

# A Simple Phenomenological Theory of Tissue Growth

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**Abstract:** A simple phenomenological framework for modeling growth of living tissues is proposed. Growth is defined as a change of mass and configuration of the tissue. Tissue is considered as an open system where mass conservation is violated and the full-scale mass balance is applied. A possible structure of constitutive equations is discussed with reference to *simple growing materials*. ‘Thermoelastic’ formulation of the simple growing material is specified. Within this framework traction free growth of cylindrical and spherical bodies is examined. It is shown that the theory accommodates the case where stresses are not generated in uniform volumetric growth. It is also found that surface growth corresponds to a *boundary layer* solution of the governing equations. This finding proves the ability of continuum mechanics to describe surface growth. The latter is contrary to the usual use of purely kinematical theories, which do not involve balance and constitutive equations, for treating surface growth.

**keyword:** Tissue growth; Constitutive behavior; Biological materials

## 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. For example, cardiac and vascular disorders, including hypertrophy, are thought to be due to the wall stress (Humphrey, 2002). It is also well known that growth and remodeling as a result of the bone-prosthesis interaction can significantly affect the healing process (Cowin, 2001). Last but not least is the understanding of the process of spatial pattern formation in living tissues and development of organs. It is very

likely that we can affect these processes by applying mechanical stimulus (Murray, 2003).

Biological or biochemical mechanisms of growth are not well understood though a plenty of scenarios exist in the biological literature (Cowin, 2000; Cowin, 2001). 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. That 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. The macroscopic parameters of tissue growth seem to be self-evident: *mass* and *form* (*configuration*). Observations on animals, including human beings, during the life time give the strict experimental proof of the change of mass and configuration.

The purpose of the present work is to develop a simple phenomenological theory of tissue growth which is based on the fundamental notion of altering mass and configuration. This will be in contrast to the existing phenomenological theories where more sophisticated basic assumptions are used including the introduction of the intermediate configurations of ‘pure growth’ with no deformation or considering tissues as mixtures: Chen and Hoger (2000); Cowin and Hegedus (1976); Drozdov (1998); Epstein and Maugin (2000); Fung (1990); Hsu (1968); Klich et al. (2001); Kuhn and Hauger (2000); Rachev (2000); Rodrigues et al. (1994); Skalak (1982); Skalak et al. (1982); Taber (1995); Taber and Perucchio (2000). 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 as, for example, the cofactors in the multiplicative decomposition of the deformation gradient, or the partial stresses and tractions in the mixture theories. This complexity prevents from the experimental calibration of the theories and application of the theories to practical problems. Besides, it should be noted that all cited works are devoted to volumetric growth while surface growth (bones, trees, shells, horns, branches etc.)

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is still considered to be out of the general framework of continuum mechanics because of the use of purely kinematical theories: Thompson (1948); Taber (1995); Skalak et al. (1997).

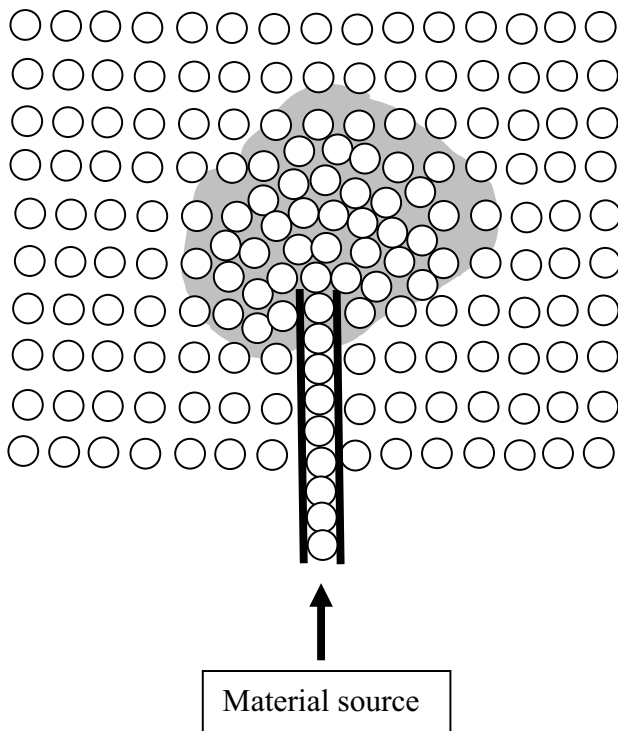
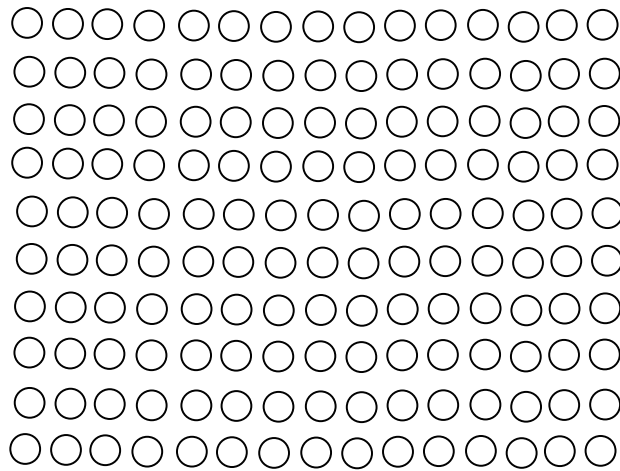
In the present work a novel continuum mechanics framework for modeling growth of living tissues is discussed. It is assumed that deformation and mass flow can describe both volumetric and surface growth of living bodies. This assumption leads to the consideration of the tissue as an open system and it leads, in turn, to the violation of mass conservation and to the introduction of the full-scale mass balance. Non-conservation of mass requires modification of the momentum balance. A possible structure of constitutive equations is discussed with reference to *simple growing materials*. ‘Thermoelastic’ formulation of the simple growing material is specified. This formulation allows for the uncoupled mass-flow/deformation problem, which is analogous to the classical quasi-static and small strain thermoelasticity.

## 2 Geometry of growth and a toy-tissue model

The assumption that the continuous deformation and mass flow can describe growth of living bodies is central for further development. To make sound this assumption, geometry of growth should be analyzed qualitatively (no set theory will be involved). Sharp distinction between the real physical material and the mathematical concept of *material particle* should be kept in mind. The mapping  $\mathbf{x} = \boldsymbol{\chi}(\mathbf{X}, t)$  is considered in the case of deformation of a non-growing body.  $\mathbf{X}$  designates an initial (reference) place of the material particle and  $\mathbf{x}$  is its current place in space.  $\mathbf{X}$  can be also interpreted as a label attached to the considered particle. Since this mapping is one-to-one, we assume that the ‘number’ of particles remains the same after deformation. For example, a rubber ball can be exposed to a significant outer pressure and its radius can decrease while preserving the spherical shape of the ball. Although the ball occupies less space after deformation, nobody doubts that the number of material particles remains the same or that the continuum mechanics mapping is applicable. The concept of the material particle is purely mathematical. Material particles do not exist: they are mathematical abstractions. Material always occupies some volume. One means a very small (infinitesimal) material volume saying ‘material particle’. Growth is considered as the deformation and mass change in this volume, i.e. in the vicinity of the

given particle. The ‘number’ of the particles, however, is not changing during growth. If the connectivity of the living body is preserved during its growth and a continuous deformation of the grown body into its initial configuration can be imagined, then it is possible to claim that the ‘number’ of material particles remains the same, by analogy with deformation of non-growing materials, and the continuum mechanics mapping  $\mathbf{x} = \boldsymbol{\chi}(\mathbf{X}, t)$  is applicable to growing bodies too. To illustrate this statement, consider two identical spheres made up of a living material. Let one sphere experience negative growth (atrophy) and the radius decrease while preserving the shape. Let the other sphere be exposed to the uniform pressure. Assume now that an observer can follow the shape changes (radius decrease) of both spheres simultaneously. If the (invisible gas) pressure increases slowly enough and the second sphere gets smaller at the same rate as the first one, it is impossible to make a *geometrical* distinction between growth and mechanical deformation. A *physical* distinction, however, exists. Growth manifests itself in the change of mass, which becomes crucial for modeling growth. Mass balance should be considered in its completeness.

