure as well as coarse changes such as thickening and fibrosis (Taber, 1995). However, the last two processes are also manifestations of growth at lower spatial scales. This example suggests that although growth and remodeling can be distinct cell driven biological processes, they often interact. One example occurs in the growth of long bones. The cartilaginous growth plate near the ends of a long bone provides an increment of length to the bone before the growth plate closes (endochondral ossification).

This additional length distorts the overall shape of the bone initiating a remodeling process that reshapes the bone. Growth and remodeling are separate processes in this case, but the former initiates the latter.¹ As another example, even if the overall mass remains constant, local cellular synthesis and degradation of extracellular matrix for purposes of remodeling necessarily involve mass turnover, that is, changes in constituent masses that again suggest an intimate coupling of the two processes (Humphrey and Rajagopal, 2002). Nevertheless, in an attempt to maintain distinct definitions, some restrict the term remodeling to signify a change in the underlying microstructure while mass is held constant (Kuhl et al., 2005; Garikipati et al., 2006).

Morphogenesis, another developmental process of fundamental importance in biology, suggests a macroscopic change in form actuated and underlain in some manner by growth or remodeling. It is the most dramatic of changes in the developing embryo, yet its continuum mechanical treatment remains the least explored of the three processes operative during development: growth, remodeling, and morphogenesis.

The emphasis in this communication is on growth, the continuum mechanical treatment of which is not without controversy. Different approaches exist to model relationships between changes in mass, kinematics, the origin of residual stress, the evolution of natural configurations of a growing body or its constituent parts, and other associated aspects of growth. For instance, because the set of material points constituting the tissue is changing due to growth, even the appropriateness of modeling growth by an elastic-growth decomposition of the deformation gradient tensor has been questioned by some. Others in the field suggest that the relation between growth-induced concentration changes and the elastic-growth decomposition of the deformation gradient is well-defined and useful, however, and that the important question is how to enrich it by drawing upon experiment and theory. Given the perspective nature of this communication—bringing together diverse ideas from different investigators—we have not attempted to forge a consensus on this controversy or others. Opposing points of view are thus expressed in this paper with the hope of promoting increased research in this important and broad area.

Apart from these topics, this paper also highlights the largely unexplored role of the thermodynamics of growth, questions of the scale at which growth theories may be employed, the robust experimental and theoretical activity in plant growth, links to the theory of structural optimization, identification of open problems and computational issues.

Perhaps most important of all, we also touch upon studies relating to the pathways by which mechanics induces chemical activity to cause growth at the molecular scale. That section (11) is focused on cancer studies, because the discovery of the importance of mechano-chemical coupling to tumor growth has fueled more research on such interactions in cancer studies than in other topics involving biological growth.

2. Kinematics

Foundational aspects of the mathematical formulation of growth and remodeling can be viewed through the modern continuum mechanical lens of kinematics, balance laws, and constitutive relations. Of these, balance laws can be said to be fairly well-understood and agreed-upon, at least for uniform media. There has been some recent disagreement on the kinematic representations as will become clear in this section. Constitutive relations for growth and remodeling are very much open as will be discussed in the next section.

2.1. Volumetric and surface growth

The kinematics of growth was cast in the mathematics of continuum mechanics by Skalak and co-workers in the 1980s (Skalak, 1981; Skalak et al., 1982) by focusing on “volumetric growth,” denoted by \mathbf{F}^g in a 3-D finite strain setting. Analogous to the deformation gradient tensor $\mathbf{F} = \nabla \boldsymbol{\varphi}$, where $\boldsymbol{\varphi}$ is the motion, the growth between two instants was thus modeled much like the strain associated with a finite deformation. Skalak referred to this process as distributed continuous growth, motivated by ideas in the historical plant and animal literature. In these papers, Skalak and co-workers also defined growth velocities and the velocities of generating cells to model surface growth that leads to the forms of horns, antlers, and shells.²

Among the concerns expressed with this approach are the following: (i) There are many situations in materials science where kinematic changes proceed from internal processes, that is, they are not determined uniquely by the load. Plastic deformation is one example, while simultaneous deformation and growth of a body is another. An effect much studied in plasticity is that of incompatible plastic deformation; it arises from the underlying incompatible nature of plastic slip or twinning deformation. In the case of biological growth, with material actually added or lost, adjacent neighborhoods of the body may not “fit together” in Euclidean space if the kinematic effect of growth alone is considered. In this sense growth, like plasticity, is said to be incompatible. One mathematical consequence is that \mathbf{F}^g cannot be expressed as the gradient of a vector field. (ii) Another difficulty with the volumetric growth approach is that, due to gain and loss of material, the mapping between physically attained configurations of the body is not represented entirely by the deformation; growth

¹ This interaction is illustrated in an animated graphical file that may be viewed at <http://depts.washington.edu/bonebio/ASBMRed/growth.html#long>.

² Biologists often refer to volumetric growth as interstitial growth and to surface growth as appositional growth.

also contributes to this mapping. While \mathbf{F}^g represents the stretching of tangent vectors due to volumetric growth in the interior of the body, the direct use of the deformation gradient and its multiplicative decomposition at a surface is not appropriate when surface growth occurs. Instead, the surface representation should be based on surface and growth velocities. Mappings between physically attained configurations must be decomposed properly into components due to surface deformation and surface growth. The work of Skalak et al. (1982) focused on this mapping when surface growth alone takes place without surface deformation (see also Cowin and Van Buskirk, 1979). The kinematics described by Skalak and co-workers (Skalak et al., 1982, 1997) or the more recent work of Ateshian (2007) and Garikipati (2009) can be applied to surface growth. Issues associated with proper extensions to combined deformation and growth are discussed below. (iii) Some investigators also perceive a difficulty associated with the gain and loss of mass, understanding it to imply that the mapping from the reference configuration to the instantaneous configuration cannot be bijective, consequently local strain measures cannot be defined. In this view, Skalak's notion of distributed continuous growth is considered by some not to be an accurate representation of actual growth processes because it assumes spatial uniformity and temporal continuity, neither of which is usually observed.

2.2. Incompatible growth and remodeling

Skalak et al. (1996) explored the question of compatibility in the case of infinitesimal and finite growth mappings and summarized compatibility conditions that are correspondingly inherited from infinitesimal and finite strain elasticity, respectively. A provocative hypothesis for this setting is that interstitial growth may be initially incompatible as new material is added. During and after the incompatible growth phase, tissue remodeling could smooth the incompatibility. This remodeling, a change in microstructure independent of growth, could happen by fine scale mass transport. Thus, initial incompatibility associated with growth is to be expected but could be eliminated naturally by remodeling. This hypothesis points to the sometimes intimate connection between growth and remodeling, and is consistent with the development of residual stress in some tissues.

Motivated by the work of Skalak and co-workers in the 1980s, the kinematics of finite growth was extended to include the effects of incompatible growth (Rodriguez et al., 1994) using a multiplicative decomposition (cf. Kröner, 1960; Lee, 1969) of the deformation gradient $\mathbf{F} = \nabla \phi$ into an elastic \mathbf{F}^e and a growth \mathbf{F}^g part, where $\mathbf{F} = \mathbf{F}^e \mathbf{F}^g$. Here, both \mathbf{F}^e and \mathbf{F}^g are incompatible, but their multiplicative composition, $\mathbf{F} = \nabla \phi$, is compatible by construction (Fig. 1).

2.3. On reference configurations for growth

There has been fairly wide agreement on the utility of this multiplicative framework to model certain aspects of biological growth (e.g., Taber, 1995; Taber and Humphrey, 2001; Lubarda and Hoger, 2002; Garikipati et al., 2004; Goriely and Ben Amar, 2007; Ambrosi et al., 2008). Nevertheless, this approach has not been employed by others (e.g., Humphrey and Rajagopal, 2002) and recent work by Ateshian (2007) has questioned it on the basis that material is added to and lost from the body as growth progresses. As a result, the notion of a fixed reference configuration is lost if the mapping between configurations is to be defined only by the deformation. From this standpoint, a major challenge encountered in the formulation of growth theories is the identification of reference configurations for the growing tissue. One approach to resolving this difficulty is to allow the reference configuration to evolve during growth. This approach also remains debated, and its resolution requires that we question some fundamental assumptions, implicit or explicit, that form the basis of classical continuum mechanics of non-growing bodies. For example, if a body increases in mass over time as a result of growth, is it legitimate to identify it as the same body in an evolved state or should it now be considered as the superposition of two bodies, one representing that which deformed but maintained its original mass and another that

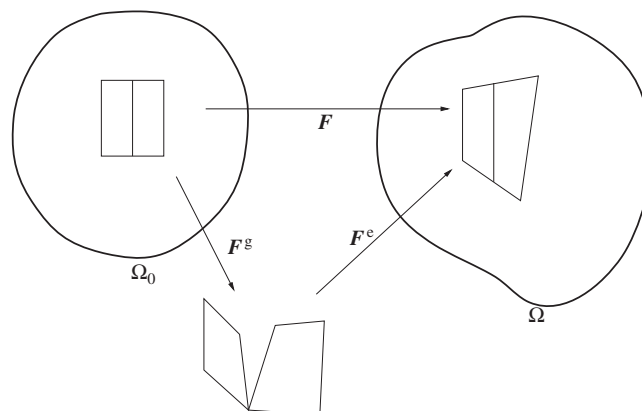


Fig. 1. The reference configuration, Ω_0 , the current configuration, Ω , and the multiplicative decomposition $\mathbf{F} = \mathbf{F}^e \mathbf{F}^g$.

arose due to growth, with suitable kinematic constraints to match their current configurations? The former description might require identifying the evolution of the body's reference configuration, whereas the latter description might keep the first body's reference configuration unchanged, while introducing new reference configuration(s) for the added mass forming the “second” body. A third approach is to consider the current unloaded body as the main configuration of interest but endowed with either a residual stress field or, equivalently, a new metric representing the residual strains. The problem is then to define the evolution and elasticity of a stressed body in the current configuration, which requires constitutive relationships that take account of both the elastic properties of the body and the residual stress field. Finally, a fourth approach to address this issue is to adopt a mixture theory wherein different constituents can possess different natural configurations; this approach is discussed below.

