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Interstitial growth and remodeling of biological tissues: Tissue composition as state variables

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ABSTRACT

Growth and remodeling of biological tissues involves mass exchanges between soluble building blocks in the tissue's interstitial fluid and the various constituents of cells and the extracellular matrix. As the content of these various constituents evolves with growth, associated material properties, such as the elastic modulus of the extracellular matrix, may similarly evolve. Therefore, growth theories may be formulated by accounting for the evolution of tissue composition over time in response to various biological and mechanical triggers. This approach has been the foundation of classical bone remodeling theories that successfully describe Wolff's law by establishing a dependence between Young's modulus and bone apparent density and by formulating a constitutive relation between bone mass supply and the state of strain. The goal of this study is to demonstrate that adding tissue composition as state variables in the constitutive relations governing the stress–strain response and the mass supply represents a very general and straightforward method to model interstitial growth and remodeling in a wide variety of biological tissues. The foundation for this approach is rooted in the framework of mixture theory, which models the tissue as a mixture of multiple solid and fluid constituents. A further generalization is to allow each solid constituent in a constrained solid mixture to have its own reference (stress-free) configuration. Several illustrations are provided, ranging from bone remodeling to cartilage tissue engineering and cervical remodeling during pregnancy.

1. Introduction

Growth processes are fundamental in nature, whether they occur in biological or non-living systems (Taber, 1995; Ambrosi et al., 2011). Theoretical frameworks for modeling growth can be used to gain insight into growth mechanics, by examining the theoretical feasibility of hypothesized growth mechanisms. Growth models may also be used to understand the evolution of tissue structure and function and to optimize growth conditions in tissue engineering studies. In the biomechanics literature, theoretical frameworks have addressed the challenge of modeling the adaptive response of tissues to loading (Cowin and Hegedus, 1976; Cowin, 1983; Huiskes et al., 1987; Weinans et al., 1992; Taber and Humphrey, 2001; Humphrey, 2009); describing morphogenesis using a kinematic description of growth (Skalak et al., 1982, 1997; Rodriguez et al., 1994; Menzel and Kuhl, 2012); accounting for distinct growth histories of the constituents of heterogeneous mixtures (Humphrey and Rajagopal, 2002; Garikipati et al., 2004; Ateshian, 2007; Wan et al., 2010; Ateshian and Humphrey, 2012; Cowin and Cardoso, 2012); describing the evolution of residual stresses due to growth (Skalak et al., 1996; Hoger, 1997; Taber and Humphrey, 2001; Guillou and Ogden, 2006; Ateshian and Ricken, 2010; Menzel and Kuhl, 2012); accounting for chemical reactions among fluid and solid constituents of a heterogeneous mixture (Garikipati et al., 2004; Ateshian, 2011, 2007; Narayanan et al., 2009); describing cell growth via osmotic mechanisms (Ateshian et al., 2009a, 2012); and other related phenomena.

Mixture theory (Truesdell and Toupin, 1960; Bowen, 1968, 1969) has been favored in many recent studies to describe growth

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mechanics (Humphrey and Rajagopal, 2002; Garikipati et al., 2004; Ateshian, 2007; Cowin and Cardoso, 2012). In this framework, interstitial growth represents the addition (or removal) of mass from the porous solid matrix of a mixture whose interstitial fluid provides the building blocks (or nutrients) for growth in the form of solutes mixed in a solvent. As such, the mass content, or composition, of the mixture represents a set of state variables in this growth framework (Ateshian, 2007, 2011; Ateshian and Ricken, 2010). Lengthy background reviews of the mixture theory framework have been presented elsewhere (Epstein and Maugin, 2000; Ateshian, 2007; Cowin and Cardoso, 2012). Given these extensive backgrounds, the objective of this review is to reformulate the salient aspects of mixture growth theory using a didactic approach that extends the framework of elasticity theory by simply adding mass content as a set of state variables. It is shown that this approach reiterates the pioneering work of Cowin and Hegedus (1976), who formulated a growth framework responsive to the loading environment without appealing explicitly to mixture theory, yet producing most of the salient findings from those subsequent derivations. This framework also serves as the foundation of the popular bone remodeling theory proposed by Huiskes et al. (1987), Weinans et al. (1992) and Mullender et al. (1994). Other examples off this growth framework are provided, which exhibit increasing levels of complexity with regard to dependence on composition, to illustrate the breadth and depth of this theoretical foundation for growth. Examples from cartilage tissue engineering provide illustrations of the interaction of proteoglycan growth and glucose supply, as well as the growth of collagen having different reference configurations at different times in the growth process. Another example proposes an approach for modeling the dramatic changes in the material behavior of the cervix over the normal period of gestation by considering the turnover of collagen from mature crosslinked fibers to immature loosely connected fibrils.