While the qualitative analysis of the geometry of tissue growth justifies the use of continuum mechanics it is insufficient for the development of the particular equations of a macroscopic phenomenological theory. Such development requires some microscopic reasoning in order to motivate the continuum field and constitutive equations. It seems that a reasonable insight into the tissue growth mechanisms can be gained by considering a very simple toy-tissue model. Such model is presented in Fig.1. The regular initial tissue can be seen on the top of the figure. This is a collection of the regularly packed balls. The balls are interpreted as the tissue elementary components – cells, molecules of the extracellular matrix, and etc. The balls are arranged in a regular network for the sake of simplicity and clarity. They can be organized more chaotically – this does not affect the subsequent qualitative analysis. Assume now that a new material, i.e. a number of new balls, is supplied pointwisely as it is shown on the bottom of Fig.1. This supply is considered as a result of injection: the tube with the new material is a syringe. Usually, the new material is created in real tissues in a more complicated manner following a chain of the biochemical transformations. However, the finally produced new material still appears pointwisely from the



**Figure 1** : Toy-tissue model: regular (top), point mass supply (bottom).

existing cells. For example, the role of the material supplying tubes is played by the osteoblasts in the case of the bone tissue. Thus, the injection of the balls is a quite reasonable model of tissue growth. Such model can be constructed physically, of course. It seems that the latter is not necessary and the toy-tissue model can be easily imagined. The result of such thought-experiment is shadowed in the figure and it can be described as follows:

- (a) The number of the balls in the toy-tissue increases with the supply of the new ones.
- (b) The new balls are concentrated at the edge of the tube and they do not spread uniformly over the tissue.
- (c) The new balls can not be accommodated at the point of their supply – the edge of the tube: they tend to spread over the area at the vicinity of the edge and the packing of the balls gets denser around the edge of the tube.
- (d) The more balls are injected the less room remains for the new ones.
- (e) The new balls press the old ones.
- (f) The new balls tend to expand the area occupied by the tissue when the overall ball rearrangement reaches the tissue surface.

These six qualitative features of the toy-tissue microscopic behavior under the material supply can be translated into the language of the macroscopic theory accordingly:

- (A) Mass of the tissue grows.
- (B) Mass growth is not uniform – the mass density changes from one point to another.
- (C) There is a diffusion of mass.
- (D) The diffusion is restricted by the existing tissue structure and its mass density: the denser is the tissue the less material it can accommodate.
- (E) Growth is accompanied by stresses.
- (F) The expansion of the tissue is volumetric – it is analogous to the thermal expansion of structural materials as steel, for example.

Three first features (A, B, C) prompt the form of the mass balance equation. Indeed, the mass change means the failure of the mass conservation law, which covers most theories of Mechanics. The mass supply in the living tissues is possible through the biochemical interaction of the tissue with its environment. This means that the living tissue is an open system. The fact that non-uniform mass growth is related with the diffusion of mass is very important. It means that the mass balance law should include both the volumetric mass source and the surface mass flux. The latter is missed in most existing theories of growth. The absence of mass diffusion in the theory leads to a nonphysical conclusion that the density of the tissue will change only at the point of the material supply, i.e. pointwisely. In order to accommodate the non-uniform mass supply the mass diffusion should take place. Exceptions to this rule occur, for example, when the material supply is uniform and the tissue is not constrained geometrically. The latter case does not require mass diffusion and the tissue grows uniformly and freely without generating stresses. Such stress-free uniform growth may be considered as a test for the theory. It will be shown in the following sections that the theory proposed in our work meets this requirement.

The rest features (D, E, F) motivate the constitutive law. They say that the stress-strain relations should be analogous to the thermoelasticity where the role of the temperature is played by the mass density: the increase of the mass density results in the volume expansion of the tissue. On the other hand, the additional mass supply should be prevented by the tissue: the denser tissue the less is the new mass accommodation. Both these tendencies will be presented in the following development of the growth theory. It is worth noting, however, that not all features of growth can be identified within the toy-tissue model. For example, the cells respond the applied mechanical stimuli biochemically – cellular mechanotransduction – by changing the program of the creation of new material. Thus, there is a competition between the stresses and the supply of new material. This process is called adaptive growth. Under some circumstances the adaptive growth can be essential. We will not consider this issue in the present work restricting consideration by the purely genetic (programmed) growth.

### 3 Simple growing materials

Guided by the previous section reasoning the balance laws, constitutive equations, and initial/boundary conditions for *simple growing materials* are presented in this section. The precise definition of simple growing materials is postponed to Section 3.3. The general theoretical concepts of continuum mechanics can be found in Truesdell and Toupin (1960) and Truesdell and Noll (1965). The features of the general theory concerning violation of mass conservation and the setting of the constitutive framework are emphasized below.

#### 3.1 Kinematics

Growth and deformation are coupled in the deformation gradient

$$\mathbf{F} = \frac{\partial \boldsymbol{\chi}}{\partial \mathbf{X}}. \quad (1)$$

It is worth emphasizing that no distinction is made between growth and purely mechanical deformation. This is in contrast to works where a multiplicative decomposition of the deformation gradient is used. The latter presupposes existence of intermediate incompatible configurations of pure growth, which cannot be readily interpreted and measured in physical/biological terms.

The velocity of the material point is defined by

$$\mathbf{v} = \frac{D}{Dt} \boldsymbol{\chi}(\mathbf{X}, t) = \frac{\partial}{\partial t} \boldsymbol{\chi}(\mathbf{X}, t), \quad (2)$$

where  $D/Dt$  denotes the material time derivative, and  $\partial/\partial t$  denotes partial time differentiation when other variables are fixed.

Relationships between the infinitesimal surface areas and volumes before and after deformation-growth accordingly are useful

$$\mathbf{n} dA = J \mathbf{F}^{-T} \mathbf{n}_0 dA_0, \quad (3)$$

$$dV = J dV_0, \quad (4)$$

$$J = \det \mathbf{F}. \quad (5)$$

Here subscript 0 denotes the reference configuration and  $\mathbf{n}$  is a unit normal to the body surface.