2.4. The mapping φ for a deformed, growing body

Yet another viewpoint arises from reconsidering the mapping φ and extending its physical interpretation to include deformation and growth. In this case, φ is a bijective map from an open set $\Omega_0 \in R^3$, the reference configuration, to another set $\Omega \in R^3$, the current configuration. Deformation and growth are included as physical processes giving rise to this mapping, which is strictly between points in R^3 . According to proponents of this viewpoint, misunderstandings arise from the use of terms such as “material particles,” whose consideration is not appropriate in this framework. The intermediate “relaxed” configuration attained by pulling back tangent vectors from Ω with \mathbf{F}^e^{-1} is, by definition, the configuration relative to which the elastic strain energy, W , is to be evaluated, where $W = W(\mathbf{F}\mathbf{F}^e^{-1}) = W(\mathbf{F}^e)$. Because of the incompatibility of growth, this intermediate configuration is not physically attained by the body and therefore the partial differential equation for balance of linear momentum cannot be written in this configuration, at least not in strong form. It is therefore usual to pull back the balance of linear momentum to Ω_0 .

2.5. Resorption at a point

Some suggest that the aforementioned multiplicative decomposition can be applied without difficulty if the tissue density ρ (or concentration) does not vanish anywhere over the body. When $\rho \rightarrow 0$ as a consequence of removal of tissue, it has been proposed (Garikipati, 2009) that the multiplicative decomposition can still be applied up to some arbitrarily set lower limit, say $\rho = \rho_{cav}$, with \mathbf{F}^e expressed as a function of ρ (see Section 3.1). If $\rho \leq \rho_{cav}$ over some subdomain, a closed surface can be defined as the boundary of this subdomain that represents a cavity, and the evolution of this surface can be governed by front tracking methods such as levelsets.

2.6. Physical and mathematical basis of the multiplicative decomposition

Aside from issues raised above, concerns have been expressed that the type of multiplicative decomposition discussed above for \mathbf{F} is well-founded in crystal plasticity, but not in biological growth. While the physics of growth is undeniably different from that of crystal plasticity, there is no fundamental reason that such a multiplicative decomposition has a more rightful basis in plasticity than in biology. In both cases there is an inelastic contribution to the kinematics, represented by \mathbf{F}^p or \mathbf{F}^e , respectively. In this regard a significant hurdle that needs to be overcome in growth kinematics is the definition of an experimentally inaccessible, evolving, incompatible state that is obtained by removing external loads on the growing body. Mathematically, this translates to evolution equations for \mathbf{F}^e . Theories incorporating inelasticity have to address this problem and provide, if not a physical justification, an explanation of this abstract concept as a useful and meaningful mathematical construct.

The multiplicative decomposition of growth is also rejected by some on the grounds that it focuses on consequences of growth (e.g., changes in form), not the biological mechanisms by which growth occurs (e.g., cell and matrix turnover). This opinion relates back to the previously noted change in viewpoint in biology, from a focus on changes in form to a focus on changes in mass, ushered in by recent advances at molecular and cellular levels. In other words, if one seeks to describe biological growth (and remodeling) in terms of the underlying biological processes (i.e., cell mediated production, reorganization, and removal of material), there is a need to develop continuum mechanical frameworks that admit such information as it becomes available (cf. Humphrey and Rajagopal, 2002). In this way, models can not only incorporate biological findings, they may also provide unprecedented predictive capability based on knowledge of genetic mutations, altered cellular phenotypes, and the like. It should be noted, therefore, that such theories of growth and remodeling will also necessarily involve sequential motions and thus (different) multiplicative decompositions for the kinematics. For example, Baek et al. (2006) show potential utility of including a hypothesis that newly synthesized matrix or proliferative cells may be incorporated within extant tissue at a preferred (homeostatic) stress or strain. In this case, one can include the so-called “deposition stretch” within a multiplicative decomposition of the overall kinematics, albeit in a very different way than suggested by the theory of volumetric growth. Nevertheless, different models yield different types of utility, and mathematical modeling can be as much about studying the consequences of a physical phenomenon as its origins. For example, myriad implementations reveal that the volumetric growth approach fulfills the important role of furnishing a framework for predicting globally (both in time and space) the evolution, stability, and material properties of diverse biological tissues. By analogy with an example in physics, although the origin of gravity is an important problem, most

interest lies in the consequences of gravity on large scales. On the other hand, whereas one usually cannot control gravity, gene expression and intracellular signaling pathways can be controlled, and thus there can be strong motivation to build models based on biological mechanisms, which fundamentally involve chemical reaction kinetics and associated changes in constituent masses. The two approaches discussed could therefore be seen as two levels in a multi-scale model of growth: the mechanism-based approach exploits information obtained by experiment and allows long-term predictions whereas the consequence-based approach focuses solely on long-time and large-scale outcomes.

3. Constitutive relations for growth

The basic continuum laws (e.g., balance of mass and linear momentum) continue to prove useful in biology and medicine, hence the development of theoretical frameworks for growth and remodeling can focus primarily on appropriate constitutive relations derived in terms of convenient continuum quantities. It is essential to remember, however, that constitutive relations do not describe materials; rather, they describe the response of a material to applied loads under specific conditions of interest. Different constitutive relations can thus be equally useful depending on the question at hand. Although there is a pressing need for more mechanobiological data (particularly on time courses of cell and matrix turnover; Humphrey, 2008), significant data are available that relate many tissue-level, cellular, and molecular responses to applied stresses or strains. It is thus appropriate and useful to formulate constitutive relations for mass production and removal, or similarly for changes in form, in response to altered states of stress/strain (the choice of metric depending primarily on the availability of data and utility). Some also seek to identify constitutive relations that relate stress/strain to changes in the primary effector molecules (e.g., growth factors, cytokines, and proteases); this will involve biochemomechanics (see §11; also Baek et al., 2007). Again, however, the search for such relations will be dictated largely by the availability of data and the problem at hand.

3.1. Scalar and tensorial constitutive laws for \mathbf{F}^g

Identification of appropriate evolution equations for the growth tensor \mathbf{F}^g remains challenging—possibly one of the most challenging problems in biomechanics according to some proponents of this approach. Since the continuum mechanics treatment of growth introduces \mathbf{F}^g as a new unknown that is not governed by a new balance law, an appropriate constitutive equation, namely an evolution law for growth, must be postulated. Such a law must relate \mathbf{F}^g to physical and chemical fields and, ultimately, biological signaling. Even if, for the sake of simplicity, one is restricted to mechanically driven growth, neglecting all other biological and chemical effects, there is no general agreement on whether growth processes relate best to stress or strain.

How can one find such growth laws? One would be denying the complexity of biological systems to believe that a simple universal law can be derived from fundamental physical principles. Attempts along these lines, based on thermodynamic arguments, have not been particularly fruitful. Another approach consists of postulating phenomenological laws based on both experiments and general observations. For instance, the notion of homeostatic stress (the idea that growth and remodeling takes place in such a way as to reduce the difference between the actual stress and a preferred stress) is central to many physiological systems and can be readily postulated as a differential law for the evolution of the growth tensor. In developmental systems, specific diffusing chemicals known as morphogens are believed to code for the location and extent of cell division and enlargement. Accordingly, the growth tensor can be related directly to these chemical fields. These phenomenological models play an important role in the development of the theory for they can be linked directly to specific experiments from which arbitrary parameters can be evaluated. From a theoretical point of view, however, there is room for a statistical mechanics formalism that starts with simple microscopic mechanisms for mass deposition, removal, and remodeling, and by coarse-graining arrives at macroscopic growth laws. By analogy, the development of the theory of rubber elasticity by Flory and others in the 1940s relied on simple observations of the microscopic structures of polymers that resulted in the derivation of the neo-Hookean potential, which, in turn, served as a basis for further refinement and development. In many ways, more is already known about growth at the cellular level than we can exploit at the tissue scale, and current attempts to develop evolution laws for growth necessarily ignore many of the fundamental molecular and cellular processes known to play a role in the process. Nevertheless, such an approach would establish a constitutive framework general enough to accommodate further refinement.

When regarded as the process of mass addition and loss, the fundamental governing equation of growth is balance of mass written in terms of either the mass or molar density, namely the concentration, ρ . This equation is arguably the starting point for describing growth, yet it is often missing from growth formulations. A key question is how ρ , a scalar measure of growth, is to be related to the growth tensor, \mathbf{F}^g .

3.2. Phenomenological evolution equations for \mathbf{F}^g

A simple *ad hoc* attempt to formulate growth laws is to introduce evolution equations for \mathbf{F}^g on a phenomenological basis. Indeed, the simplest approach is to assume isotropic growth whereby $\mathbf{F}^g = \vartheta \mathbf{I}$ can be characterized through a single scalar-valued variable ϑ scaling the second order isotropic tensor \mathbf{I} . Its evolution could be driven by the density ρ or, if the mass balance equation is not included in the formulation, by a pressure expressed in terms of the trace of the second Piola

Kirchhoff stress (i.e., $\text{tr}(\mathbf{S}^e)$; Taber, 1995) or of the Mandel stress (i.e., $\text{tr}((\mathbf{F}^{eT} \cdot \mathbf{F}^e) : \mathbf{S}^e)$; Himpel et al., 2005). Because most soft biological tissues possess a highly anisotropic microstructure, it seems natural to incorporate effects of anisotropic growth parallel or perpendicular to characteristic microstructural directions \mathbf{n} . The growth tensor $\mathbf{F}^g = \eta \mathbf{I} + [\eta - \vartheta] \mathbf{n} \otimes \mathbf{n}$ would then be characterized through two variables η and ϑ , where the former accounts for growth parallel to the direction \mathbf{n} and the latter accounts for growth perpendicular to \mathbf{n} , respectively (Taber, 1995). Although the mathematical understanding of these evolution equations seems to be fairly intuitive, their clear biomechanical interpretation is still widely debated, particularly when defining appropriate stress- or strain-based mechanical driving forces. It thus seems natural to seek further insight through micromechanical phenomena that are related to isotropic and anisotropic tissue growth on the cellular level.

