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Continuum mechanical modeling of developing epithelial tissues with anisotropic surface growth

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ABSTRACT

In this study, we address the computational modeling of biological soft tissue growth, focusing on the development of epithelial tissues. The formulation of the corresponding constitutive growth law using non-linear continuum mechanics and its implementation within a total-Lagrangian-type finite element method are described. In describing the growth law, we use multiplicative decomposition of the deformation gradient into a growth part and an elastic part. We propose two surface growth deformation gradients; isotropic surface growth and anisotropic surface growth with relative shrinkage in the principal direction of maximum stress at the initial state. We first apply our laws to a hollow thick-walled hemiellipsoid that idealizes a structure generally observed in the early development of epithelial tissues. Our simulation shows the following: (i) under isotropic surface growth, the hemiellipsoid becomes sphere-like, i.e., the ratio between the longest and shortest axial length tends to 1; (ii) in contrast, under anisotropic surface growth, the tissue elongates and flattens, i.e., the ratio between the longest and shortest axial length is enhanced. These results motivate us to apply the latter growth law to the realistic example of a vertebrate limb bud, which shows similar elongation and flattening during development. As expected, our numerical simulation succeeded in reproducing the essential aspects of morphological change in the limb bud, providing a new hypothesis for the vertebrate limb development.

1. Introduction

Biological tissues are continuously undergoing processes of growth, remodeling and morphogenesis. These processes include the addition/subtraction of mass through the cell growth and death, active deformation via cell rearrangement, and changes in mechanical properties in response to surrounding mechano-chemical environments [1–3]. While such processes are not generally observed in engineering materials, they often characterize the mechanical behavior of biological tissues. By undergoing growth, remodeling and morphogenesis, biological tissues can appropriately achieve their specific shapes and functions.

The past two decades have seen a considerable amount of biomechanical research concerning growth, remodeling and morphogenesis [1,3–5]. Among these processes, soft tissue growth has attracted much attention from researchers of many different subject areas. First, this interest can be attributed to the availability of new information pertaining to the mechanical aspects of biological soft tissues resulting from advances in measurement techniques. Second, increasing computing power, which enables more realistic simulations, has made such a complicated nonlinear problem more accessible. From a mechanical perspective, a continuum mechanics approach has been widely adopted for the analysis of soft tissue growth; the main issue being how to formulate the constitutive law of growth. In constructing the constitutive law, growth is characterized as the addition/subtraction of mass by multiplicative decomposition of the deformation gradient into a growth part and an elastic part [6], as introduced in the context of the finite-strain elastoplasticity theory [7,8]. While the multiplicative decomposition of the deformation gradient has become a standard approach to growth modeling, identifying the appropriate types of growth deformation gradients suitable for focal phenomena is not an easy task. Due to the complicated molecular and cellular responses which affect growth, there has been no agreement on which mechanical variables, such as stress or strain, are suitable for modeling this growth [1,3]. At present, the continuum mechanical approach to the study of growth is at the stage in which constitutive laws that could explain individual growth process in each species or tissue can be proposed and demonstrated. Until now, the growth of various types of mature soft tissues, such as the arterial wall, skin, heart, and mus-

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cle, have been studied and appropriate constitutive laws have been established based on continuum mechanics and numerical analysis [9–16].

In contrast, compared to the mechanical study of growth in mature soft tissues, the mechanical study of embryonic tissue development, as another example of growth, is a relatively young field. The limited research in this area might be attributed to the complexities of developing tissues. Unlike the growth of mature soft tissues, such as the enlargement (hypertrophy) of arterial walls and cardiac muscles or, the formation of tumors (tumorigenesis), developing tissues grow in such a way that they build highly reproducible morphologies specific to the corresponding organs such as the limbs, brain and intestine. Thus far, in mechanical studies of the developing tissues, instability and buckling analysis has been a hot issue. For example, the patterns of the brain gyri, the gastrulation process, and the development of periodic looping structures such as the intestine have been simulated based on the buckling of hyperelastic materials [17–19]. Such simulations have succeeded in reproducing similar morphologies to those observed during development. In addition to the morphological change primarily driven by external load or determined by boundary conditions, recent observations of developing tissues have shown that most cells are more or less motile and frequently change their relative position. This is especially true in the development of epithelial tissues, where this behavior is known as cell rearrangement or intercalation. Moreover, experimental studies have suggested a relationship between such cellular behaviors and the stress within tissues [20,21].

Based on these background studies, here, we examine the effects of stress-dependent active and anisotropic growth on the morphology of developing tissues. In describing the growth law, i.e., constitutive growth law, we assume that cell rearrangement actively occurs within a preferable direction determined by the directions of principal stresses. As an example, we apply our proposed law to a hollow thick-walled hemiellipsoid which is an idealized structure generally observed in the early development of epitherlal tissues. Under this law, we show that the hemiellipsoid elongates along its semi-major axis and collapses along its semi-minor axis, which leads to the elongation and oblateness of the epithelial tissue.