Finally, the Reynolds transport theorem for a scalar field  $\pi$  over the body  $\Omega$  reads

$$\frac{D}{Dt} \int_{\Omega} \pi dV = \int_{\Omega} \left( \frac{\partial \pi}{\partial t} + \text{div}(\pi \mathbf{v}) \right) dV. \quad (6)$$

### 3.2 Mass and momentum balance

Mass is always conserved in a closed system. In the case of tissue growth the closed system should include tissue environment which is permanently changing and hard to define. Moreover, the latter is not necessary. The tissue can be considered as an open system and the general law of mass balance for the living body  $\Omega$  at time  $t$  can be set in the form

$$\frac{D}{Dt} \int_{\Omega} \rho(\mathbf{x}, t) dV = \int_{\Omega} \xi(\mathbf{x}, t) dV + \int_{\partial\Omega} \phi(\mathbf{x}, \mathbf{n}, t) dA, \quad (7)$$

where  $\rho$  is the *mass density* at point  $\mathbf{x}$ ;  $\xi$  and  $\phi$  are *mass supply* per unit volume and surface accordingly. Using the Cauchy tetrahedron argument, it is possible to introduce vector  $\boldsymbol{\psi}$  of *mass flux*

$$\phi = \boldsymbol{\psi} \cdot \mathbf{n}. \quad (8)$$

Substituting Eq.(8) in Eq.(7) and applying the divergence theorem and the Reynolds transport theorem we localize the mass balance

$$\frac{\partial \rho}{\partial t} = \text{div}(\boldsymbol{\psi} - \rho \mathbf{v}) + \xi. \quad (9)$$

The linear momentum law takes the following form

$$\begin{aligned} \frac{D}{Dt} \int_{\Omega} \rho(\mathbf{x}, t) \mathbf{v}(\mathbf{x}, t) dV \\ = \int_{\Omega} \rho(\mathbf{x}, t) \mathbf{b}(\mathbf{x}, t) dV + \int_{\partial\Omega} \mathbf{t}(\mathbf{x}, \mathbf{n}, t) dA, \end{aligned} \quad (10)$$

where  $\mathbf{b}$  designates a body force per unit mass. Traction  $\mathbf{t}$  takes the following form by introducing Cauchy's stress tensor  $\boldsymbol{\sigma}$

$$\mathbf{t} = \boldsymbol{\sigma} \mathbf{n}. \quad (11)$$

Generally, new volumetric and surface momentum supply is generated by the new mass. This should be taken into account in the momentum balance by adding the integrands, pre-multiplied by velocity  $\mathbf{v}$ , from the right-hand side of Eq.(7) to the corresponding integrands on the right-hand side of Eq.(10):

$$\frac{D}{Dt} \int_{\Omega} \rho \mathbf{v} dV = \int_{\Omega} (\rho \mathbf{b} + \xi \mathbf{v}) dV + \int_{\partial\Omega} (\mathbf{t} + \phi \mathbf{v}) dA.$$

However, the process of growth, which admits the time-scale from hours to years, is slow as compared to a typical dynamical process, which admits the time-scale from microseconds to seconds, so the additional terms are negligible for dynamic analysis of living tissues and these terms can be dropped from the equations as it has been done in Eq.(10).

Localizing Eq.(10) and accounting for Eq.(11) we have

$$\frac{\partial(\rho \mathbf{v})}{\partial t} = \text{div}(\boldsymbol{\sigma} - \rho \mathbf{v} \otimes \mathbf{v}) + \rho \mathbf{b}. \quad (12)$$

Assuming again that the inertia effect of the volume and surface mass supply does not affect dynamics it is possible to derive the standard local form of the angular momentum balance

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^T. \quad (13)$$

Being natural for the formulation of the fundamental balance laws the Eulerian description is not well suited for analysis of solid bodies and the Lagrangean form of the balance laws is worth deriving. For this purpose, the integral equation of mass balance should be rewritten accounting for  $\mathbf{x} = \boldsymbol{\chi}(\mathbf{X}, t)$  and Eqs.(3)-(5)

$$\frac{D}{Dt} \int_{\Omega_0} \rho_0(\mathbf{X}, t) dV_0 = \int_{\Omega_0} \xi_0(\mathbf{X}, t) dV_0 + \int_{\partial\Omega_0} \phi_0(\mathbf{n}_0, \mathbf{X}, t) dA_0, \quad (14)$$

where,

$$\rho_0(\mathbf{X}, t) = \rho(\boldsymbol{\chi}(\mathbf{X}, t), t) J(\mathbf{X}, t), \quad (15)$$

$$\xi_0(\mathbf{X}, t) = \xi(\boldsymbol{\chi}(\mathbf{X}, t), t) J(\mathbf{X}, t), \quad (16)$$

$$\phi_0 = \phi dA/dA_0 = \boldsymbol{\psi}_0 \cdot \mathbf{n}_0, \quad (17)$$

$$\boldsymbol{\psi}_0 = J \mathbf{F}^{-1} \boldsymbol{\psi}, \quad (18)$$

$$\mathbf{n}_0 = \mathbf{F}^T \mathbf{n} dA / (J dA_0), \quad (19)$$

Localizing the mass balance equation we get

$$\frac{\partial \rho_0}{\partial t} = \text{Div} \boldsymbol{\psi}_0 + \xi_0. \quad (20)$$

The classical law of the conservation of mass is obtained when  $\boldsymbol{\psi}_0 = \mathbf{0}$  and  $\xi_0 = 0$ .

The balance of linear momentum in the Lagrangean description takes the form

$$\begin{aligned} & \frac{D}{Dt} \int_{\Omega_0} \rho_0(\mathbf{X}, t) \mathbf{v}(\boldsymbol{\chi}(\mathbf{X}, t), t) dV_0 \\ & = \int_{\Omega_0} \rho_0(\mathbf{X}, t) \mathbf{b}(\boldsymbol{\chi}(\mathbf{X}, t), t) dV_0 + \int_{\partial\Omega_0} \mathbf{t}_0(\mathbf{X}, \mathbf{n}_0, t) dA_0, \end{aligned} \quad (21)$$

where

$$\mathbf{t}_0 = \mathbf{t} dA / dA_0 = \mathbf{P} \mathbf{n}_0, \quad (22)$$

$$\mathbf{P} = J \boldsymbol{\sigma} \mathbf{F}^{-T}. \quad (23)$$

Here  $\mathbf{P}$  is the first Piola-Kirchhoff stress tensor. With the help of the divergence theorem the local equation of motion emerges

$$\frac{\partial}{\partial t}(\rho_0 \mathbf{v}) = \text{Div} \mathbf{P} + \rho_0 \mathbf{b}. \quad (24)$$

It is important to emphasize that the unknown mass density is involved in Eq.(24). This is not the case of the classical continuum mechanics with mass conservation ( $J\rho = \rho_0 = \text{constant}$ ). The balance of angular momentum reads as in the classical formulation

$$\mathbf{P} \mathbf{F}^T = \mathbf{F} \mathbf{P}^T. \quad (25)$$

It is convenient to remove the non-linearity from the balance of angular momentum by introducing the second Piola-Kirchhoff stress tensor

$$\mathbf{S} = \mathbf{F}^{-1} \mathbf{P} = J \mathbf{F}^{-1} \boldsymbol{\sigma} \mathbf{F}^{-T}. \quad (26)$$

