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Mathematical framework for modeling tissue growth

K.Y. Volokh
Faculty of Civil and Environmental Engineering, Technion, Haifa 32000, Israel
E-mail: cvolokh@tx.technion.ac.il

Abstract. A phenomenological continuum mechanics framework for modeling growth of living tissues is proposed. Tissue is considered as an open system where mass is not conserved. The momentum balance is completed with the full-scale mass balance. Constitutive equations define *simple growing materials*. 'Thermoelastic' formulation of a simple growing material is specified. Within this framework traction free growth of a cylinder is considered. 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.

Keywords: Living tissue, volumetric growth, surface growth, mass balance

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 treatment of pathological conditions and offer new prospects in tissue engineering. Though the early works on growth were kinematical [19], using continuum mechanics is now widely accepted for describing growth, remodeling, and morphogenesis [17]. Since the work of Hsu [8], there appeared various models of growth [2–4,6,7,9–12,14,15,18]. Multiplicative decompositions of the displacement gradient underlie many publications on analytical modeling of growth. In this case an intermediate configuration is introduced where the free deformation-growth is considered in the vicinity of every material point. Geometrical compatibility of the grown material particles is ensured by additional deformation and stress. Another line of the growth modeling is presented in [10] where tissue is considered as a classical mixture of solid and fluid. These authors show that several well-known models of adaptive growth can be embedded in their general theory. It should be noted that all cited works are devoted to volumetric growth while surface growth is still out of the scope of continuum mechanics [16,17]. Mathematical description of existing approaches is rather sophisticated and it includes variables that may be difficult to interpret in simple terms and to assess in measurements.

In the present work a novel continuum mechanics framework for modeling growth of living tissues is considered. It is assumed that deformation and mass flow can describe both volumetric and surface growth of living bodies. This assumption leads to the violation of mass conservation and to the introduction of the full-scale mass 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 leads to the uncoupled mass-flow/deformation problem, which is analogous to the classical quasi-static and small strain thermoelasticity. Within this framework traction free growth of a cylindrical body is considered. 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. This is in contrast to the widespread point of view that only purely kinematical theories are suitable for modeling surface growth.

2. Governing equations

The assumption that the continuous deformation and mass flow can describe growth of living bodies is central for further development. 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 material particle. Since this mapping is one-to-one, we tacitly assume that the 'number' of material 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. It is physically meaningless. Particles-points 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 material 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 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 a sphere made up of a living material. Let this material experience negative growth (atrophy) and the radius decrease while preserving the shape. Assume now that an observer can follow both deformation of the sphere under pressure and negative growth of the living material simultaneously. If the (invisible gas) pressure increases slowly enough and the sphere gets smaller at the same rate, it is impossible to make a geometrical distinction between growth and 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

$$\frac{\partial \rho_0}{\partial t} = \mathrm{Div}\boldsymbol{\psi}_0 + \xi_0, \tag{1}$$

where $\rho_0 \neq \mathrm{const}$ is the Lagrangian (referential) mass density; $\boldsymbol{\psi}_0$ is the Lagrangian mass flux per unit surface; ξ_0 is the Lagrangian mass supply per unit volume.

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

The balance of linear and angular momentum takes the following form

$$\frac{\partial}{\partial t}(\rho_0 \mathbf{v}) = \mathrm{Div}(\mathbf{FS}) + \rho_0 \mathbf{b}, \tag{2}$$

$$\mathbf{S} = \mathbf{S}^{\mathrm{T}}. \tag{3}$$

where $\mathbf{v} = \partial\boldsymbol{\chi}/\partial t$ is the velocity vector; $\mathbf{b}$ is the body force per unit mass; $\mathbf{S}$ is the 2nd Piola–Kirchhoff stress tensor. Growth and deformation are coupled in the deformation gradient $\mathbf{F} = \partial\boldsymbol{\chi}/\partial\mathbf{X}$. It is worth emphasizing that no distinction is made between growth and purely mechanical deformation. This is in contrast to the 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.