3.3. Micromechanically motivated evolution equations for \mathbf{F}^g —an example

The trend from phenomenological to micromechanical modeling reflects what is observed in the constitutive characterization of a range of engineering materials such as metals, concrete, soils, or polymers. When aiming to describe biological growth, however, this approach faces greater complications since it ultimately requires *in vivo* characterization of structural and functional changes in living tissues. Moreover, the type of growth is likely to depend on the type of tissue under consideration. It is unlikely that a unique overall growth law could be general enough for all types of tissue. It thus proves convenient to choose particular model systems to start with for which growth is sufficiently well characterized. Typical examples are arterial and cardiac tissues. The heart, for example, displays ventricular dilation and wall thinning in response to volume overload and hypertrophic wall thickening in response to pressure overload (Allen et al., 2001). Cardiac growth can be modeled using micromechanically motivated constitutive equations that account for alterations of cardiac cell geometry. It is well-documented that heart muscle cells, or cardiomyocytes, tend to elongate upon volume overload and thicken upon pressure overload (Hunter and Chien, 1999). Cardiac growth thus manifests phenomenologically as an anisotropic growth, say $\mathbf{F}^g = \eta \mathbf{I} + [\eta - \vartheta] \mathbf{n} \otimes \mathbf{n}$ where the perpendicular growth $\vartheta = \vartheta(\text{tr}(\mathbf{S}^e))$ is driven by the pressure $\text{tr}(\mathbf{S}^e)$ and the longitudinal growth $\eta = \eta(\lambda)$ is driven by longitudinal cell stretch λ . Once calibrated on the cellular level via measurements from histology, the growth equations can be validated experimentally through well-documented animal infarct models characterizing growth on the tissue or organ level. A common procedure used to introduce cardiac growth is the controlled initiation of ischemia through the partial occlusion of the coronary arteries. Cardiomyocyte death due to insufficient blood supply in the region close to the infarct takes place almost instantaneously and can be observed in acute infarct models. Ventricular dilation and remodeling that occur during the following weeks can only be assessed in chronic infarct models (Cheng et al., 2006; Doyle et al., 2007). Modern invasive and non-invasive imaging techniques can be applied to assess cardiac function via ventricular volumes, cardiac output, ejection fraction, and wall dynamics.

4. The role of mixture theory

Many current theories of biological growth model the tissue as a homogenized (single-constituent) solid continuum. For the balance of mass, this approach assumes that the mass supply needed to drive this growth is available from implicit sources. When extended to the balance of energy and the entropy inequality, this approach corresponds to classical open system thermodynamics. While this approach can yield self-consistent frameworks, it may also overlook phenomena that can play important biological roles during growth, including reaction and transport of nutrients, enzymes, and by-products. Another example of an overlooked mechanism is the role of osmotic pressure in the interstitial fluid of a soft tissue. If the solid matrix is charged, as is often the case in tissues containing proteoglycans, a Donnan osmotic pressure will result in tissue swelling, typically in a non-homogeneous manner. If the growth process involves changes in proteoglycan content, a common occurrence in many tissues, the resulting change in the osmotic pressure of the interstitial fluid will play an important role in the evolution of the tissue response. Thus, formulation of a framework for biological growth can benefit from the use of mixture theory so as to include contributions of diverse constituents (solid and fluid as well as electrolytes, growth factors and cytokines, and nutrients and waste products within the interstitial fluid) involved in the underlying biochemical and biophysical process. Subsequent simplifications may then be adopted in the derivation of more elementary theories, when a clearer understanding is available with regard to the significance of neglected terms.

The continuum theory of mixtures is similarly useful for modeling evolving contributions of the different solid constituents that comprise a tissue or cell and influence its growth and remodeling. Examples of structurally important solid-like constituents within soft tissues are the fibrillar collagens, elastic fibers, proteoglycans, and muscle; examples within cells are F-actin, microtubules, intermediate filaments, and stress fibers. These solid constituents exhibit distinct natural configurations, material properties, and rates of turnover, thus emphasizing the potential utility of materially nonuniform theories. For example, Humphrey and Rajagopal (2002) suggested that full mixture equations for mass balance (to include reaction–diffusion effects of vasoactive, mitogenic, synthetic, proteolytic, and inflammatory molecules) be used in combination with classical equations for linear momentum balance written in terms of rule-of-mixture relations for the stress response. Reasons for this include the advantages of including contributions of individual constituents while avoiding difficulties associated with prescribing partial traction boundary conditions in real problems and the yet unknown exchanges of momentum between individual constituents as they turnover. By prescribing separate mass balance relations for structurally insignificant (soluble) and structurally significant (insoluble) constituents, one can

begin to introduce biochemomechanical modeling. Although any mixture theory of growth and remodeling will involve potentially large numbers of constitutive relations and associated material parameters, such models should be formulated so that important data can be incorporated as they become available, guidance can be given for needed experiments, and new hypotheses can be generated and tested.

4.1. Constrained mixture theory

This specialization of mixture theory assumes that growth and remodeling seeks to maintain constant a preferred (homeostatic) biomechanical state, which is achieved via reorganizing or replacing previously existing constituents with new constituents that may have new natural configurations, orientations, and mass fractions, but otherwise similar mechanical properties. Basic hypotheses are that structural constituents are constrained to move together despite having different/evolving natural configurations, that new constituents are incorporated within extant matrix at preferred deposition stretches, and that rates of turnover (prescribed via production and survival functions) depend on changes in chemomechanical stimuli from baseline. This basic theoretical framework has been used to model salient features of the enlargement of cerebral aneurysms (Baek et al., 2006), the development and resolution of cerebral vasospasm (Baek et al., 2007), and arterial adaptations to altered blood flow and pressure (Valentin et al., 2008). It has also been shown that related computational growth and remodeling codes can be combined with fluid–solid–interaction codes to develop a new class of fluid–solid–growth codes that may be useful in cardiovascular medicine and surgery (Figuerola et al., 2008). Such applications serve as reminders that growth and remodeling research should not only seek to promote understanding of basic physiology and pathophysiology, it should also seek to improve clinical intervention, particularly via medical device design, regenerative medicine, and tissue engineering.

4.2. Thermodynamics and dissipation

The constitutive relations that govern material response in the sense of mechanics, both passive and active, have received much attention. The thermodynamic aspects, however, have remained fairly underdeveloped.

If a body is treated as a mixture, the balance of energy includes inter-species energy exchange terms, which must be modeled if the energy balance needs to be resolved for each species (see e.g., Garikipati et al., 2004). It is not yet known what form these interaction terms take. The entropic changes also remain largely unaddressed apart from the recognition that constitutive laws for growth, such as for \mathbf{F}^g must comply with the dissipation inequality. Instead, the inelastic kinematics of growth is exploited to write the corresponding contribution to thermodynamic dissipation as the scalar product of the appropriate stress and growth rate tensor. Maximum dissipation due to growth has been postulated in some cases (Fusi et al., 2006) to obtain restrictions on the constitutive relation for \mathbf{F}^g . However, there have not been studies comparing such a model with experiment to suggest that maximum dissipation is indeed a principle that is observed during biological growth.

Specifically, there is a need for constitutive equations for growth that can be tested using the expression for thermodynamic dissipation. The dissipation so modeled can then be related to measurable energetic and metabolic quantities at the cellular and molecular level. The formal expertise developed in continuum thermodynamics can thus make fundamental contributions to understanding the energetic basis of growth in normal and pathological states. Such an approach was recently adopted by Narayanan et al. (2010) in an *in silico* study of the free energy changes during growth of solid tumors. The authors grew tumor spheroids of a human colon cancer adenocarcinoma cell line and characterized the growth and mechanical properties of these tumor spheroids. Additional data were obtained from the literature on tumor spheroids and cancer cells. With these, they carried out continuum mixture theory-based computations for the development of a representative tumor spheroid system over 28 days during which it grew from a radius of ~ 50 to ~ 200 μm . Their model included the biochemo-mechanical processes of cell proliferation, death and migration, extra-cellular matrix production, oxygen and glucose transport and consumption, and mechanical growth against stress. They also derived free energy rates associated with these biochemo-mechanical processes. Their preliminary computations suggested that the free energy rates associated with the mechanical processes of cell migration and growth against stress are dwarfed by many orders of magnitude when compared with the biochemical processes of cell proliferation and death, extra-cellular matrix (ECM) production, and oxygen and glucose transport and consumption (Fig. 2). This finding suggested that reports of stress-induced retardation of tumor spheroid growth (Helmlinger et al., 1997), and of arrest of cancer cells' growth cycle (Chang et al., 2008), involve chemo-mechanical signaling that is more complex than direct energy starvation by manipulation of mechanical properties or boundary conditions. The paper also pointed to the need for a multiscale study of the free energy changes associated with cell motion.

