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Editorial

Growing matter: A review of growth in living systems

ARTICLE INFO

Keywords:
Biomechanics
Continuum mechanics
Finite elements
Growth
Remodeling
Available online 28 October 2013

ABSTRACT

Living systems can grow, develop, adapt, and evolve. These phenomena are non-intuitive to traditional engineers and often difficult to understand. Yet, classical engineering tools can provide valuable insight into the mechanisms of growth in health and disease. Within the past decade, the concept of incompatible configurations has evolved as a powerful tool to model growing systems within the framework of nonlinear continuum mechanics. However, there is still a substantial disconnect between the individual disciplines, which explore the phenomenon of growth from different angles. Here we show that the nonlinear field theories of mechanics provide a unified concept to model finite growth by means of a single tensorial internal variable, the second order growth tensor. We review the literature and categorize existing growth models by means of two criteria: the microstructural appearance of growth, either isotropic or anisotropic; and the microenvironmental cues that drive the growth process, either chemical or mechanical. We demonstrate that this generic concept is applicable to a broad range of phenomena such as growing arteries, growing tumors, growing skin, growing airway walls, growing heart valve leaflets, growing skeletal muscle, growing plant stems, growing heart valve annuli, and growing cardiac muscle. The proposed approach has important biological and clinical applications in atherosclerosis, in-stent restenosis, tumor invasion, tissue expansion, chronic bronchitis, mitral regurgitation, limb lengthening, tendon tear, plant physiology, dilated and hypertrophic cardiomyopathy, and heart failure. Understanding the mechanisms of growth in these chronic conditions may open new avenues in medical device design and personalized medicine to surgically or pharmacologically manipulate development and alter, control, or revert disease progression.

1. Motivation

Growth is a distinguishing feature of all living things. Throughout the past century, the growth of living systems has fascinated plant physiologists, biologists, clinical scientists, mathematicians, physicists, computer scientists, and engineers alike (Taber, 1995). An intriguing feature of growth is the interplay of form and function, or, more specifically, the ability of the growing system to manipulate its microenvironment and, vice versa, the ability of the microenvironment to manipulate the microstructural architecture of growth (Ambrosi et al., 2011). The former is typically associated with growth-induced instabilities and growth-induced stresses, or, in a more abstract sense, with characterizing the impact of biology on the mechanics of the system (Li et al., 2012). The latter is associated with exploring the mechanisms that cause the system to grow, stretch, strain, or stress, or, abstractly, with understanding how mechanics can drive the biology of the system (Menzel and Kuhl, 2012). In the literature, these classifications go hand in hand with the notions of biomechanics and mechanobiology.

The first type of phenomena, growth-induced microenvironmental changes, has been studied intensely in plant physiology (Atkinson, 1900; Vandiver and Goriely, 2009), applied mathematics (Dervaux and Ben Amar, 2011; Goriely and BenAmar, 2007), and theoretical mechanics (Cai et al., 2010; Jin et al., 2011), and is now recognized to benefit from computational modeling in various clinical applications. Fig. 1 shows an example of growth-induced microenvironmental changes in a female red-eared slider turtle (Minnesota Department of Natural Resources, 2013). The turtle was found wearing a plastic six-pack ring around its shell. At the time of

Fig. 1 – Growth-induced microenvironmental changes in a nine-year old female red-eared slider turtle trapped in a plastic six-pack ring. At the time of capture, the turtle had worn the ring for five years. During this time, the ring had constrained the growth of the outer shell and created growth-induced stresses on the inner organs. X-ray imaging revealed that, except for the shell and the lung, all organs had grown and developed normally; adopted from Minnesota Department of Natural Resources (2013).