Constitutive equations must be added to the mass and momentum balance. A possible form of these equations is as follows

$$\boldsymbol{\psi}_0(t) = \hat{\boldsymbol{\psi}}_0^{(t)}(\rho_0, \mathrm{Grad}\rho_0, \mathbf{F}, \mathbf{X}), \tag{4}$$

$$\mathbf{S}(t) = \hat{\mathbf{S}}^{(t)}(\rho_0, \mathrm{Grad}\rho_0, \mathbf{F}, \mathbf{X}), \tag{5}$$

$$\xi_0(t) = \hat{\xi}_0^{(t)}(\rho_0, \mathrm{Grad}\rho_0, \mathbf{F}, \mathbf{X}), \tag{6}$$

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 [21], these equations define *simple growing materials*. It is essential that the mass density gradient *must* be included in the constitutive law. Indeed, after substituting (4)–(6) in (1), (2), (3), the system of governing equations is of the second order in spatial derivatives of ρ_0. The latter allows for imposing two boundary conditions on ρ_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 ρ_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 the inconsistency of this kind can be found in [22] within the context of metal plasticity. The requirement of the 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*.

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

$$\boldsymbol{\chi} = \boldsymbol{\chi}^* \in \partial\Omega_{\boldsymbol{\chi}}, \qquad \mathbf{t}_0 = \mathbf{F}\mathbf{S}\mathbf{n}_0 = \mathbf{t}_0^* \in \partial\Omega_{\mathbf{t}}, \qquad \boldsymbol{\chi}(t=0) = \boldsymbol{\chi}^{**} \in \Omega, \qquad \mathbf{v}(t=0) = \mathbf{v}^{**} \in \Omega, \tag{7}$$

where $\mathbf{n}_0$ is a unit normal to the referential boundary surface; $\partial\Omega_{\boldsymbol{\chi}} \cup \partial\Omega_{\mathbf{t}} = \partial\Omega$; $\partial\Omega_{\boldsymbol{\chi}} \cap \partial\Omega_{\mathbf{t}} = 0$. The additional 'growth' conditions can be written as follows

$$\rho_0 = \rho_0^* \in \partial\Omega_\rho, \qquad \phi_0 = \boldsymbol{\psi}_0 \cdot \mathbf{n}_0 = \phi_0^* \in \partial\Omega_\phi, \qquad \rho_0(t=0) = \rho_0^{**} \in \Omega, \tag{8}$$

where $\partial\Omega_\rho \cup \partial\Omega_\phi = \partial\Omega$; $\partial\Omega_\rho \cap \partial\Omega_\phi = 0$. All quantities with the asterisk are given.

Constitutive relations (4)–(6) are not specified yet. It is possible to specify them relying on the Skalak's [14] qualitative idea that growth is analogous to thermal expansion. The physical or biological basis for the analogy between growth and thermal expansion is simple: the increasing number of cells or the newly produced extracellular matrix material tends to expand the occupying volume as the increasing temperature does in structural materials.

It is assumed that (a) the process is quasi-static, i.e. transient behavior and inertia effects are ignored, and (b) deformations are small and body forces are ignored. The first restriction is reasonable because of the very slow growth process. The second restriction suppresses the difference between the Lagrangian and Eulerian descriptions of growth-deformation. Simplifying the notation ($\mathbf{S} = \boldsymbol{\sigma}$, Div = div, $\boldsymbol{\psi}_0 = \boldsymbol{\psi}$, $\xi_0 = \xi$, $\rho_0 = \rho$, Grad = ∇) we have for isotropic materials:

$$\mathrm{div}\boldsymbol{\psi} + \xi = 0, \tag{9}$$

$$\mathrm{div}\boldsymbol{\sigma} = \mathbf{0}, \tag{10}$$

$$\boldsymbol{\sigma} = \lambda \mathrm{tr}(\boldsymbol{\varepsilon})\mathbf{1} + 2\mu\boldsymbol{\varepsilon} - (3\lambda + 2\mu)\alpha\rho\mathbf{1}, \tag{11}$$

$$\boldsymbol{\psi} = \beta\nabla\rho, \tag{12}$$

$$\xi = \omega - \gamma\rho, \tag{13}$$

where $\rho := \rho(\omega) - \rho(0)$; $\boldsymbol{\varepsilon} = (\nabla\mathbf{u} + \nabla\mathbf{u}^{\mathrm{T}})/2$; $\mathbf{u} = \boldsymbol{\chi}(\mathbf{X}) - \mathbf{X}$; λ and μ are the Lame coefficients; $\mathbf{1}$ is the second-order identity tensor.