5. The cellular and sub-cellular scale for growth models

To date, most theoretical studies of growth and remodeling have been based on tissue-level phenomenological models. These models have improved our understanding of macroscopic responses. Yet, growth and remodeling is accomplished via cell mediated production (e.g., cell hypertrophy/proliferation and matrix synthesis) and removal (cell atrophy/death and matrix degradation). From the perspective of biomechanics, one of the most important discoveries in cell biology

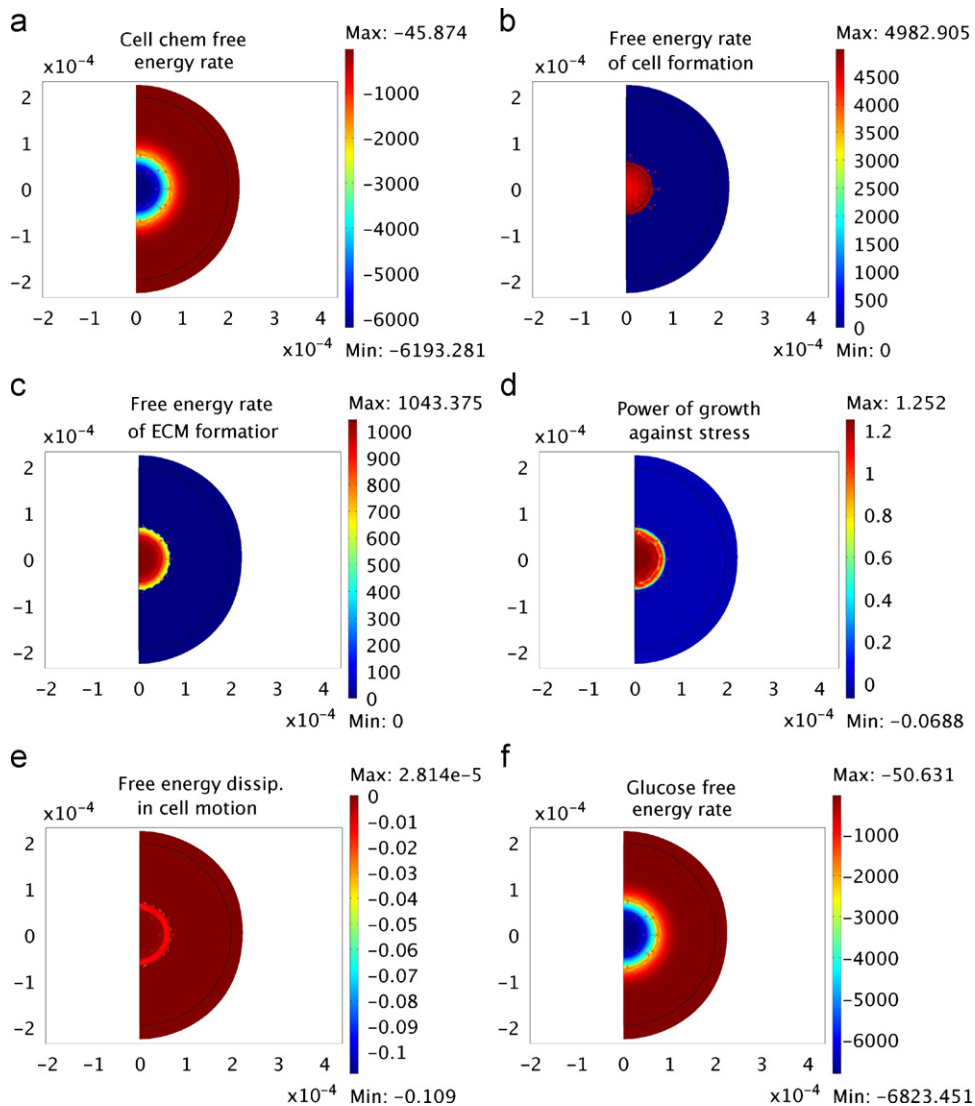


Fig. 2. Surface plot of the free energy rates associated with tumor growth. All units are W m^{-3} . (a) The rate of change of chemical free energy density stored in the cells. (b) The rate of change of free energy density stored in newly formed cells. (c) The rate of change of free energy density stored in newly produced ECM. (d) The rate at which free energy density is dissipated into work done as the tumor spheroid grows against stress. (e) The rate at which free energy density is dissipated due to cell motion. (f) The rate of change of free energy density due to glucose consumption. See Narayanan et al. (2010).

(in the 1970s) was that many types of cells respond to changes in their mechanical environment via altered gene expression. These mechanobiological responses involve three basic processes: transduction, transcription, and translation. It is hoped that parallel advances in systems biology and biomechanics will one day enable multiscale models that link these fundamental processes at the molecular level with the tissue level manifestations that present clinically and require intervention. Clearly, this endeavor poses a number of extremely challenging issues regarding how the various scales will be linked. In the end, however, this research should help answer a number of fundamental questions such as: What mechanical stimuli regulate growth and remodeling? Why do some tissues seem to grow and remodel toward certain preferred states of stress or strain? How do mechanical stimuli affect gene expression and vice versa?

This line of thought leads to the choice of scale and system to model. Notwithstanding the importance of continuum mechanical treatments of growth and remodeling at the tissue scale, there are unparalleled opportunities at the cellular and sub-cellular scales. As the basic unit of life, the functionally adaptive growth processes so unique to living biological materials begin and end with the effector cell. Consider this: The cell is a well-defined domain with clear boundaries and interior. Its boundary, the cell membrane, is subject to influx and efflux of mass via ion channels, pumps, and direct diffusion; it has distinct boundary subdomains where tractions are applied, exerted, and sensed. These regions include focal adhesions, cadherins junctions, and other receptor-mediated attachments. The cell, itself, is subject to finite strains.

There is a great deal of data on the mechanical properties of intracellular components (actin filaments, microtubules, and intermediate filaments) and of the viscoelastic response of the cell as a whole. Moreover, the cell cycle — through the phases of gap1 (G1), the growth phase of synthesis (S), gap2 (G2), and mitosis (M) — is well-characterized. At the larger scale of the tissue, boundaries are sometimes hard to define and transport across them is not always well-characterized. The higher degree of variability and mechanical complexity of the tissue structure also seems to have rendered mechanical testing more difficult. These reasons offer strong motivation to apply the continuum theory of coupled transport, reaction, and mechanics to the cell at least as much as to tissues. Moreover, such research may afford a favorable framework by which to link macroscopic to microscopic scales (Na et al., 2007; Humphrey, 2008). Such an integration of scales will be a prerequisite to joining advances made in computational tissue engineering (macro) to those in computational biology and bioinformatics (micro) in order to realize *in silico* platforms for patient-specific regenerative medicine (Semple et al., 2005).

6. Morphogenesis

Morphogenesis is the creation of biological form. This subject offers a wide range of challenging and important problems that barely have been touched outside the field of developmental biology. Problems include the development of the heart, blood vessels, brain, lungs, gut, eye, and musculoskeletal system (Taber, 1995, 2001; Murray, 2002). In addition, tissue engineers can benefit greatly from knowledge of how tissues develop in nature.

Growth and remodeling play important roles during development, but changes in form or shape result primarily from viscoelastic deformation of cells and tissues in response to both external and internal loads. Internal loads include those generated by cytoskeletal contraction, actin polymerization, microtubule elongation and shortening, adhesion, differential growth, and swelling of ECM. Cells also migrate through the embryo and exchange neighbors (intercalate) to change tissue shape. At the tissue level, many of these processes can be simulated using the theory of Rodriguez et al. (1994) for finite volumetric growth (Taber and Perucchio, 2000; Taber, 2001).

In the embryo, cells move either individually (mesenchyme) or in sheets (epithelia). The heart, brain, and gut begin as epithelia. Muscles and bone arise from clusters of mesenchymal cells.

In early work on modeling the mechanics of epithelial morphogenesis, Odell et al. (1981) proposed a 2D model for an epithelium in which each cell is treated as a viscoelastic truss-like element with a contractile apex. These authors used this model to simulate the invagination that occurs during gastrulation and neurulation. Since then, other models for epithelial morphogenesis have been used to study neurulation (Brodland and Clausi, 1994; Brodland, 2002; Chen and Brodland, 2008), gastrulation (Davidson et al., 1995; Munoz et al., 2007), and cardiac looping (Ramasubramanian et al., 2006, 2008).

A pioneering model for mesenchymal morphogenesis is the Murray-Oster theory, which is based on continuum mechanics for a mixture of cells and matrix and includes the effects of cell traction, mitosis, matrix secretion, cell migration, and differential adhesion (Murray et al., 1983; Oster et al., 1983). The governing equations produce a reaction–diffusion type system similar to those studied extensively in biochemical models of pattern formation (Murray, 2002). Using this theory, Manoussaki et al. (1996) and Namy et al. (2004) studied two-dimensional models for vasculogenesis. For appropriately chosen parameters, their model yielded networks of cord-like cell aggregates resembling those that form when endothelial cells are cultured *in vitro* (Folkman and Haudenschild, 1980). The tissue development model of Barocas and Tranquillo (1997) is based on an extension of the Murray–Oster theory.

Genes play a central role in regulating the forces that drive morphogenesis. Gene activity, however, is affected by feedback from the mechanical environment, and the nature of this feedback has been a subject of considerable speculation. Computational models with mechanical feedback have been developed for a number of morphogenetic processes, including gastrulation (Odell et al., 1981; Taber, 2008, 2009), neurulation (Clausi and Brodland, 1993; Brodland and Clausi, 1994), cardiac looping (Nerurkar et al., 2006; Ramasubramanian et al., 2008), and bone development (Carter, 1987). The behavior of these models depends on postulated feedback laws based on stress, strain, or strain-energy density.

There is no clear consensus on the specific mathematical form that biomechanical feedback laws should take, and some investigators argue that it is unlikely that such laws even exist. Clearly, biological systems must obey the quantitative laws of physics, but it is not clear whether they also obey quantitative laws of biology. For example, Forgacs and Newman (2005) note that, in contrast to inanimate systems, living systems are governed by the laws of evolution. To increase their chances of surviving natural selection, therefore, species develop adaptive mechanisms which differ among species. Moreover, different tissues serve different functions and likely are optimized to carry out these functions. Hence, if mathematical feedback laws exist, they may be different for each organism and each tissue type. On the other hand, for undifferentiated cells in the early embryo, such laws may have a certain universal character.

Based on decades of experiments with embryos, the developmental biologist Lev Beloussov has suggested that a universal principle for morphomechanics does indeed exist (Beloussov, 1998). According to his hyperrestoration (HR) hypothesis, a perturbation in tissue stress induces an active mechanical response which is directed toward restoring the initial stress value, but generally overshoots to the opposite side. Each response changes tissue shape and induces a new stress perturbation, which elicits a new response, and so on, until the proper form is created. Beloussov (1998) has shown that this idea can explain in qualitative terms a number of experimental observations for embryos undergoing various morphogenetic processes, including cleavage, gastrulation, and neurulation. Ultimately, computational models are needed to test this idea (Belintsev et al., 1987; Nerurkar et al., 2006; Ramasubramanian et al., 2008; Taber, 2008). Thus far, the

results are mixed. Nevertheless, the HR hypothesis or a modified version of this theory (Taber, 2009) remains an intriguing idea to be pursued in the future.