In this case the balance of linear and angular momentum is written as follows

$$\frac{\partial}{\partial t}(\rho_0 \mathbf{v}) = \text{Div}(\mathbf{F} \mathbf{S}) + \rho_0 \mathbf{b}, \quad (27)$$

$$\mathbf{S} = \mathbf{S}^T. \quad (28)$$

### 3.3 Constitutive equations

Twenty-nine unknowns  $\{\boldsymbol{\chi}, \mathbf{v}, \rho_0, \xi_0, \boldsymbol{\Psi}_0, \mathbf{F}, \mathbf{S}\}$  are involved in the nineteen independent equations (1), (2), (20), (27), (28). Ten independent constitutive equations must be added. A possible form can be written as follows

$$\boldsymbol{\Psi}_0(t) = \hat{\boldsymbol{\Psi}}_0^{(t)}(\rho_0, \text{Grad} \rho_0, \mathbf{F}, \mathbf{X}), \quad (29)$$

$$\mathbf{S}(t) = \hat{\mathbf{S}}^{(t)}(\rho_0, \text{Grad} \rho_0, \mathbf{F}, \mathbf{X}), \quad (30)$$

$$\xi_0(t) = \hat{\xi}_0^{(t)}(\rho_0, \text{Grad} \rho_0, \mathbf{F}, \mathbf{X}), \quad (31)$$

where caps designate constitutive functionals for the materials *with memory* up to the time  $t$ .

It is worth noting that these equations provide coupling between mass and momentum balance. Extending terminology of Truesdell and Noll (1965), these equations define *simple growing materials*. They are *simple* because only first gradients of deformation and mass density fields are involved. It is essential that the mass density gradient *must* be included in the constitutive law. Indeed, after substituting (29)-(31) in (20), (24), (25), the system of governing equations is of the second order in spatial derivatives of  $\rho_0$ . The latter allows for imposing two boundary conditions on  $\rho_0$  on opposite sides of the considered body. Assume, for example, that the constitutive relations do not include the mass density gradients:  $\boldsymbol{\Psi}_0 = \hat{\boldsymbol{\Psi}}_0(\rho_0, \mathbf{F}, \mathbf{X})$ ,  $\mathbf{S} = \hat{\mathbf{S}}(\rho_0, \mathbf{F}, \mathbf{X})$ , and  $\xi_0 = \hat{\xi}_0(\rho_0, \mathbf{F}, \mathbf{X})$ . Substituting these relations in the balance equations, we obtain a system of governing equations of the first order in spatial derivatives of  $\rho_0$ . The first order differential equations require only one boundary condition and, generally, it is impossible to satisfy two boundary conditions on opposite sides of the body. It is also hardly possible to give an acceptable physical interpretation to such inconsistency between the number of reasonable boundary conditions and the order of the differential equations. The solution of the differential equations can be called over-determined in this case. In contrast to the over-determinacy, the use of the higher-grade materials where higher order gradients are presented in the constitutive equations can lead to the under-determinacy of differential equations. The latter happens if no additional boundary conditions are imposed. An example of inconsistency of this kind can be found in Volokh and Hutchinson (2002) within the context of metal plasticity. The requirement of strict correspondence between the number and character of boundary conditions and the structure of balance constitutive laws can be called the requirement of *mathematical consistency*.

### 3.4 Initial/boundary conditions

In order to complete the formulation of the initial boundary value problem (IBVP) for simple growing materials it is necessary to formulate initial and boundary conditions

as follows

$$\boldsymbol{\chi} = \boldsymbol{\chi}^* \in \partial\Omega_{\boldsymbol{\chi}}, \quad (32)$$

$$\mathbf{t} = \mathbf{t}^* \in \partial\Omega_{\mathbf{t}}, \quad (33)$$

$$\boldsymbol{\chi}(t=0) = \boldsymbol{\chi}_0^* \in \Omega, \quad (34)$$

$$\mathbf{v}(t=0) = \mathbf{v}_0^* \in \Omega, \quad (35)$$

$$\partial\Omega_{\boldsymbol{\chi}} \cup \partial\Omega_{\mathbf{t}} = \partial\Omega; \quad \partial\Omega_{\boldsymbol{\chi}} \cap \partial\Omega_{\mathbf{t}} = 0, \quad (36)$$

$$\rho = \rho^* \in \partial\Omega_{\rho}, \quad (37)$$

$$\phi = \phi^* \in \partial\Omega_{\phi}, \quad (38)$$

$$\rho(t=0) = \rho_0^* \in \Omega, \quad (39)$$

$$\partial\Omega_{\rho} \cup \partial\Omega_{\phi} = \partial\Omega; \quad \partial\Omega_{\rho} \cap \partial\Omega_{\phi} = 0, \quad (40)$$

where the quantities with the asterisk are given.

#### 4 ‘Thermoelastic’ model of growth

Following the qualitative analysis of the toy-tissue model presented in Section 2 we develop a ‘thermoelastic’ model of growth. It should be mentioned that the qualitative idea that growth is analogous to thermal expansion is due to Skalak (1982). No quantitative theory, however, has been proposed to develop this idea. We attempt to fill this gap in the present section. It is shown that the proposed ‘thermoelastic’ constitutive model can accommodate both volumetric and surface growth. The latter is in contrast to the traditional point of view that only volumetric growth can be described by using continuum mechanics while surface growth is out of the scope of continuum mechanics and only purely kinematical theories are available for describing surface growth (Thompson, 1948; Taber, 1995; Skalak et al., 1997).

##### 4.1 Restrictions

In order to specify the described general framework analogously to the classical thermoelasticity the following restrictions are imposed:

- (1) The process is quasi-static, i.e. transient behavior is ignored.
- (2) Deformations are small and body forces are ignored.

The first restriction is reasonable because of the very slow growth process and it leads to the following mass and momentum balance laws

$$\operatorname{div}\boldsymbol{\Psi} + \boldsymbol{\xi} = 0, \quad (41)$$

$$\operatorname{div}\boldsymbol{\sigma} = \mathbf{0}. \quad (42)$$

There is no difference between the Lagrangean and Eulerian descriptions because of the second restriction. The second restriction is justified for hard tissues like bones and trees and it is not justified for soft tissues like muscles and arteries. If, however, the large mechanical deformations are excluded from behavior of soft tissues and pure growth is considered then the small deformation restriction seems to be applicable because of the slow growth process. Of course, consideration of such issues as the organ development or branching of trees requires the extension of the theory to large deformations. The latter exceeds the scope of the present work.

##### 4.2 ‘Thermoelastic’ model of growth

Introducing an infinitesimal strain measure as a symmetric part of the displacement gradient

$$\boldsymbol{\epsilon} = (\nabla\mathbf{u} + (\nabla\mathbf{u})^T)/2, \quad (43)$$

$$\mathbf{u} = \boldsymbol{\chi}(\mathbf{X}) - \mathbf{X}, \quad (44)$$

we define the following constitutive equations:

$$\boldsymbol{\sigma} = \lambda \operatorname{tr}(\boldsymbol{\epsilon})\mathbf{1} + 2\mu\boldsymbol{\epsilon} - (3\lambda + 2\mu)\alpha\rho\mathbf{1}, \quad (45)$$

$$\boldsymbol{\Psi} = \beta\nabla\rho, \quad (46)$$

$$\boldsymbol{\xi} = \boldsymbol{\omega} - \gamma\rho, \quad (47)$$

$$\rho := \rho(\boldsymbol{\omega}) - \rho(0), \quad (48)$$

where  $\lambda$  and  $\mu$  are the Lamé coefficients;  $\mathbf{1}$  is the second-order identity tensor.