Increment of *mass supply* $\omega > 0$ is analogous to a quasi-static mechanical load. In contrast to the latter, however, ω is controlled by the tissue itself and its proper determination requires experiments. The dimension of ω 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.

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. The second term on the right-hand side of Eq. (13) 'brakes' mass supply when the density increases. Roughly speaking, the more cells appear the less room remains for the new cells. The dimension of γ is the dimension of ω per a unit of mass density.

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 vector of mass flux 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. (11) is nothing but the thermoelastic generalization of the Hooke's law, and Eq. (12) is just the Fourier law of heat conduction [1]. The constitutive law analogous to Eq. (13), however, is usually absent in thermoelasticity because of the lack of volumetric heat sources. The thermoelastic analogy allows for 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 the changing temperature without directly defining what the heat is. The same is true for the mass flow. We 'feel' it by the changing mass density without directly defining what it is.

It is worth noting that the volumetric mass supply should include stresses or strains on the right-hand side of Eq. (13) when the *adaptive growth* is considered. However, we do not consider this issue in the present work. This allows for the uncoupling of the mass and momentum balance equations. Indeed, substituting Eqs (5) and (6) in Eq. (1) and assuming $\beta =$ constant we have

$$\beta\nabla^2\rho - \gamma\rho + \omega = 0. \qquad (14)$$

Substituting solution of Eq. (14) in Eqs (11) and (9) it is possible to find the deformation characteristics and the corresponding stress field.

3. Results

We examine the proposed theory by considering traction-free radial growth of an infinite cylinder. The inner radius of the cylinder is a and the outer radius is $3a$.

In the case of volumetric growth we assume that material is supplied uniformly $\omega =$ constant, and $\gamma =$ constant, and boundary conditions take the form $\rho(r = a, 3a) = \rho^* = \omega/\gamma$. Solution of Eq. (14) is evident $\rho = \omega/\gamma$. This is the case of the uniform growth. Substituting this solution in Eqs (10)–(11) we get for the displacements and stresses $u = \alpha(1+\nu)r\omega/\gamma$; $\sigma_{rr} = \sigma_{\theta\theta} = 0$ (ν is the Poisson ratio). Thus uniform and traction-free growth does not produce stresses.

In the case of surface growth we assume that material is supplied on the outer surface only: $\omega = 0$; $\rho(r = a) = 0$; $\rho(r = 3a) = \rho^*$. Radial distributions of normalized mass densities, displacements, radial and circumferential stresses: $\bar{\rho} = \rho/\rho^*$; $\bar{u} = u/(\alpha\rho^* a)$; $\bar{\sigma}_{rr} = \sigma_{rr}/(\alpha\rho^* E)$; $\bar{\sigma}_{\theta\theta} = \sigma_{\theta\theta}/(\alpha\rho^* E)$ (E is the elasticity modulus) were computed for the different values of the normalized coefficient of tissue resistance $\tau = \sqrt{\gamma/\beta}$ (Fig. 1). All numerical results were calculated for $\nu = 1/4$. It is important to emphasize that mass densities, displacements, and circumferential stresses localize in a *boundary layer* at $r = 3a$ with increasing τ, while their magnitudes outside the boundary layer tend to zero. This is the surface growth.

4. Conclusions

The problem of establishing a simple analytical framework for modeling growth of living tissues has been addressed. 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 counterpart of this equation is 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 indicates close resemblance between growth and thermal expansion. Examples of volumetric growth of the living cylinder 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. The latter appears as the *boundary layer solution* of governing equations. Thus surface growth may be interpreted as localization of growth in the vicinity of the surface. This finding seems to be of the principle matter