7. Plant growth

The involvement of mechanics in plant growth has been known for more than a century (Sachs, 1875). The early recognition of the importance of mechanics is largely due to the fact that residual stresses in plants are large and ubiquitous. In that sense, plant growth shares many similarities with animal tissue growth and remodeling (Cowin, 2004). However, some fundamental differences between the structure of plant and animal cells need to be taken into account in modeling growth. The goal of this section is to present the key mechanical aspects of plant growth.

7.1. The mechanics of growth at the cell level

Many of the features of plant growth find their explanation at the cell level. It is therefore useful to focus first on the growth of plant cells. Plant cells differ from animal cells in that they are surrounded by a thin but stiff extracellular matrix, the cell wall, made of highly organized cellulose microfibrils embedded in a pectin matrix (Preston, 1974; Cosgrove, 1997; Peters et al., 2000; Baskin, 2005). For a plant cell to increase its volume, it must expand the cellulosic wall that surrounds it. Whether wall assembly will contribute to cell surface expansion depends on the mode of insertion of new wall material. Two contrasting mechanisms exist — wall assembly by apposition and by intussusception. Appositional wall assembly implies that new material is added to the inner surface of the pre-existing wall thus increasing wall thickness. Intussusception is growth where new wall components are deposited within the existing polymer network thus leading to increased surface area of the cell. Ever since the two modes of wall deposition were recognized, plant biologists have debated their relative importance (Noll, 1887; Jost, 1907; Ray, 1967). It now seems clear that wall assembly proceeds mostly by apposition as far as cellulose deposition is concerned, while other wall components can be incorporated in the wall with some degree of intussusception (Ray, 1967).

Wall deposition and assembly is, however, only one aspect of plant cell growth. Plant cell expansion also requires that the cellulosic wall be put under tension. The strength of the wall is such that a considerable stress is required to cause it to creep. This stress is provided by the internal hydrostatic pressure of the cell known as turgor. A turgor pressure of approximately 0.5 MPa is common in plant cells (Green et al., 1971; Zhu and Boyer, 1992). Cells develop this pressure by maintaining an osmotic gradient between their cytoplasm and the environment thus allowing water to move into the cell and build up a large pressure. Cell expansion occurs only when the cell's turgor pressure exceeds some critical value thus underlining the fact that at the macroscopic level cell walls possess a plastic yield stress above which irreversible expansion is observed and below which deformations are elastic and therefore reversible (Green et al., 1971; Cosgrove, 1985, 1986). The most compelling evidence of the complementary role of wall deposition and of pre-stresses in driving growth comes from the analysis of cells growing under reduced turgor pressure. Under these conditions, it is common for cell expansion to stop completely while wall deposition proceeds unaffected, leading to a rapid wall thickening (Kiermayer, 1964). Clearly, wall deposition must be complemented with a certain level of stress to allow normal cell growth. Thus plant cells offer a striking example of a stress-dependent growth process of the kind described above.

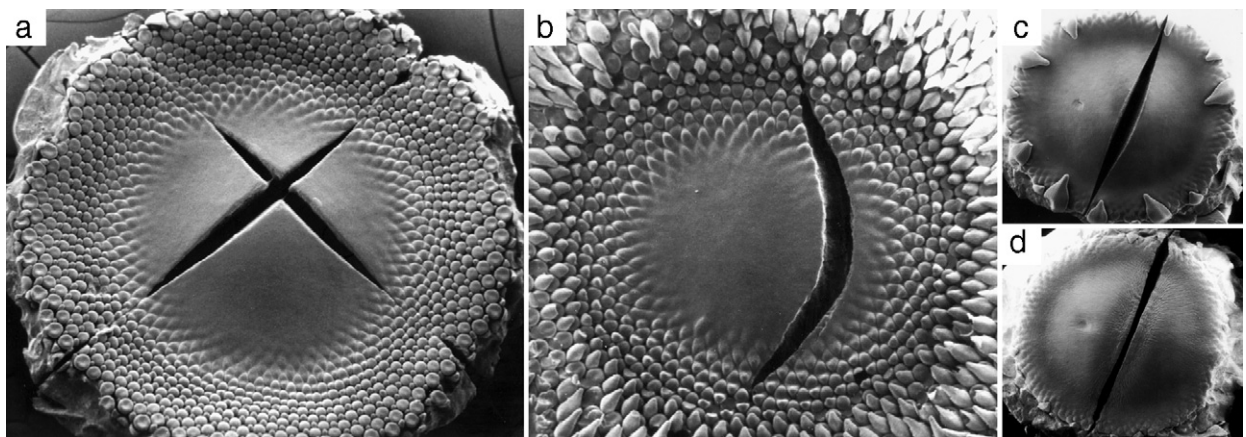


Fig. 3. Growth stresses in the young sunflower head. (a) The head was cut along two orthogonal lines. The cuts gape widely in the central region while they remain closely appressed in the peripheral region where new organs are being formed. This gaping pattern demonstrates the presence of radial tension and circumferential compression in the head. (b) Typical arcuate crack created when the surface of the head is put in tension. The crack propagates predominantly in the circumferential direction thus releasing the tensile stresses in the radial direction. (c) and (d) The same head before (c) and after (d) reducing the turgor pressure of the cells. The characteristic gaping of the cut has been lost after decreasing the pressure. (In all images, the head is about 5 mm in diameter.)

Although few studies have focused on the constitutive behavior of the growing cell wall, other mechanical aspects of plant cell expansion have been analyzed in detail (Lockhart, 1965; Green et al., 1971; Sellen, 1983; Zhu and Boyer, 1992; Goriely and Tabor, 2003; Dumais et al., 2006; Bernal et al., 2007). In particular, pressurized shell models with simple constitutive relations can predict cell surface expansion with surprising accuracy (Sellen, 1983; Dumais et al., 2006; Bernal et al., 2007).

7.2. Tissue growth

The mechanism of plant cell expansion has one obvious consequence for the growth of plant tissues — growth can proceed only if the walls of the many cells within a tissue are under tension. Therefore, the large residual stresses present in growing plant structures are as much a prerequisite for growth as they are a consequence of it. The main residual stresses in plant organs come from the strong osmotic gradients that maintain the turgor pressure within cells (Hejnowicz and Sievers, 1995a,b, 1996). This conclusion is supported by a simple experiment. When a growing stem is cut along its length, the two halves spring apart thus demonstrating that residual strains (and stresses) are present (Peters et al., 2000). However, when the same stem is placed in a solution with high concentration of sugar or salt such that the pressure within the cells is reduced, it shows little or no response to a longitudinal cut. Clearly, the residual stresses present in the stem are dependent on the internal pressure of the cells.

Residual stresses were also uncovered in the shoot apex whose growth produces most of the above-ground organs of plants (Snow and Snow, 1951; Hussey, 1973). The stress field is especially intricate in the sunflower head where the outer epidermal layer is under radial tension and circumferential compression (Dumais and Steele, 2000) (Fig. 3). These large residual stresses are revealed either with cuts of the meristem surface (Fig. 3a) or by propagating cracks that invariably follow circumferential trajectories in order to release the radial tension on the surface (Fig. 3b). Interestingly, the pattern of residual stresses can be explained solely by assuming that the cells within the meristem exert a uniform pressure on the meristem surface (Dumais and Steele, 2000). As with other plant structures, the residual stresses vanish when the apex is plunged in a salt solution to lower the turgor pressure of the cells (Figs. 3c, d). The consequences of these residual stresses on the overall mechanical properties of plants can be studied within the context of a multiplicative decomposition growth theory as shown by Vandiver and Goriely (2008).

8. Structural optimization and bone remodeling

There is a close connection between the objectives of computational bone remodeling and the field of structural optimization (Petersen and Bendsoe, 1999; Bendsoe, 1995). *Structural optimization* is a term used to cover a number of optimization techniques associated with structural mechanics; it includes shape, size, and topological optimization. It also includes material optimization, which overlaps strongly with material design. *Shape optimization* is the term used to describe the process of finding the optimum shape of a domain, the shape being the design variable; see Haftka and Grandhi (1986). *Size optimization* is the term used to describe the process of finding the optimum dimension of a structural shape, say, the thickness of a plate. *Topology optimization* is a method that applies equally well to determine the connectivity of a structural domain or

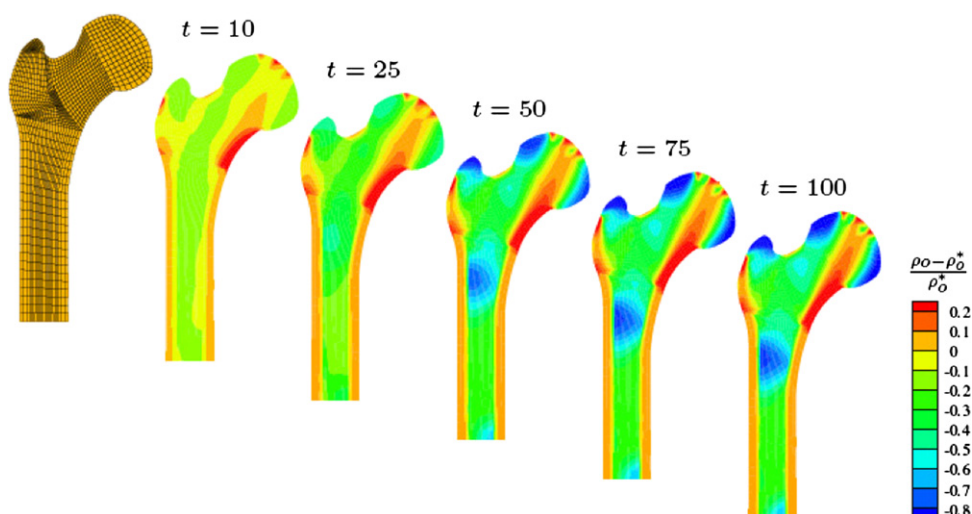


Fig. 4. Example of structural optimization and bone remodeling: Typical benchmark problem of the proxima femur. A finite element-based smooth topology optimization algorithm can be used to predict the physiological density profile in response to the three most relevant muscle groups activated during abduction, adduction, and the midstance phase of gait. The converged density profile displays the characteristic dense system of compressive trabeculae carrying the load from the superior contact surface to the calcar region, a secondary arc system of trabeculae through the infero-medial joint surface, Ward's triangle as an area of low density, and a dense cortical shaft.

the material optimization (design). For a survey of structural optimization, see Bendsøe (1995) and for applications Petersen and Bendsøe (1999). Surface bone remodeling bears a great deal of similarity to shape optimization because surface bone remodeling has to do with changes in the overall shape of a single bone. Internal bone remodeling has many characteristics and techniques in common with topology optimization. One application of topology optimization is to fashion the shape of a truss from an amorphous structural domain in a manner similar to a sculptor fashioning a sculptural art form from an amorphous marble domain. Internal bone remodeling is used in a manner similar to topology optimization to fashion local trabecular architecture. Trabecular architecture is treated as both a structure and a material in mechanics. Similar remarks may be made about topology optimization because it is applied to both structures and to material optimization. An interesting point concerning these optimization algorithms and surface bone remodeling models is that the optimization algorithms are global and the surface bone remodeling models are local yet they often produce similar results for similar problems and the connection between the two has not been established to date.