Increment of *mass supply*  $\boldsymbol{\omega} > 0$  is analogous to a quasi-static mechanical load. In contrast to the latter, however,  $\boldsymbol{\omega}$  is controlled by the tissue itself and its proper determination requires experiments. The dimension of  $\boldsymbol{\omega}$  is a unit of mass per volume and time. Time is not involved directly in quasi-static problems and can be replaced by some conditional units (analogous to Newtons in dynamics).

Coefficient of growth expansion  $\alpha > 0$  determines how much the relative volume changes for the given increment of mass density. Its dimension is an inverse of a unit of mass.

Mass conductivity of solid  $\beta > 0$  determines how much the mass supply changes for a given increment of the gradient of mass density. Its dimension is a unit of mass supply times length per mass density.

Coefficient of tissue resistance  $\gamma > 0$  reflects the resistance of the tissue to accommodate new mass for increasing mass density. Roughly speaking, the more new material the less room for it remains. The second term on the right-hand side of Eq.(47) limits mass supply when the density increases. The dimension of  $\gamma$  is the dimension of  $\omega$  per a unit of mass density.

All these coefficients can be inhomogeneous.

The similarity between the two first constitutive laws of growth and thermoelasticity is obvious after replacing the mass density increment by the temperature increment; the mass flow vector by the vector of heat flux; the coefficient of growth expansion by the coefficient of thermal expansion; and the mass conductivity of solid by the thermal conductivity of solid. In this case Eq.(45) is nothing but the thermoelastic generalization of the Hooke's law, and Eq.(46) is just the Fourier law of heat conduction (Boley and Weiner, 1997). The constitutive law analogous to Eq. (47), however, is usually absent in thermoelasticity because of the lack of volumetric heat sources. The thermoelastic analogy allows better understanding parameters of the growth model. The vector of mass flux is analogous to the vector of heat flux. We feel the heat flow by changing temperature without directly defining what the heat is. The same is true for the mass flow. We 'feel' it by changing mass density without directly defining what it is.

Substituting Eqs.(46) and (47) in Eq.(41) and assuming  $\beta = \text{constant}$  we have

$$\beta \nabla^2 \rho - \gamma \rho + \omega = 0. \tag{49}$$

Substituting solution of Eq.(49) in Eqs.(45) and (42) it is possible to find the deformation characteristics and the corresponding stress field.

In summary, the proposed constitutive model allows for decoupling of the growth-deformation equations. First, it is necessary to find the mass density field by solving Eq.(49) with the proper boundary conditions (37), (38).

Second, the obtained distribution of the mass density is used in the generalized Hooke's law (45) and equilibrium equation (42) in order to find the stress/displacement field accounting for the proper boundary conditions (32), (33).

### 4.3 Example I: a cylinder

Let's consider radial growth of an infinite cylinder with the inner radius  $a$  and the outer radius  $b$ . In this case equilibrium equations in terms of displacements take the form

$$\frac{d}{dr} \left[ \frac{d(ru)}{rdr} \right] = \frac{3\lambda + 2\mu}{\lambda + 2\mu} \alpha \frac{d\rho}{dr} = \frac{1 + \nu}{1 - \nu} \alpha \frac{d\rho}{dr}, \tag{50}$$

where Lamé coefficients are replaced by Young modulus  $E$  and Poisson ratio  $\nu$ :

$$\lambda = \frac{E\nu}{(1 + \nu)(1 - 2\nu)}, \quad \mu = \frac{E}{2(1 + \nu)}. \tag{51}$$

Traction-free boundary conditions read

$$\sigma_{rr}(r = a, b) = 0. \tag{52}$$

This boundary value problem admits analytical solutions

$$u = \frac{\alpha}{r(1 - \nu)} \left\{ (1 + \nu) \int_a^r \rho r dr + \frac{(1 - \nu - 2\nu^2)r^2 + a^2(1 + \nu)}{b^2 - a^2} \int_a^b \rho r dr \right\}, \tag{53}$$

$$\sigma_{rr} = \frac{\alpha E}{(1 - \nu)r^2} \left\{ \frac{r^2 - a^2}{b^2 - a^2} \int_a^b \rho r dr - \int_a^r \rho r dr \right\}, \tag{54}$$

$$\sigma_{\theta\theta} = \frac{\alpha E}{(1 - \nu)r^2} \left\{ \frac{r^2 + a^2}{b^2 - a^2} \int_a^b \rho r dr + \int_a^r \rho r dr - \rho r^2 \right\}. \tag{55}$$

The unknown field of mass densities can be found from the following BVP

$$\beta \frac{1}{r} \frac{d}{dr} \left( r \frac{d\rho}{dr} \right) - \gamma \rho + \omega = 0, \tag{56}$$

$$\rho = \rho^* \in \partial\Omega_\rho, \tag{57}$$

$$\phi = \frac{\partial \rho}{\partial r} = \phi^* \in \partial\Omega_\phi, \tag{58}$$

We consider two particular cases.



#### 4.3.1 Volumetric growth

Assuming that material is supplied uniformly  $\omega = \text{constant}$ , and  $\gamma = \text{constant}$ , the boundary conditions take the form

$$\rho(r = a, b) = \rho^* = \omega/\gamma, \quad (59)$$

Solution of Eq.(56) is evident

$$\rho = \omega/\gamma, \quad (60)$$

This is the case of homogeneous growth. Substituting Eq.(60) in Eqs.(53)-(55) we have

$$u = \alpha(1 + \nu)r\omega/\gamma, \quad (61)$$

$$\sigma_{rr} = 0, \quad (62)$$

$$\sigma_{\theta\theta} = 0. \quad (63)$$

Thus, homogeneous growth does not produce stresses for the specific situation described.

#### 4.3.2 Surface growth

Assuming that material is not supplied volumetrically  $\omega = 0$  but at the outer surface where mass density increases, the boundary conditions take the form

$$\rho(r = a) = 0, \quad \rho(r = b) = \rho^*. \quad (64)$$

Solution of Eq.(56) with boundary conditions (64) is

$$\rho = C_1 I_0(r\tau) + C_2 K_0(r\tau), \quad \tau = \sqrt{\gamma/\beta}, \quad (65)$$

where  $I_0$  and  $K_0$  are zero order Bessel functions. Constants of integration can be found by substituting Eq.(65) in Eq.(64). After that, the stress-displacement field is computed by using Eqs.(53)-(55). Radial distribution of normalized mass densities, displacements, radial and circumferential stresses:  $\bar{\rho} = \rho/\rho^*$ ;  $\bar{u} = u/(\alpha\rho^*a)$ ;  $\bar{\sigma}_{rr} = \sigma_{rr}/(\alpha\rho^*E)$ ;  $\bar{\sigma}_{\theta\theta} = \sigma_{\theta\theta}/(\alpha\rho^*E)$ ; are given in Fig.(2) for different values of  $\tau$ . These numerical results have been calculated for  $\nu = 1/4$  and  $b = 3a$ .