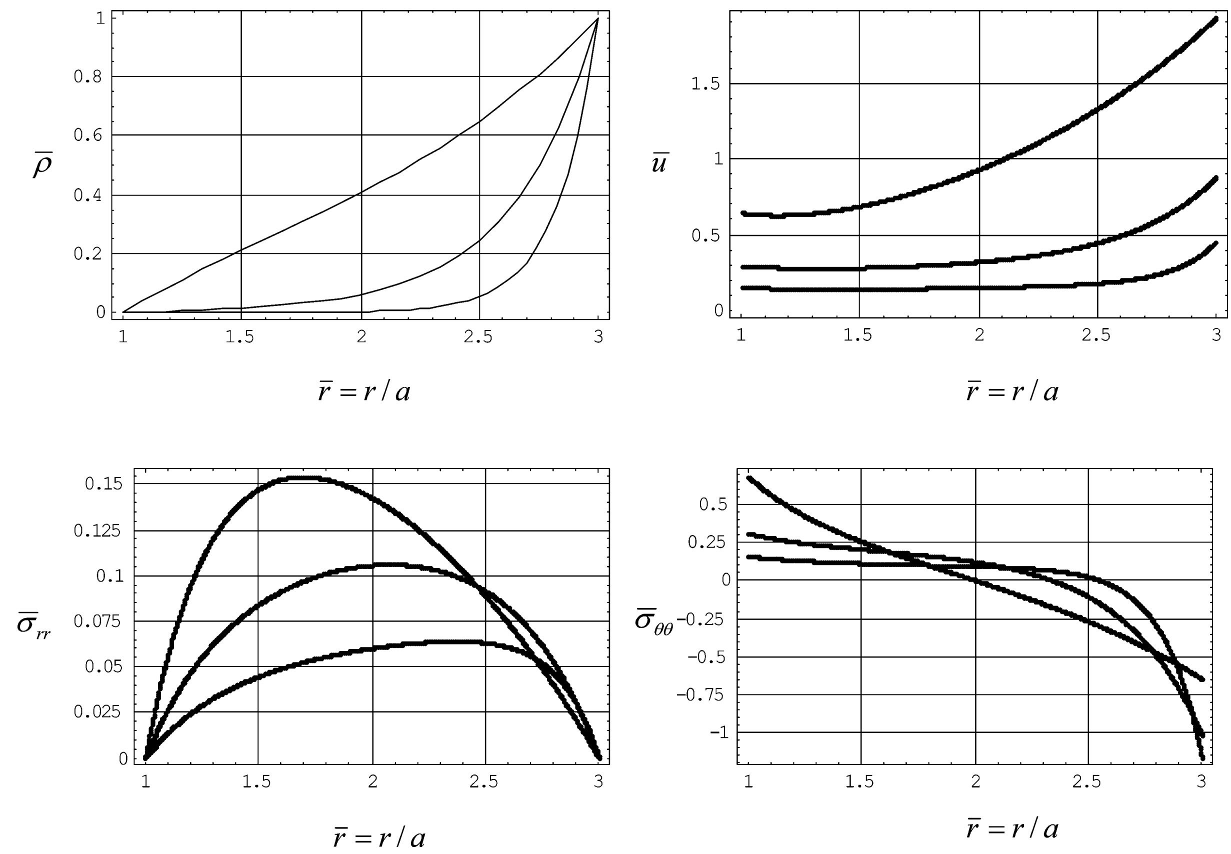

Fig. 1. Surface growth of the cylinder. Normalized density, displacements, radial stresses, and circumferential stresses along normalized radius for different values of the normalized coefficient of tissue resistance $\tau = \sqrt{\gamma/\beta}$. Graphs approach zero with increasing parameter $\tau =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

proving the power of continuum mechanics to treat the phenomenon of surface growth. Traditionally, the description of surface growth is restricted by purely kinematical theories.

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 biological scenarios of the cells' evolution. Such evolution can occur volumetrically or at the surface or following some more complicated scenario. Information about the biological 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 structural materials [5].

Finally, it should be kept in mind that *only physically observable quantities – displacements and mass densities – are used as variables in the mathematical formulation*. Only these quantities should be measured in order to calibrate the theory. Recent developments in computer vision techniques (MRI, PET) [11,20] combined with the noninvasive densitometry (based, for example, on X-ray techniques) will hopefully allow for the calibration of the proposed analytical model.

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