Figs. 4–6 show a typical example of bone remodeling around implants (Kuhl et al., 2003). Using a relaxed topology optimization algorithm in which the density is treated as an internal variable that is allowed to change gradually, bone

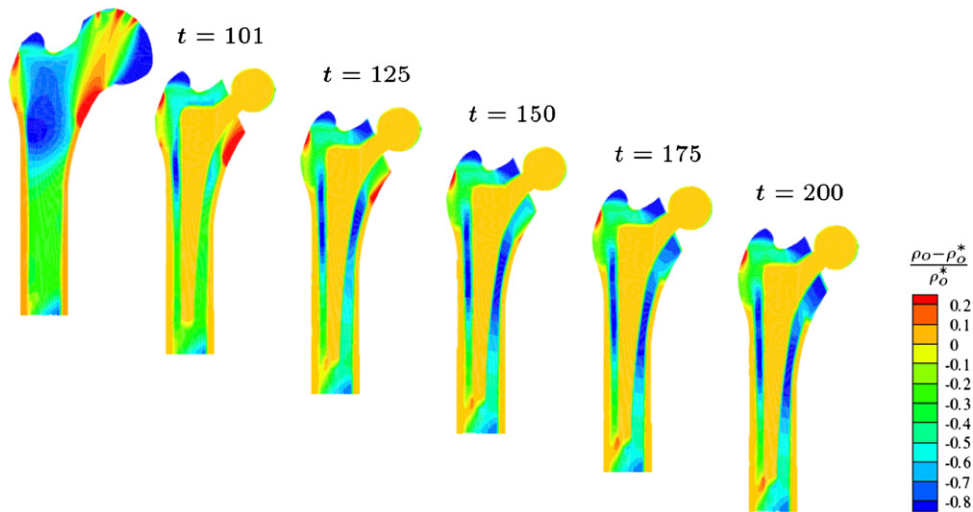


Fig. 5. Example of structural optimization and bone remodeling: Virtual implantation of traditional hip prosthesis. The stiff titanium transfers the joint forces down the distal portion of the implant stem. At the distal tip of the stem, forces are transferred to the outer bone shaft. This triggers the pronounced deposition of bone mass at the distal tip of the prosthesis while the unloaded proximal regions of the femur undergo a severe bone loss that is typically accompanied with aseptic loosening and the need for refixation.

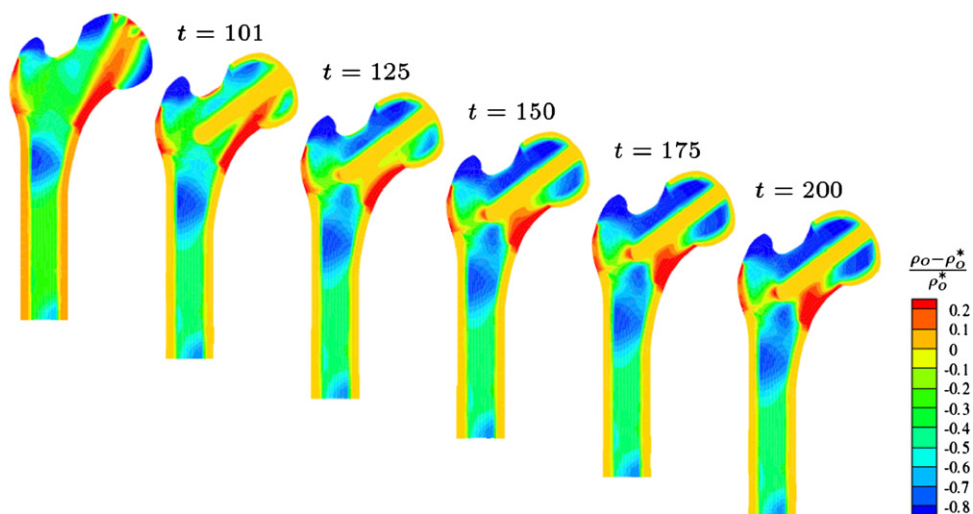


Fig. 6. Example of structural optimization and bone remodeling: Novel hip resurfacing technique. To avoid the undesirable long-term effects associated with traditional implants, a novel technique has been developed that is based on local femur hip resurfacing. The new nail-shaped implant shows a much better ingrowth with an increased density at the medial side. In contrast to the classical implantation technique, the shaft remains virtually unaffected by the treatment.

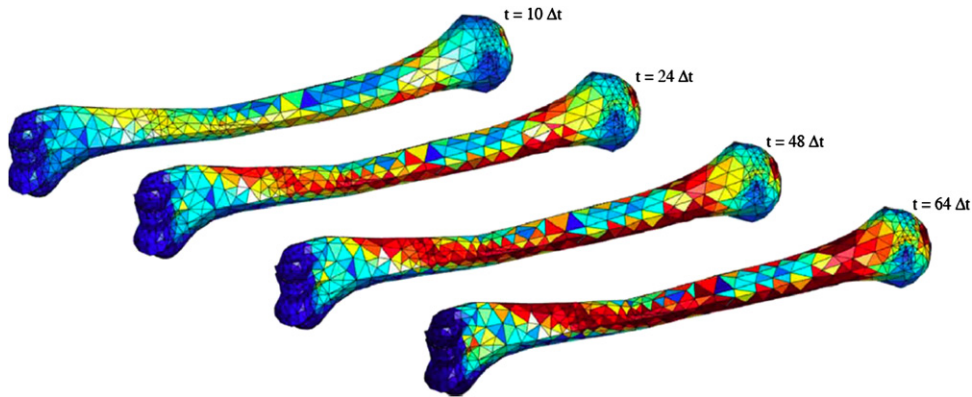


Fig. 7. Example of structural optimization and bone remodeling: Functional adaptation of bone density in the humerus of high performance tennis players. Severe humeral torsion during the serve induces bone remodeling which results in a non-physiological twisted density profile with high density areas wound around the long axis of the bone.

density profiles can be generated by laying down material in areas of high stress concentrations while areas with low stress undergo bone resorption. Fig. 4 illustrates the classical benchmark problem of the proximal femur loaded by three different muscle groups that are activated during abduction, adduction, and the midstance phase of gait. The underlying topology algorithm converges towards a physiological density profile with the characteristic dense system of compressive trabeculae carrying the load from the superior contact surface to the calcar region, a secondary arc system of trabeculae through the infero-medial joint surface, Ward's triangle as an area of low density, and a dense cortical shaft. Fig. 5 documents the evolution of the density profile in response to the virtual implantation of a traditional prosthesis. The stiff titanium transfers the joint forces down the distal portion of the implant stem. At the distal tip of the stem, forces are transferred to the outer bone shaft. This triggers the pronounced deposition of bone mass at the distal tip of the prosthesis while the unloaded proximal regions of the femur undergo a severe bone loss that is typically accompanied with aseptic loosening and the need for refixation. To avoid these undesirable long-term effects, a novel technique has been developed that is based on local femur hip resurfacing. Fig. 6 demonstrates its advantages over traditional hip implants. The new nail-shaped implant shows a much better ingrowth with an increased density at the medial side. In contrast to the classical implantation technique, the shaft remains virtually unaffected by the treatment. These examples demonstrate the ability of bone to change its local microstructure in response to loading and document how the functional adaptation could potentially be predicted using finite element algorithms in combination with topology optimization. Another example of bone remodeling is illustrated in Fig. 7. It shows the functional adaptation of bone density in high performance tennis players. Severe humeral torsion during the serve induces bone remodeling which results in a twisted density profile with high density areas wound around the long axis of the bone (Taylor et al., 2009).

9. Some open problems in growth and remodeling

The mathematical modeling of growth and remodeling can be expected to provide fertile ground for research over the next decade and beyond. For example, the endothelial cells, lining the arterial wall and resting on a thin basal membrane, “recognize” (shear) stress and (shear) strain in a still unknown manner but regulate many of the functions of the wall; smooth muscle cells, which reside in an extracellular matrix within the media, recognize cyclic stress and strain, and in response regulate the diameter, thickness, length, stiffness, and tone of the artery; fibroblasts, which reside in matrix within the adventitia are similarly responsive to changes in cyclic stress or strain and maintain adventitial structure by producing and degrading matrix and can migrate to inner portions of the wall to facilitate growth, remodeling, and repair. It is thus accepted that one trigger for growth and remodeling comes from mechanical stimuli which, in arterial walls, stimulate endothelial cells through the activation of mechanosensors. Such mechanotransduction leads to modulations of protein expression and other cellular functions (see §11; also Chien, 2007).

