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Stresses in growing soft tissues

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Abstract

Biochemical processes of tissue growth lead to production of new proteins, cells, and other material particles at the microscopic level. At the macroscopic level, growth is marked by the change of the tissue shape and mass. In addition, the appearance of the new material particles is generally accompanied by deformation and, consequently, stresses in the surrounding material. Built upon a microscopic toy-tissue model mimicking the mechanical processes of mass supply, a simple phenomenological theory of tissue growth is used in the present work for explaining residual stresses in arteries and studying stresses around growing solid tumors/multicell spheroids. It is shown, in particular, that the uniform volumetric growth can lead to accumulation of residual stresses in arteries because of the material anisotropy. This can be a complementary source of residual stresses in arteries as compared to the stresses induced by non-uniform tissue growth. It is argued that the quantitative assessment of the residual stresses based on *in vitro* experiments may not be reliable because of the essential stress redistribution in the tissue samples under the cutting process. Concerning the problem of tumor growth, it is shown that the multicell spheroid or tumor evolution depends on elastic properties of surrounding tissues. In good qualitative agreement with the experimental *in vitro* observations on growing multicell spheroids, numerical simulations confirm that stiff hosting tissues can inhibit tumor growth.

Keywords: Growth; Soft tissue; Artery; Residual stresses; Tumor

1. Introduction

Understanding growth of living tissues is of fundamental theoretical and practical interest. Analytical models of growth of both plant and animal tissues can predict the evolution of the tissue, which may improve the treatment of pathological conditions and offer new prospects in tissue engineering. Biological or biochemical mechanisms of growth are not well understood although plenty of scenarios exist in the biological literature. There is no doubt that biochemistry is the driving force of tissue growth. Understanding the biochemistry of growth is most desirable. Biochemistry can explain why a tissue grows. This is not enough, however. It is also necessary to know how a tissue grows. The latter means macroscopic description in terms of the macroscopically measurable parameters. There is no shortage of macroscopic models of soft tissue growth [1–18]. However, the mathematical apparatus of the existing approaches is rather complicated and it includes variables that are difficult to interpret in simple terms and to assess in measurements, such as the cofactors in the multiplicative decomposition of the deformation gradient or the partial stresses and tractions in the mixture theories. This complexity requires an additional effort for the careful experimental calibration of the theories as, for example, in the case of the cartilage growth considerations by Klisch et al. [19,20].

In the present work, a continuum mechanics framework for modeling growth of living tissues is used, which does not include internal variables [21,22].[2] Moreover, this

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[2] Guillou and Ogden [23] present an alternative theory of soft tissue growth without the internal variables.

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theory is driven by a simple microstructural model of material supply that motivates the balance and constitutive equations. Two applications of the growth theory presented are considered.

First, the formation of residual stresses in arteries under the restriction of purely genetic and uniform mass supply is studied. It is shown that the arterial anisotropy can play the crucial role in the appearance and accumulation of stresses in growth. This is complementary to a more traditional point of view, which attributes residual stresses to non-uniform (differential) growth. We emphasize that the quantitative assessment of the residual stresses in arteries would require *in vivo* experiments. The existing *in vitro* experiments may lead to inaccurate estimates of residual stresses because of the necessity to cut the arterial pieces. The cutting process is accompanied by a redistribution of stresses, which can essentially affect their estimates. We propose a possible experiment in order to emphasize the stress redistribution issue in the *in vitro* tests.

Second, we apply the theory to the study of stresses around growing solid tumors. A growing tumor may press neighbor tissues and lead to their remodeling and necrosis or, ultimately, to the failure of organs to carry out their regular functions. For example, expanding tumors can initiate the collapse of immature blood vessels formed during the angiogenic phase, and the inflation and rupture of capsules, membranes and ducts the tumor grows into. Another example is an expanding brain tumor, which can deform brain areas responsible for various kinds of human activity and disturb the normal action of the organism. Thus, it can be important to know what is the expected tumor shape and mass for planning the date and strategy of operative invasion. A simplistic description of tumor development is attributed to Winsor [24], who adapted Gompertz's [25] empirical formula for modeling tumor growth: $\ln(\ln(V/V_0)) = -vt + V_{\max}/V_0$, where V is a measure of tumor size, V_0 the initial size, and $V_{\max}$ the final size. The rate of cell proliferation is v and t is time. Evidently, this formula accounts neither for tissue elasticity nor for material supply. However, recent experiments with tumor cell spheroids demonstrate the importance of these issues and the deficiency of the Gompertz simple formula. In particular, mimicking tumor development *in vivo*, Helmlinger et al. [26] considered *in vitro* growth of multicell tumor spheroids embedded in agarose gels. Spheroids were cultured in gels of increasing agarose concentration, thereby increasing the stiffness of the embedding matrix. It was observed that tumor growth was inhibited by the increasing gel stiffness. Evidently, this result emphasizes the role of the hosting tissue in the tumor growth process *in vivo*. Mathematical modeling of solid tumor growth has a long history [27]; however, the main emphasis of the research has been on problems of fluid transport and chemical reactions during the process of tumor formation [28–44]. Elasticity of the tumor/multicell spheroid was recently considered by Ambrosi and Mollica [45,46] who used a rather abstract approach, typical of the theories of soft tissue growth when the deformation gradient is decomposed into growth and elastic cofactors that correspond to the incompatible 'pure growth' of the material and the elastic deformation providing the final material compatibility. Contrary to Refs. [45,46] we will use a growth theory that does not introduce internal variables and that can be directly calibrated in experiments. We will show that stiff hosting tissues can inhibit tumor growth in a good qualitative agreement with the *in vitro* observations of growing multicell spheroids.

2. Methods

2.1. Governing equations

The assumption that continuous deformation and mass flow can describe the mechanics of growing living bodies is central to further development. To make this assumption sound, the geometry of growth should be analyzed qualitatively. A sharp distinction between the real physical material, i.e., material particles comprising continuum, and the mathematical concept of material point should be kept in mind. This distinction is illustrated in Fig. 1, where material deformation-growth is considered on different length scales. On the macroscopic scale, we assume that a material body can be divided into an infinite set of material points. It is assumed that position $\mathbf{X}$ in the physical space can be ascribed to every material point before growth-deformation. These material points form the material continuum. It is further assumed that during growth-deformation every point moves to a new position $\mathbf{x} = \boldsymbol{\chi}(\mathbf{X})$ preserving the compatibility of the body. This mapping is smooth to the necessary degree. Moreover, it is assumed that the mapping is one-to-one, i.e., the 'infinite number' of material points is

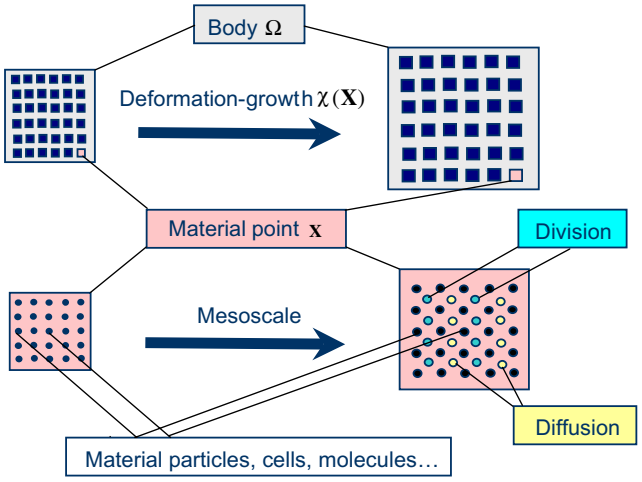

Fig. 1. Multiscale mechanics of growth.

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