It is important to emphasize that mass densities, displacements, and circumferential stresses localize in a *boundary layer* at  $r = b$  with increasing  $\tau$ , while their magnitudes outside the boundary layer tend to zero. This is the surface growth.

#### 4.4 Example II: a sphere

Let's consider radial growth of a sphere with the inner radius  $a$  and the outer radius  $b$ . In this case equilibrium equations in terms of displacements take the form

$$\begin{aligned} \frac{d}{dr} \left[ \frac{d(r^2 u)}{r^2 dr} \right] &= \frac{3\lambda + 2\mu}{\lambda + 2\mu} \alpha \frac{d\rho}{dr} \\ &= \frac{1 + \nu}{1 - \nu} \alpha \frac{d\rho}{dr}, \end{aligned} \quad (66)$$

Traction-free boundary conditions read

$$\sigma_{rr}(r = a, b) = 0. \quad (67)$$

This boundary value problem admits analytical solutions

$$u = \frac{\alpha}{(b^3 - a^3)} \left( \frac{3\lambda + 2\mu}{\lambda + 2\mu} \right) \left\{ \frac{a^3}{r^2} \int_r^b \rho r^2 dr + \frac{b^3}{r^2} \int_a^r \rho r^2 dr + \frac{4\mu r}{3\lambda + 2\mu} \int_a^b \rho r^2 dr \right\}, \quad (68)$$

$$\begin{aligned} \sigma_{rr} &= \frac{4\mu\alpha}{(a^3 - b^3)} \left( \frac{3\lambda + 2\mu}{\lambda + 2\mu} \right) \\ &\left\{ \frac{a^3}{r^3} \int_r^b \rho r^2 dr + \frac{b^3}{r^3} \int_a^r \rho r^2 dr - \int_a^b \rho r^2 dr \right\}, \end{aligned} \quad (69)$$

$$\begin{aligned} \sigma_{\theta\theta} &= \sigma_{\phi\phi} \\ &= \frac{2\mu\alpha}{(b^3 - a^3)} \left( \frac{3\lambda + 2\mu}{\lambda + 2\mu} \right) \\ &\left\{ \frac{a^3}{r^3} \int_r^b \rho r^2 dr + \frac{b^3}{r^3} \int_a^r \rho r^2 dr + 2 \int_a^b \rho r^2 dr - (b^3 - a^3)\rho \right\}. \end{aligned} \quad (70)$$

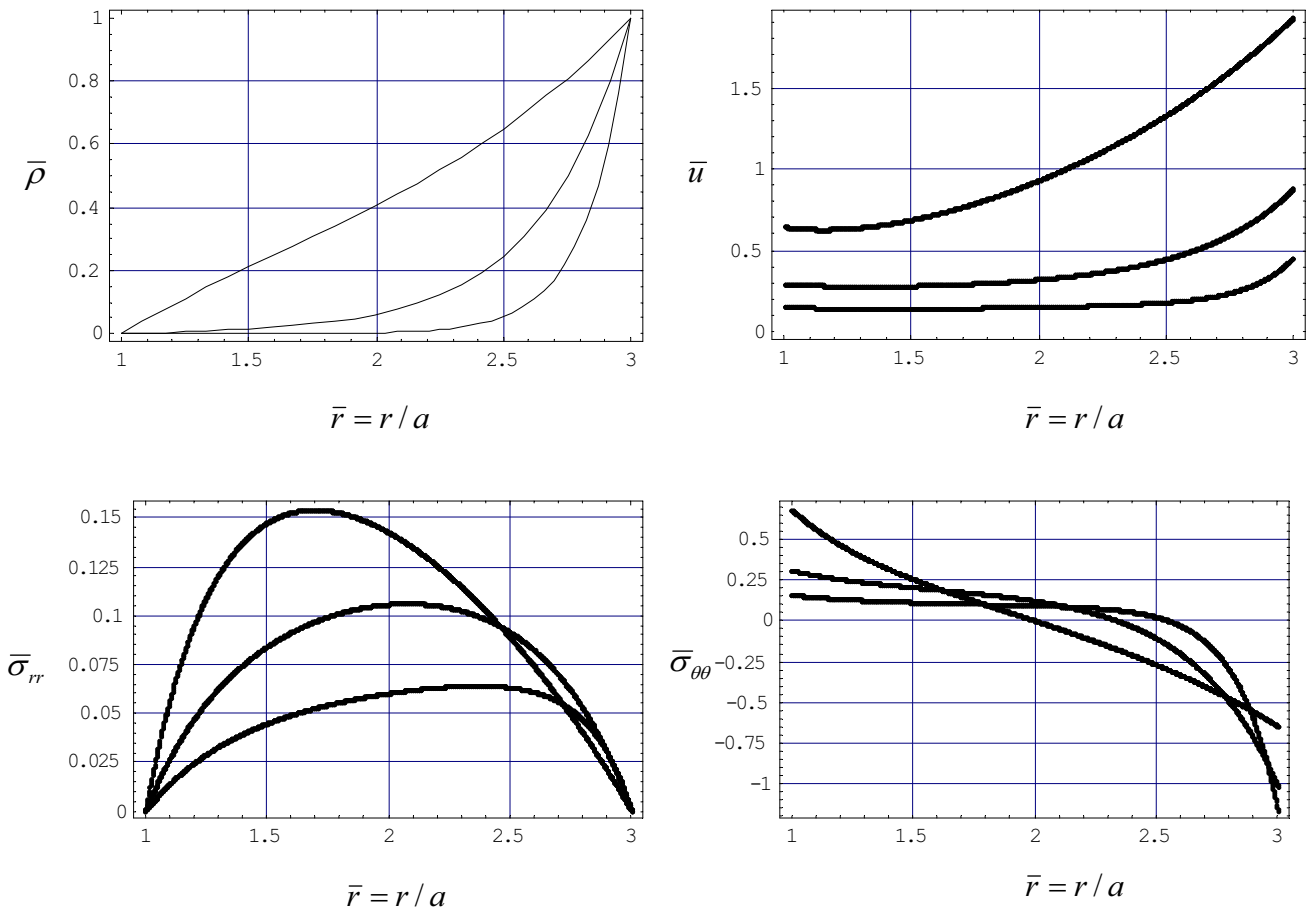
The unknown field of mass densities can be found from the following BVP

$$\beta \frac{1}{r^2} \frac{d}{dr} \left( r^2 \frac{d\rho}{dr} \right) - \gamma\rho + \omega = 0, \quad (71)$$

$$\rho = \rho^* \in \partial\Omega_\rho, \quad (72)$$

$$\phi = \frac{\partial\rho}{\partial r} = \phi^* \in \partial\Omega_\phi, \quad (73)$$

We consider two particular cases.



**Figure 2 :** Surface growth of the cylinder. Normalized density, displacements, radial stresses, and circumferential stresses along normalized radius for different values of the normalized coefficient of tissue resistance  $\tau = \sqrt{\gamma/\beta}$ . Graphs approach zero with increasing parameter  $\tau = 1, 3, 6$ .