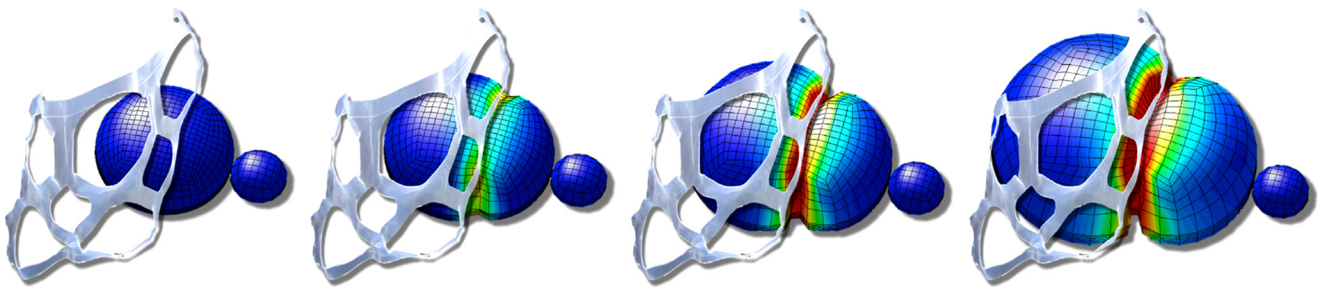

Fig. 2 – Growth-induced microenvironmental changes in a model turtle trapped in a plastic six-pack ring. The plastic ring constrains the growth of the shell and triggers growth-induced instabilities, which result in buckling and folding of the outer shell. Red regions close to the plastic ring are high-stress regions of constrained growth; blue regions away from the ring are stress-free regions of unconstrained growth. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

capture, the turtle was a nine years old and had worn the ring for approximately five years. During this time, the ring had constrained the growth of the outer shell and created growth-induced stresses on the inner organs. Fortunately, X-ray imaging revealed that all organs, except for the shell and the lung, were able to grow and develop normally. Fig. 2 illustrates a finite element simulation of the growing turtle. Constraining the deformation during growth triggers growth-induced instabilities, which result in buckling and folding of the outer shell (Cai et al., 2012). The red regions close to the ring are exposed to constrained growth and experience growth-induced stresses. The blue regions away from the ring can grow unboundedly and are stress free. Finite element simulations have the potential to predict the formation of growth-induced instabilities and identify regions of growth-induced stresses (Papastavrou et al., 2013). Computational modeling of growth might have immediate clinical implications in tumor growth during cancer (Narayanan et al., 2010), airway wall remodeling during asthma and chronic bronchitis (Moulton and Goriely, 2011), cortical folding during brain development (Bayly et al., this issue), crypt formation (Nelson et al., 2011), and gut looping during organogenesis (Savin et al., 2011). Beyond applications in developmental biology, understanding the morphogenesis and origin of shape may have broad applications in the natural sciences such as gap growth in dynamical systems (van den Bedem, 2001), mineral growth in geology (Kuhl and Schmid, 2007), or rock folding in tectonophysics (Jager et al., 2008).

The second type of phenomena, mechanically induced microstructural changes, has been studied in various types of soft tissues throughout the past decade. The crucial question here is not so much how growth induces instabilities or stress, but rather what it is that drives the growth process (Menzel and Kuhl, 2012). Research in this field has identified close correlations between the nature of the mechanical driving forces and the microstructural appearance of growth (Menzel, 2005). For example, it seems intuitive to hypothesize that volume growth, growth that is identical in all three directions in space, is driven by an isotropic mechanism such as the pressure (Himpel et al., 2005). Indeed, high blood pressure, or in clinical terms, hypertension, is a chronic condition that manifests itself in thickened arterial walls and thickened heart muscle (Kuhl et al., 2007). Similarly, we can postulate that area growth, growth that takes place in a particular plane of interest, is driven by a planar mechanism such as the area stretch (Socci et al., 2007). And indeed, plastic surgeons artificially create microenvironments with a controlled elevated area stretch to grow extra skin for defect repair (Buganza Tepole et al., 2011). Finally, it seems natural to assume that longitudinal growth, growth that takes place along a particular direction, is controlled by a unidirectional mechanism such as the fiber stretch (Barnett et al., 1980). A typical example is the controlled longitudinal growth of muscle fibers in clinical procedures such as limb lengthening (Zöllner et al., 2012). In all these cases, finite element simulations may play a crucial role in predicting, manipulating, and possibly reverting the natural progression of growth. This could have immediate applications in hypertension (Rausch et al., 2011), in-stent restenosis (Kuhl et al., 2007),