For example, after stretching a substrate on which a cell is attached, a net stimulus acts on cell–matrix contacts, which, via integrins, induce signaling pathways that ultimately affect the nucleus. One effect is an up-regulation of the synthesis of a matrix protein and a down-regulation of protease expression. Subsequently, the cell will try to reach a new equilibrium state in which external and internal forces are balanced, signaling via integrins becomes quiescent, and the cell–matrix contacts are restructured (Chiquet, 1999). Hence, the activity of cells depends strongly upon mechanical stimuli mediated by the matrix. An important goal is translate information from cell or tissue culture studies to clinical medicine wherein, for example, growth and remodeling of arterial walls under physiological (morphogenesis) or pathophysiological (aneurysm growth) conditions are fundamental to patient health.

9.1. Collagen fiber remodeling in arterial walls

Hariton et al. (2007a) proposed a remodeling model for collagen fibers in arterial walls that is stress modulated, i.e., the angle of collagen alignment depends on a ratio of the magnitudes of the principal stresses. With consecutive iterations the authors solved boundary-value problems using an external load and an anisotropic constitutive function according to Holzapfel et al. (2000). The remodeling strategy works within a standard finite element framework with the remodeling equations being evaluated at the integration points. Fig. 8a illustrates results for the apical ridge of a human carotid bifurcation (Hariton et al., 2007b). The two families of collagen fibers at the apex are oriented almost along the direction of the apical ridge and resemble a tendon-like structure, which is in agreement with the physiological collagen structure; see the uniform size and co-aligned collagen fibers of apex adventitia in the transmission electron photomicrograph depicted in Fig. 8b—adopted from Finlay et al. (1998). The fibers have a single preferred direction.

9.2. Cerebral aneurysms

There is an urgent need to better understand the etiology of aneurysms and to establish reliable criteria by which surgeons can predict the risk of rupture and thus the need for intervention. The aneurysmal wall is a living and metabolizing structure, able to add to and reinforce itself. Much is known about the natural history of aneurysms, yet little is known about the details of how they actually originate, enlarge, and rupture (Humphrey, 2002). In order to analyze the process of aneurysm development, a number of animal model aneurysms have been developed (see, for example, Zhang et al., 2003, with more references therein). Animal models may give some guidance concerning the natural history of these lesions, but it remains unclear to what extent they actually reflect the etiology of human aneurysms. There is a need, therefore, for increased experimental and clinical information on human lesions.

In cerebral aneurysms fibroblasts are mainly responsible for the production of (Type I) collagen. These cells therefore play a key role in aneurysmal growth. More specifically, cyclic deformation induced by pulsatile blood flow (which, for example, fibroblasts embedded in an arterial wall are exposed to) is known to govern the proliferation of and rate of collagen production by fibroblasts, which are important for the growth of aneurysmal tissue.

We need to better understand the structural development of human aneurysms not only in terms of biology, but also from a biomechanical point of view. Cerebral aneurysms are thin-walled and balloon-like structures with a dominant collagen-rich adventitia and weakness in media that causes structural defects. The first model for saccular cerebral

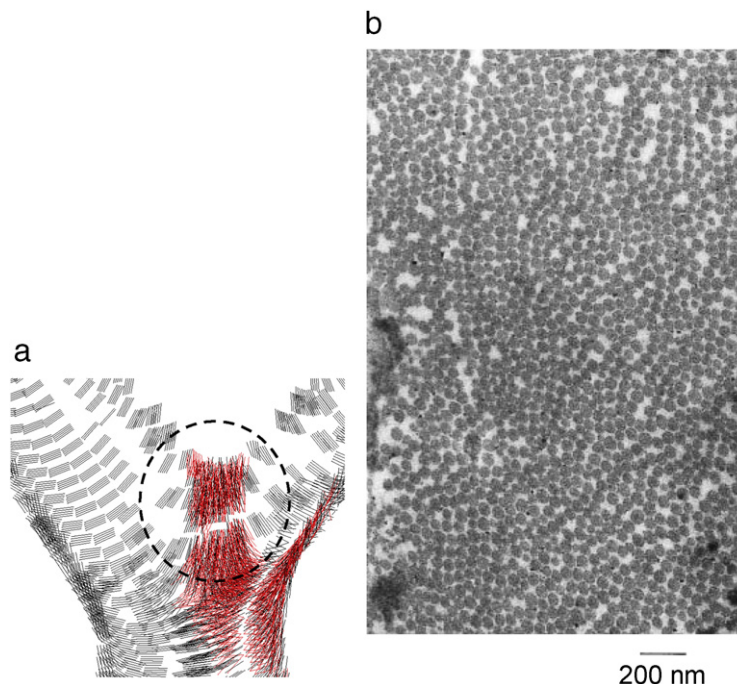


Fig. 8. (a) Principal stress directions (segments of black lines) and collagen fiber morphology (segments of red curves). The dashed circle shows a region at the vicinity of the apex where collagen fibers are oriented almost along the direction of the apical ridge resembling a tendon-like structure; taken from Hariton et al. (2007b); (b) Transmission electron photomicrograph of collagen fibrils of an apex adventitia ($\times 40000$). Fibrils in the apex region are of uniform size and are co-aligned; taken from Finlay et al. (1998). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

aneurysm growth seems to be the one by Kroon and Holzapfel (2007, 2008, 2009). This model is based on the assumption that a collagen fabric is the only load-bearing constituent in the aneurysmal wall, and that the turnover of collagen is responsible for the growth and morphological changes of the aneurysm. The aneurysm is modeled as a multi-layered membrane, and results agree with clinical observations and mechanical test results for aneurysmal tissue.

More experimental and theoretical work is needed to understand how the collagen fabric evolves during the development of aneurysms. See Baek et al. (2006) and Watton et al. (2009) in this regard. The former illustrates the importance of understanding stress-mediated orientation of newly synthesized collagen, not just the rate of deposition. The latter similarly addresses a conceptual theoretical model to reflect the development of fusiform and saccular cerebral aneurysms. The constitutive framework is based on (i) functions of strain energies stored in elastin and collagen, (ii) elastin degradation, (iii) remodeling of the collagen fibers, and (iv) growth/atrophy of collagen.

10. Computational issues

10.1. Computational framework for multiplicative growth

Irrespective of the choice of the particular growth law, the equations for growth of soft biological tissues are typically, highly non-linear, anisotropic, and heterogeneous. Especially for complex animal or patient specific geometries, they do not succumb to analytic methods. The finite element method provides a unique computational framework that can incorporate growth in a simple and straightforward way. From an implementational point of view, the growth tensor, or rather its characteristic variables η and ϑ , introduced previously, can be introduced as internal variables at integration points (Himpel et al., 2005). Provided the evolution equations are not too complicated, they can be discretized in time with implicit time stepping schemes, linearized consistently, and then embedded within an incremental, iterative Newton Raphson solution scheme. Accordingly, algorithmic modifications only affect the constitutive level and can thus be incorporated into any non-linear finite element tool in a straightforward manner. Typical examples of isotropic arterial wall growth and in-stent restenosis in response to a virtual stent implantation (Kuhl et al., 2007), and anisotropic ventricular wall growth in hypertrophic dilation and wall thickening are illustrated in Figs. 9–11, respectively.

10.2. Numerical algorithms

If the formulation of a growth problem is based on mixture theory a number of partial differential equations need to be solved. For soft tissue there could be distinct momentum balance equations for the solid and fluid phases, mass transport of

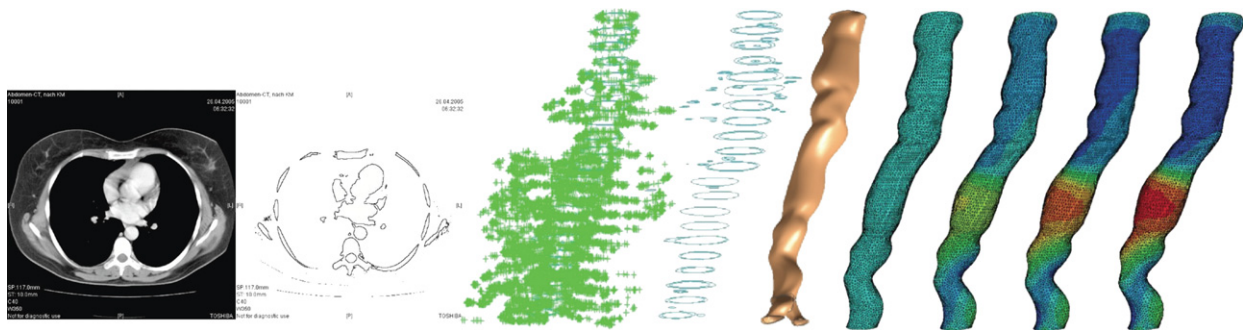


Fig. 9. Isotropic growth based on phenomenological growth laws (Allen et al., 2001). Patient-specific virtual stent implantation. CT of human aorta, Bezier spline interpolation, solid aorta model, finite element discretization, and simulation of wall growth and in-stent restenosis (from left to right).

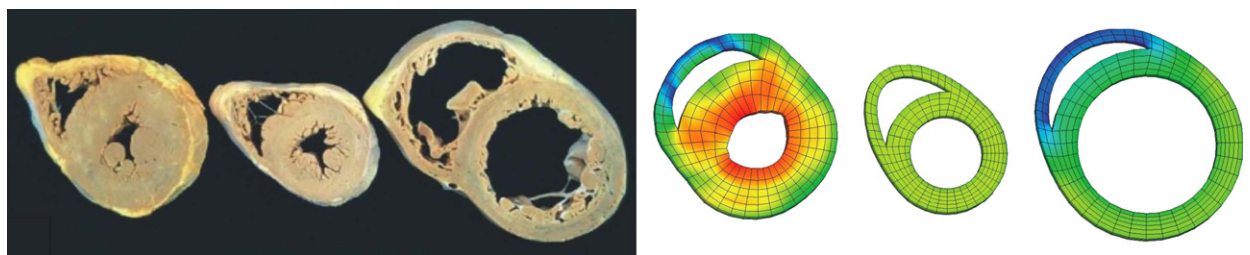


Fig. 10. Anisotropic growth based on microscopically-motivated growth laws. Ventricular growth and remodeling. Pressure overload-induced hypertrophy in response to aortic stenosis, normal heart, and volume overload-induced dilation in response to myocardial infarction. Sections from Hunter et al. (1999) (left) and finite element simulation (right).