4.4.1 Volumetric growth

Assuming that material is supplied uniformly  $\omega = \text{constant}$ , and  $\gamma = \text{constant}$ , the boundary conditions take the form

$$\rho(r = a, b) = \rho^* = \omega/\gamma, \tag{74}$$

Solution of Eq.(71) is evident

$$\rho = \omega/\gamma, \tag{75}$$

This is the case of homogeneous growth. Substituting Eq.(75) in Eqs.(68)-(70) we have

$$u = \alpha r \omega / \gamma, \tag{76}$$

$$\sigma_{rr} = 0, \tag{77}$$

$$\sigma_{\theta\theta} = \sigma_{\phi\phi} = 0. \tag{78}$$

Thus, homogeneous growth does not produce stresses as in the case of the cylinder.

4.4.2 Surface growth

Assuming that material is not supplied volumetrically  $\omega = 0$  but at the outer surface where mass density increases, the boundary conditions take the form

$$\rho(r = a) = 0, \quad \rho(r = b) = \rho^*. \tag{79}$$

Solution of Eq.(71) with boundary conditions (79) is

$$\rho = C_1 \frac{\cosh(r\tau)}{r\tau} + C_2 \frac{\sinh(r\tau)}{r\tau}, \quad \tau = \sqrt{\gamma/\beta}. \tag{80}$$

Constants of integration can be found by substituting Eq.(80) in Eq.(79). After that, the stress-displacement

field is computed by using Eqs.(68)-(70). Radial distribution of normalized mass densities, displacements, radial and circumferential stresses:  $\bar{\rho} = \rho/\rho^*$ ;  $\bar{u} = u/(\alpha\rho^*a)$ ;  $\bar{\sigma}_{rr} = \sigma_{rr}/(\alpha\rho^*E)$ ;  $\bar{\sigma}_{\theta\theta} = \sigma_{\theta\theta}/(\alpha\rho^*E)$ ; are given in Fig.(3) for different values of  $\tau$ . These numerical results have been calculated for  $\nu = 1/4$  and  $b = 3a$ .

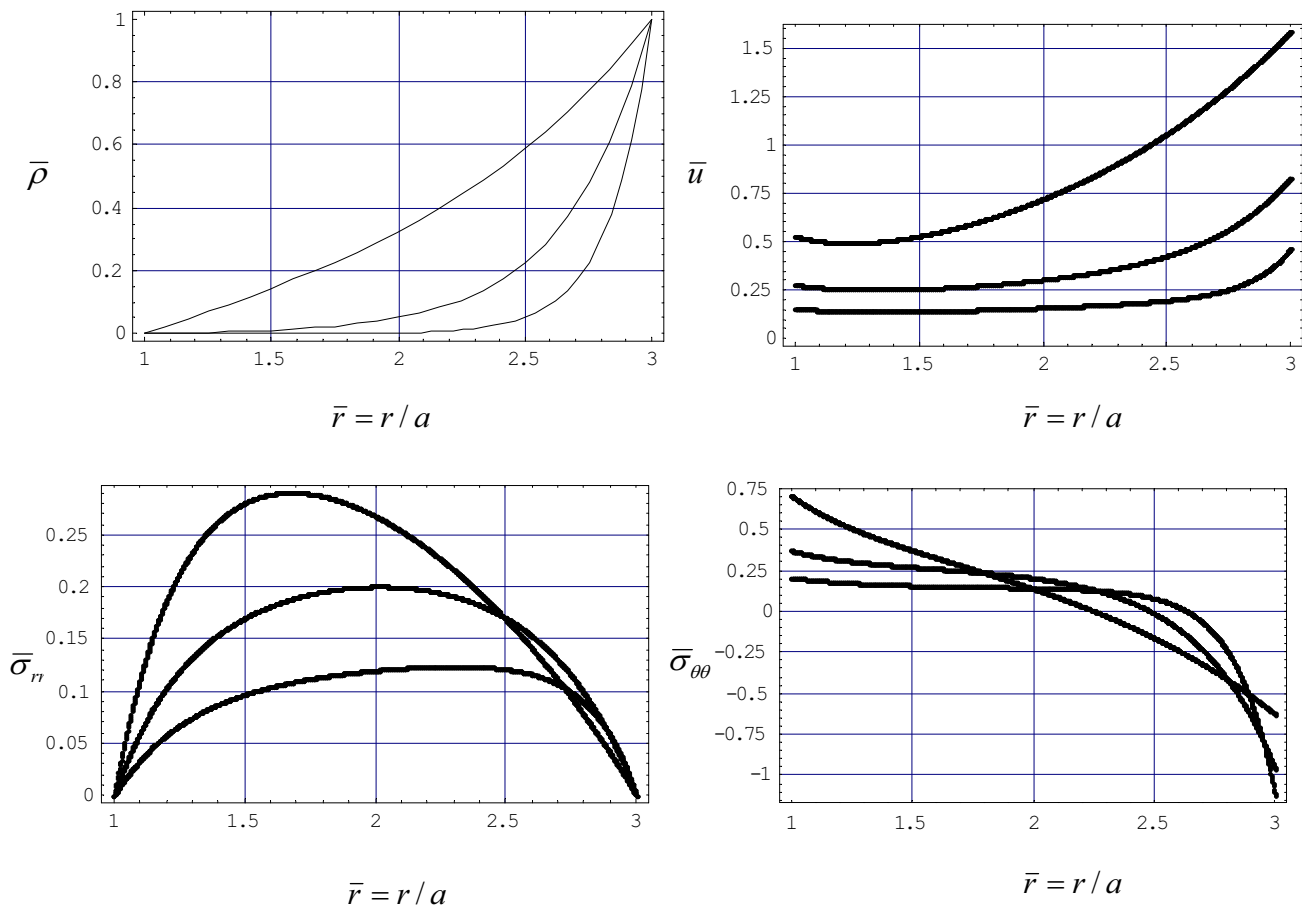
Again, like in the case of the cylinder, mass densities, displacements, and stresses localize in a *boundary layer* at  $r = b$  with increasing  $\tau$ , while their magnitudes outside the boundary layer tend to zero. This is the surface growth, of course.

## 5 Discussion

The obtained results of modeling volumetric and surface growth of living bodies can be qualitatively compared with the predictions of the toy-tissue model and observations on real tissues. As it was argued by using the microscopic reasoning the free uniform volumetric growth of both the cylinder and the sphere does not lead to the appearance of stresses. In this case all newly produced material is uniformly distributed over the body and the latter expands with no geometric constraints. This is entirely analogous to the free thermal expansion of structural steels, for instance. In the case of surface growth a boundary layer of dense material is formed at the outer surface of the body. This result is in remarkable correspondence with the experimental observations on the bone tissue. It is well established (Cowin, 2001) that bone material is mainly the *cancellous* bone. This is a porous material of the relatively low mass density, which fills in the bone cylinder-like volume. However, the outer surface of the bone is formed by the *cortical* bone. This material is much denser. It protects the internal bone from the intervention of the undesirable environmental factors. The formation of the cortical bone is a complicated biochemical process. It can not be described within the framework of the phenomenological theory considered in this work. Nonetheless, such important macroscopic parameter as the mass density can be readily analyzed experimentally and theoretically. The cortical bone can be interpreted as the high density boundary layer of the cancellous bone which is created at the surface. Such boundary layer is clearly seen in Fig.2 for the density distribution. The larger is the relative tissue resistance parameter ( $\tau$ ) the thinner is the boundary layer, i.e. the thickness of the cortical bone. Though it is impossible yet to provide the quantitative estimates at this

stage of the theory development, the qualitative similarity between the theory prediction and the bone tissue observation seems to be inspiring.