2. Growth mechanics

2.1. Hyperelasticity

In classical hyperelasticity theory, the constitutive relation relating stress to strain in a solid is derived from an energy potential, usually described as the strain energy density, and more generally known as the Helmholtz free energy density. This energy potential is conventionally expressed as the free energy in the current configuration per volume of the solid in the reference configuration, where the reference configuration represents a stress-free state; it is denoted here as Ψ_r. Since all strain measures may be derived from the deformation gradient of the solid, $\mathbf{F}^s$, the Helmholtz free energy density may be constitutively expressed as a function of this measure, $\Psi_r(\mathbf{F}^s)$. Following standard procedures involving entropy inequality, the Cauchy stress is then given by

$$\boldsymbol{\sigma} = \frac{1}{J^s}\frac{\partial \Psi_r}{\partial \mathbf{F}^s}\cdot(\mathbf{F}^s)^T, \tag{2.1}$$

where $J^s = det\,\mathbf{F}^s$. Any number of constitutive relations may be formulated for $\Psi_r(\mathbf{F}^s)$ and their associated material properties are necessarily constants. This constitutive formulation may be slightly generalized by letting the free energy also depend on absolute temperature, θ, but not its gradient, thus limiting analyses to isothermal problems. With $\Psi_r(\theta,\mathbf{F}^s)$, the material properties associated with the stress–strain response may vary with temperature, and the entropy density (entropy per volume of the solid in the reference configuration) of the system is no longer zero

$$H_r = -\frac{\partial \Psi_r}{\partial \theta}. \tag{2.2}$$

When solving problems in hyperelasticity, it is necessary to also recognize that the mass density ρ^s of the solid is constrained by the relation

$$\rho^s = \rho^s_r / J^s, \tag{2.3}$$

where ρ^s_r is the mass density in the reference configuration, which is invariant. This constraint is obtained from the balance of mass relation for the solid,

$$\frac{D^s\rho^s}{Dt} + \rho^s\,div\,\mathbf{v}^s = 0, \tag{2.4}$$

where $\mathbf{v}^s$ is the velocity of the solid and $D^s(\cdot)/Dt$ is the material time derivative in the spatial frame, following the solid. Recognizing from kinematics that $div\,\mathbf{v}^s = (J^s)^{-1}(D^sJ^s/Dt)$, the mass balance equation may also be written as $D^s(\rho^sJ^s)/Dt = 0$, which may be integrated to produce the result of Eq. (2.3). Eqs. (2.1)–(2.4) provide a succinct summary of the classical framework for hyperelasticity in the absence of any growth processes.

2.2. Interstitial growth of a single solid constituent

Interstitial growth is the process that adds or removes solid mass at locations inside a solid material. For this process to occur, there must be interstitial space within this material to allow atoms or molecules to bind to the underlying substrate. For biological tissues, this is typically the pore space normally filled with the interstitial fluid that carries those molecules. Therefore, it is helpful to recognize the solid material as a porous matrix, whose pores fill with additional solid material during growth or conversely become more porous with negative growth (desorption of the solid). Growth may occur within cells as well as in the extracellular matrix (ECM) of a tissue. Both the cell and the ECM may be treated as mixtures with a porous matrix and an interstitial fluid consisting of a solvent and solutes. In a porous solid, the solid mass density ρ^s is called the *apparent* density, since it measures the mass of the solid per volume of an elemental region that contains porous solid and interstitial fluid (the mixture). Since mass is exchanged between the porous solid and the interstitial fluid, the mass balance relation for the solid must account for this exchange

$$\frac{D^s\rho^s}{Dt} + \rho^s\,div\,\mathbf{v}^s = \hat{\rho}^s, \tag{2.5}$$

with $\hat{\rho}^s$ representing the mass supply to the solid from all solute species in the interstitial fluid. Using the kinematic relation relating the divergence of the solid velocity to the determinant of the deformation gradient, this balance relation may be rewritten as

$$\frac{D^s\rho^s_r}{Dt} = \hat{\rho}^s_r, \tag{2.6}$$

where $\rho^s_r = \rho^sJ^s$ and $\hat{\rho}^s_r = \hat{\rho}^sJ^s$. This relation shows that ρ^s_r is no longer invariant when growth occurs, though its evolution over time may be obtained by integrating Eq. (2.6) when given a suitable constitutive relation for $\hat{\rho}^s_r$. This type of constitutive relation may be derived from chemistry (Prud'homme, 2010) to determine the rate of the chemical reaction for the exchange of mass with the solid, or from mechanics, as proposed by Cowin and Hegedus (1976) and further illustrated below.

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