As a realistic biological application, we apply this law to the early development of the chick limb bud which is characterized by the structural change described above, i.e., the elongation along one axis and flattening along another axis. To illustrate the mechanism of how the limb bud elongates, researchers have proposed several hypotheses especially focused on the spatially-biased growth of its inner component (the mesenchyme), enveloped by its outer component (the epithelium) [22,23]. However, it has been shown that the mesenchymally-biased-growth model can not fully explain the observed, in that the quantified deformation pattern that occurs during chick limb development is quite different from the pattern expected based on the model (see Refs. [24,25] for more details). Given the above considerations, here we focus on the growth of the epithelium that previously has received little attention as a determining component in limb-specific morphogenesis.

For the methodology, we adopt the multiplicative decomposition of the deformation gradient similar to that used in previous works on mature soft tissues [26,27]. We formulate two growth deformation gradient tensors and simulate the phenomena using the finite element method (FEM). The corresponding constitutive initial/boundary-value problem is formulated to be suitable for the conventional total-Lagrangian-type FEM and the comprehensive description of this methodology is detailed in a general setting.

2. Methods I: constitutive law for the growth

Throughout this paper, the term *growth* is defined as the process by which a material changes actively in form with the addition/subtraction of mass without changing its mechanical properties. In this section, a constitutive law for the growth is formulated in the framework of continuum mechanics.

2.1. Kinematics

Let the position of the material point in the initial configuration $\Omega_0 \subset \mathbb{R}^3$ be $\boldsymbol{X}$, the position of the same point at time t in the current configuration $\Omega \subset \mathbb{R}^3$ be $\boldsymbol{x}$, and the displacement vector be $\boldsymbol{u} = \boldsymbol{x} - \boldsymbol{X}$. We assume a deformation mapping $\varphi(\cdot, t) : \Omega_0 \to \Omega$ that is smooth enough, orientation preserving, and bijective at any time t such that $\boldsymbol{x} = \varphi(\boldsymbol{X}, t)$. At each material point $\boldsymbol{X}$ and time t, the deformation gradient tensor $\boldsymbol{F}$ with Jacobian $J := \det \boldsymbol{F} > 0$ is then defined as $\boldsymbol{F} := \partial\varphi(\boldsymbol{X}, t)/\partial\boldsymbol{X}$. As strain measures, we use the right Cauchy-Green strain tensor $\boldsymbol{C}$ defined as $\boldsymbol{C} := \boldsymbol{F}^{\mathrm{T}}\boldsymbol{F}$.

2.2. Multiplicative decomposition of deformation gradient tensor

As shown in Fig. 1, the deformation mapping φ of the growth can be decomposed into two parts, as introduced in the context of finite-strain elastoplasticity theory [7,8]. Firstly, every material point either increases or decreases. This increasing/decreasing part of the deformation mapping φ_g, called growth deformation, results in an intermediate configuration $\hat{\Omega}$ that does not necessarily have to be compatible, i.e., parts of the material may intersect or separate. Hence, an additional elastic deformation mapping φ_e, called elastic deformation, might be needed to ensure the compatibility of the deformation φ. In this way, the deformation mapping is decomposed into two mappings and described as $\varphi = \varphi_e \circ \varphi_g$. Analogously, the deformation gradient tensor $\boldsymbol{F}$ of Ω_0 onto Ω is decomposed into two components as

$$\boldsymbol{F} = \boldsymbol{F}_e\boldsymbol{F}_g, \tag{2.1}$$

where $\boldsymbol{F}_g$ and $\boldsymbol{F}_e$ are the growth deformation gradient and elastic deformation gradient, respectively. In this decomposition, we assume that the growth deformation φ_g occurs without generating stresses, and therefore the intermediate configuration $\hat{\Omega}$ is stress free. Furthermore, during this growth deformation, the mass density is assumed to be unchanged. In other words, the mass density of the intermediate configuration is the same as that of the initial configuration, namely $\rho_0(\boldsymbol{X})$. However, the mass density $\rho(\boldsymbol{x}, t)$ of the current configuration Ω may change during the elastic deformation φ_e, because we do not assume that the material is incompressible, i.e., $\rho_0(\boldsymbol{X}) \neq \rho(\boldsymbol{x}, t)$.

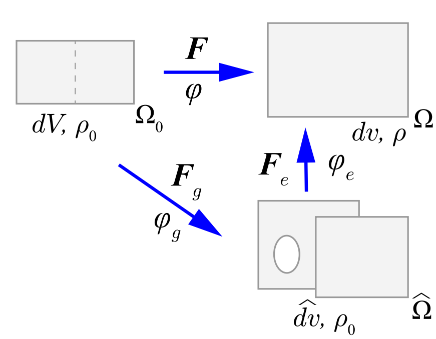

Fig. 1. Decomposition of deformation mapping φ and deformation gradient $\boldsymbol{F}$ into a growth part and an elastic part.