The variety of the tissue growth theories put forward the necessity to compare between them. It would be attractive to compare the predictions of the different growth theories by studying the same test problems both theoretically and experimentally. This is achievable, however, when the grounds for various possible theories are common and well established. Consider, for example, various plate theories. In this case, the geometrical sizes, material properties, boundary conditions, and loads can be readily defined for a given real plate. After that, the stress, strain, and displacement fields can be computed within the frameworks of different theories based, for example, on the equations of Germain-Kirchhoff or Reissner-Mindlin. The computed fields can be directly compared to the experimental measurements of the displacements and strains what allows for concluding about the applicability and efficiency of the different plate theories. It is worth emphasizing that the quantities measured in experiments – displacements and strains – are the main variables of the different theories. Thus the theories guide the experiment making it meaningful. It should not be missed that the mathematical structure of the mentioned theories is very different because the order of the differential equations and the number and character of the boundary conditions are different. Particularly, the Germain-Kirchhoff theory is of the 4<sup>th</sup> order and it requires two boundary conditions while the Reissner-Mindlin theory is of the 6<sup>th</sup> order and it requires three boundary conditions. Nonetheless, the grounds – main variables – of both theories are the same and the theories can be perfectly compared within the test studies. The plate theories were being developed during more than one century before reaching their maturity and comparability. This is not the case of the growth theories. These theories are young and there is no agreement about the possible grounds of the growth theories. Moreover, many scholars consider volumetric and surface growth as entirely different from the point of view of mechanics. The volumetric growth is considered within the traditional scheme of continuum mechanics while the surface growth is reduced mainly to the kinematical theories of the surface evolution. The lack of agreement about the grounds of growth mechanics makes it impossible to propose a general test for the comparison of the differ-



**Figure 3 :** Surface growth of the sphere. Normalized density, displacements, radial stresses, and circumferential stresses along normalized radius for different values of the normalized coefficient of tissue resistance  $\tau = \sqrt{\gamma/\beta}$ . Graphs approach zero with increasing parameter  $\tau = 1, 3, 6$ .

ent theories and experiments. One can only qualitatively compare some general settings of the different theories. Particularly, we will emphasize the main features of our approach as compared to the other ones.

### 6 Conclusions

The problem of establishing a simple analytical framework for modeling growth of living tissues has been addressed. A general model of simple growing materials is presented where growth is considered as a mass-flow-deformation process. A novel theory of tissue growth is specified. This theory is analogous to thermoelasticity where temperature is replaced by mass density. In order to solve the growth problem for the given living body, it is necessary first to find the distribution of mass density from the mass balance equation. The thermoelastic coun-

terpart of this equation is the equation of heat conduction. When the mass density distribution is known, it is possible to find deformation from the momentum balance accounting for the generalized Hooke's law. The latter reveals close resemblance between growth and thermal expansion. Examples of volumetric growth of the living cylinder and sphere reveal the capacity of the theory to accommodate materials that can grow freely and uniformly without generating stresses. An important feature of the proposed theory is its ability to reproduce surface growth. This can be clearly seen in Figs 2-3 where the normalized mass density, displacements, and circumferential stresses are presented for growing cylindrical and spherical bodies. Qualitatively the graphs indicate the following tendency. The densities, displacements, and stresses tend to zero within the whole body

area except for the boundary where new material is supplied. At the boundary all parameters increase. The larger is the ratio between the tissue resistance to accommodate the new material and the mass conductivity of the tissue the sharper is the area where nonzero densities, displacements, and stresses are observed. Thus surface growth may be interpreted as a localization of growth in the vicinity of the surface. From the mathematical point of view the growth localization appears as the boundary layer solution of governing equations as a result of the introduction of mass diffusion in the full-scale mass balance equation. It seems that the latter is also important from the biological point of view. Indeed, some diffusion of newly produced cells and extra-cellular matrix material always exists and its degree depends on the specific material. This situation is typical for living biological materials. It is generally different for engineering materials. For example, growth of multilayers, like thermal coatings, by the evaporation-condensation process is not accompanied by diffusion of the new material into the bulk. This is the fundamental difference between the 'dead' engineering material and the living biological material, which is the source of itself. The finding of surface growth as the localization of growth in a thin surface layer seems to be of the principle matter proving the power of continuum mechanics to treat the phenomenon of biological surface growth. Traditionally, the description of surface growth is restricted by purely kinematical theories which do not use balance and constitutive equations.

It is worth noting that the proposed approach is not restricted by a specific biological mechanism of growth. Indeed, the analytical model of growth is based on macroscopic variables: displacements and mass densities. It does not matter, in principle, what are the possible biochemical scenarios of the cell evolution. Such evolution can occur volumetrically or at the surface or following some more complicated scenario. Information about the biochemical processes underlying macroscopic growth can be useful in creating phenomenological theories. Unfortunately, the cross-link between macro- and micro-scales remains an open challenging problem. The latter is true not only for living materials but even for much simpler engineering materials (Dvorak, 2000).

The fact that the proposed phenomenological continuum mechanics framework is based on two observable variables – displacements and mass densities – is of the cru-

cial importance from the point of view of the experimental calibration of the theories within the framework of simple growing materials. Only displacements and mass densities should be measured in experiments and recent developments in computer vision techniques (MRI, PET) (Papademetris, 1999; Thompson, 2000) combined with the noninvasive densitometry (based, for example, on X-ray techniques) will hopefully allow for finding the density and displacement fields in vivo. When these fields are known for successive stages of the tissue evolution then the *inverse* continuum mechanics problem is solved within the proposed framework. Such inverse problem may be solved for a real tissue configuration with the help of the finite element methods, for example, or some other numerical discretization techniques. It should be emphasized that the simplicity of the proposed phenomenological framework encourages experiments. This is not the case of most competing theories. Indeed, the question 'what should be measured in experiments?' is not readily answered within the theories where the multiplicative decomposition of the deformation gradient is used. What should be measured in experiments guided by the mixture theories is also hard to formulate. These remarks must be understood correctly. We are not in a position to decline more sophisticated theories. We believe, however, that more sophisticated theories should be introduced when more simple theories fail to describe experimental observations. Experimental verification of growth theories belongs to the future. Growth theories are in their infancy – at the stage of the very basic formulation. It seems, however, that many scholars working in the field try to create basic theories as sophisticated as possible accounting for all 'factors'. Such tendency in mechanics of growth of biological materials is entirely opposed to the history of mechanics of engineering materials, which development was always from simple theories to the sophisticated ones. Our work is a search for simplicity which proved itself in mechanics of engineering materials. We believe that simple theories are worth searching for. Biological materials comprise a number of different constituents. The same is true for soils or composites. The simplest elasticity and plasticity theories are very successful for soils and composites. By analogy, there is no rationale to expect failure of simple growth theories in advance.

Finally, it is worth mentioning that not only the experimental calibration of the proposed theory is necessary.

Further development of the theory is desirable. Such development should include large deformation description and the full coupling between the mass and momentum balances. The latter is important when the tissue remodeling is considered.

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