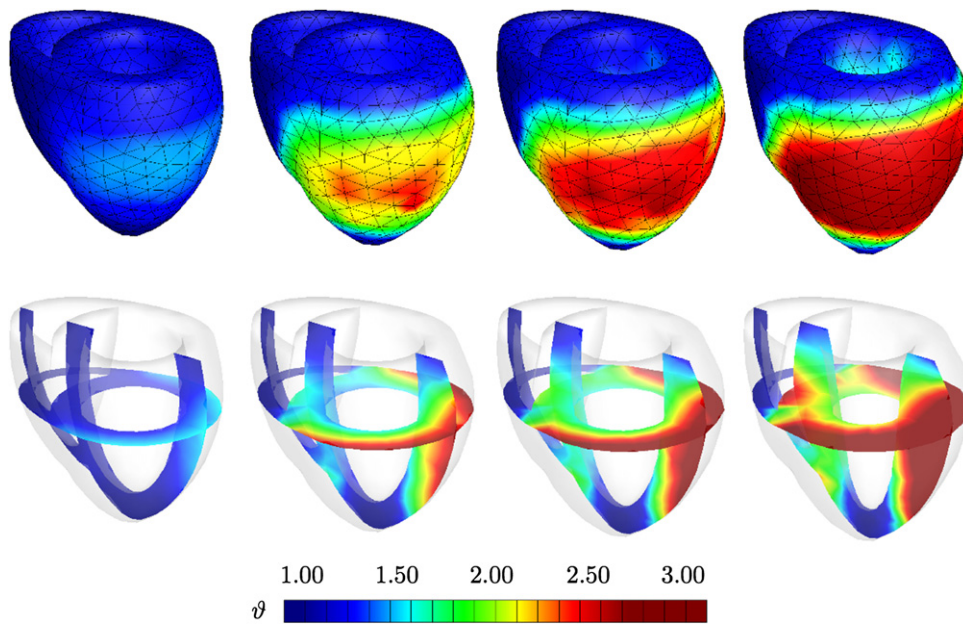


Fig. 11. Anisotropic growth based on microscopically-motivated growth laws. Cardiac wall thickening, stress-driven concentric growth, and transmural muscle thickening at constant cardiac size. The concentric growth multiplier gradually increases from 1.00 to 3.00 as the individual heart muscle cells grow concentrically. On the macroscopic scale, cardiac wall thickening manifests itself in a progressive transmural muscle growth to withstand higher blood pressure levels while the overall size of the heart remains constant. Since the septal wall receives structural support through the pressure in the right ventricle, wall thickening is slightly more pronounced at the free wall where the wall stresses are higher.

the fluid, mass production or consumption (growth and resorption, respectively) of the solid phase and reaction-transport equations for key nutrients, reactants, and waste products. These equations are coupled due to both balance laws and constitutive relations. A large matrix problem results upon discretization by the finite element method. The direct approach to solving this matrix problem consists of the so-called monolithic schemes, where the coupling is held unchanged in the numerical algorithm. Monolithic schemes have the advantage of inheriting the stability properties of the underlying physics, but suffer from the drawback of large matrix–vector problems. As an example, on a coarse finite element mesh with 10^3 hexahedral elements the solution of a growth problem with three concentration fields (solid, fluid, and one reactant) and two momentum equations (solid and fluid) involves linear solves of 1.2×10^4 equations. Since the momentum equations are nonlinear and the mass balance equations possibly so, iterative procedures such as the Newton–Raphson Method must be used separately of any iterative linear solver. Monolithic schemes can therefore become very expensive for large problems.

The alternative staggered schemes are based on formal operator-splitting methodologies. These consist of solving each equation (a momentum or mass balance equation) for its primitive variable while holding fixed the primitive variables of the other equations. Smaller systems have to be solved; in the above example, each momentum equation would require the solution of $\sim 4 \times 10^3$ equations. Further iterations are required over and above those with monolithic schemes to ensure that a self-consistent solution has been attained. While staggered schemes can deliver efficiency with large problems, the operator split can introduce numerical instabilities. A significant body of literature exists on the stability properties of staggered schemes for thermo-mechanics and bi-phasic mechanics. Due to the common parabolic nature of the heat equation and the mass transport problem, much of these numerical developments are relevant to the growth problem. Recently, the influence on numerical stability of staggered schemes due to the choice of strain and stress homogenization assumptions in soft tissue mechanics was studied by Narayanan et al. (2009). If a poroelastic model is adopted for soft tissue mechanics without the explicit solution of coupled momentum equations for the solid and fluid, a further assumption of homogenization becomes necessary. The authors showed, by analysis and computation, that homogenization of the strain field over the solid phase and the fluid-filled pores results in a scheme that is slow to converge when compared with a stress homogenization assumption over the solid and fluid phases. Iterations to self-consistent solutions converge at a rate that is two orders of magnitude higher if stress homogenization is used. Failure to converge to self-consistent solutions with the strain homogenization scheme eventually causes numerical instabilities and divergence of the solution.

11. Links to molecular mechanisms in the context of tumor growth

To date, it is mainly in the context of cancer that studies have appeared to link the mechanical aspects of growth with molecular biology. Even in this case, any experimental evidence that mechanics can affect a tumor's progression has

appeared only recently. Helmlinger et al. (1997) found a suppression of growth of tumor spheroids derived from colon cancer LS174T cells when subjected to compressive stress by an encapsulating hydrogel. In a follow-up study Koike et al. (2002) demonstrated that externally applied mechanical stress aided the formation of multicellular tumor spheroids in the highly metastatic Dunning R3327 rat prostate carcinoma AT3.1 cells, while the less metastatic AT1 cells formed spheroids even without the applied stress. This study thus pointed to cancerous tissue growth by agglomeration of otherwise dispersed cells under stress.

Chang et al. (2008) showed that in four different cell lines shear stress led to cell cycle arrest in the G2/M phase, thus directly targeting cell growth. This result was associated with increased expression of cyclins B1 and p21^{CIP1}, and decreased expression of cyclins A, D1, and E, cyclin-dependent kinases (cdk) -1, -2, -4, -6 and p27^{KIP1}, as well as decreased cdk-1 activity. Reviews by Kumar and Weaver (2009), Butcher et al. (2009), and Suresh (2007) have pointed to the decreased stiffness and altered cytoskeletal rheology of cancer cells from several different cell lines when compared with normal cells. These phenotypes promote greater motility and therefore probably favor invasion of the cancer into surrounding tissue, which at a continuum scale manifests itself as growth.

Cells also impose traction forces on the ECM, and Gordon et al. (2003) found that larger traction forces near the edge of tumor spheroids with the human U87MGmEGFR glioblastoma cell line led to greater depths of invasion (tumor growth) into the ECM. Many cell types form focal adhesions with the ECM, and the force developed in the actin cytoskeleton is regulated by a dynamic interaction between focal adhesions, the cytoskeleton and the ECM (Geiger and Bershadsky, 2001, and references therein). Perhaps the most far-reaching studies of the direct interaction between stress and protein expression/inhibition may be found in studies of focal adhesion growth. These adhesive structures have been observed to show modes of growth, treadmilling and resorption as a function of the applied force (see Olberding et al., 2010, for a recent theoretical treatment of focal adhesion dynamics). A central hypothesis in this field is that conformational changes of certain focal adhesion proteins such as vinculin (Zamir and Geiger, 2001) or ECM proteins such as fibronectin (Geiger et al., 2001) are favored under tension. Focal adhesion kinase (FAK) is another protein whose action is widely understood to be enhanced under force (Tomar and Schlaepfer, 2009). The activation of these proteins, whether under force or otherwise, is required at crucial steps in the growth of focal adhesions. Such studies provide a direct link between mechanics and growth at the sub-cellular scale. In turn, since focal adhesion formation, treadmilling and disassembly is necessary for cell migration a link is provided to tumor invasion (growth at the continuum scale).

The chemo-mechanical regulation represented by the above mechanisms may further influence the chemical signaling in cancer cells (Kumar and Weaver, 2009, and references therein), and tumor growth by cell proliferation. Butcher et al. (2009) have also pointed to altered “mechanoreciprocity” (the development of force within the cell in response to ECM-imposed strain) by which higher-than-normal forces are applied to cell–cell junctions causing them to lose their integrity, thereby aiding in tissue invasion. Weaver et al. (1997) found that mechanical interactions between integrins and the ECM altered the phenotype of human breast cancer cells and that under certain interventions these cells reverted to the normal phenotype. Such mechanisms bear relevance not only to growth but also resorption as seen at the continuum scale. Padera et al. (2004) demonstrated that mechanical stress created by growing tumors compresses blood vessels supplying the tumors and thereby interferes with the delivery of both nutrients and drugs, thus regulating tumor growth. Levental et al. (2009) showed that ECM stiffness affects tumor growth via the mechanisms of focal adhesion formation, growth factor signaling and breast tumor malignancy.

12. Concluding remarks

From a sociological point of view, it is interesting to note that mechanical theories of the growth and/or remodeling of biological systems (cells, tissues, organs, and organisms) are now a popular theme of research in many different scientific communities, including physiology, plant biology, agronomy, food science, biology, physics, engineering, computer sciences, medical sciences, and applied mathematics. These scientific communities do not usually overlap despite their common interests. Nevertheless, all are confronted with similar conceptual problems such as the proper definition of residual stresses, the notion of evolving reference configurations, the decomposition of deformation into elastic and growth components, evolution equations for growth, the challenges of formulating and solving real problems using the theory of mixtures, and perhaps most important of all for biology, the actual pathways by which mechanics is translated to chemical activity to effect growth. Some of these issues have been discussed in the mechanics literature, some in relation to elasto-plasticity, transport phenomena, and mixtures. Unfortunately, many of these discussions are shrouded in precise but esoteric language addressed to the happy few. Therefore, the mechanics community not only has an opportunity to play a central role in advancing the field, but also a responsibility to popularize complicated concepts and reach out to different scientific communities.

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