Theoret. Appl. Mech., Vol.32, No.1, pp. 21–38, Belgrade 2005

The role of material inhomogeneities in biological growth

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Abstract

We investigate the influence of the material inhomogeneities that are generated by anisotropic growth on the source of mass acting within a growing living tissue. In order to do that, we need to study the interaction between these material inhomogeneities and the chemical agents dissolved within the tissue. For this purpose, we use some ideas and methods from Condensed Matter Physics (e.g., the Path Integral technique employed in modelling Brownian processes) and apply them to the Continuum Mechanics description of volumetric Growth. We believe that this approach may provide new physical insight into the interactions between the macroscopic dynamics of living systems and the evolution of the subsystems which activate biological processes.

Key words: path integrals, diffusion, vorticity, material inhomogeneities, growth, mass source.

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1 Introduction

A living tissue is said to experience growth when it undergoes a mass variation process [1,2]. Although mass variations can be either positive or negative, only mass production processes will be considered in this paper. The production of mass is permitted by the availability of several chemical substances, and is modulated by the environment [1]. Chemical agents, such as nutrients and growth factors, "feed" cells and take part in chemical reactions, while the environmental factors, such as thermo-mechanical stimuli, influence the macroscopic dynamics of the tissue [1], and interact with chemical constituents. The availability of chemical substances is related to their concentration, and availability varies as they are carried by the interstitial fluid of the tissue [3].

The continuum mechanics description of growth is based on the existence of a source of mass within the tissue. When growth is viewed as a merely thermo-mechanical phenomenon (i.e., chemical agents are not explicitly considered), the mass source is assumed to be a smooth field that can be determined by self-consistent equations involving mechanical factors [4,5]. On the other hand, when chemical agents are explicitly taken into account, the mass source is given as a functional of mechanical variables, and the concentration of chemical substances [6-8]. For this case, the model of growth is formulated as a boundary-value-problem in which the evolution of each chemical constituent is described by a reaction-advection-diffusion equation [8]. In each equation of this type, the interaction between the diffusive process and the motion of the medium in which the constituent is dissolved is described by the *drift* term, qv_d, where q is the concentration of the substance, and v_d is the drift velocity.

In the biological context, the transport of chemical factors is expected to be mainly due to diffusion rather than drift because the ratio between $\| qv_d \|$ and the amplitude of the Fickean-type current, $\| D\nabla q \|$ (here, D denotes the diffusion coefficient), is usually small in living tissues (the ratio $Pe = \| qv_d \| / \| D\nabla q \|$ is said to be the *Peclét* number). Therefore, the drift term may be neglected without compromising the results. However, the drift term should be considered when the model of growth contains a continuum mechanics description of the tissue that is linked with the study of the evolving subsystems within the whole tissue de-

scription (i.e., chemical substances).

Following Epstein and Maugin [4], we would like to show how the material inhomogeneities produced by growth influence the source of mass through the action that they exert on the concentration of the chemical constituents. For this purpose, we investigate the case of *anisotropic* growth, and consider only nutrient factors among the chemical constituents [3,7]. Our approach is based on the theory reported in the article by Moffatt [9] which we adapt to the current problem (cfr. Section 2). In Ref.[9], the effect of vorticity on the diffusion of a generic physical quantity (e.g., a heat-spot) carried by a fluid in turbulent flow ($Pe \gg 1$) is presented. Although we deal with the opposite physical situation (i.e., $Pe \ll 1$), the presence of a *vorticity field* in the tissue suggested us to undertake the treatment of growth presented in this paper.

We base our work on the following two considerations:

(i) the mass source intensity increases in regions where the availability of nutrients is high;

(ii) the nutrient concentration is given by the *probability* density distribution for nutrient particles to occupy a certain point of the tissue at a given instant of time.

Since we expect that cells can be "fed" more easily when nutrients are permitted to move within a confined region of the tissue, we associate the concept of "availability of nutrients" with the *return* probability, i.e. the probability density distribution for a nutrient particle to return to the point from which it originated at some previous instant in time.

If we apply the Path Integral method [10] to the formal calculation of nutrient concentrations (cfr. Section 2), we notice that the return probability is enhanced by the drift velocity if, and only if, v_d is associated with a *vorticity*, i.e. $\omega_d = \nabla \times v_d \neq 0$. If we invoke Stokes Theorem, and apply the multiplicative decomposition of the deformation gradient tensor [4] (cfr. Section 3), we can determine the vorticity flux caused by the production of material inhomogeneities. Since the vorticity flux can be viewed as the correction to the return probability of nutrients in the absence of a material anisotropy source (i.e., anisotropic growth), we interpret it as the "modulation" exerted by material inhomogeneities on the source of mass (cfr. Section 4).

The particular attention devoted to anisotropic growth is motivated by the necessity of studying growth in anisotropic materials of biomechanical interest (a general thermo-mechanical constitutive theory of growth for anisotropic biomaterials has been presented by Lubarda and Hoger [11]). On the basis of the works by Federico *et al.* [12,13], our long-term-goal is to investigate the interaction of growth with the internal micro-structure of anisotropic biological composites (such as articular cartilage), and to test the possibility of modulating anisotropic growth with external electromagnetic fields.

2 The evolution of chemical substances

In this Section, all physical quantities are assumed to be described in the Eulerian framework, i.e., current configuration of the tissue.

Nutrients can be modelled as a system with a large number of identical, non-interacting Brownian particles which diffuse throughout the tissue [14]. Assuming a constant diffusivity, D, the evolution of these particles is described by the reaction-advection-diffusion equation [15,10,14]

$$\partial_t q + \nabla \cdot (q v_d) = D \nabla^2 q - A q, \tag{2.1}$$

where, $q(t,x)$ is the concentration of nutrients, $v_d(t,x)$ is the *drift* velocity, i.e. the velocity of the medium in which the Brownian particles are dissolved, and $A(t,x)$ is the annihilation rate [16,6], i.e. the probability per unit time for the Brownian particle to be absorbed by the tissue.

When Eq.(2.1) is applied to particles evolving in a region sufficiently far from boundaries, a formal solution can be found by using the *Path Integral* method proposed by Wiener [10]. By applying the transformation [17,10]

$$q = f \exp(\lambda), \quad \lambda(t,x) = \frac{1}{2D} \int_{\mathcal{C}(x_0,x)} v_d(t,\xi) \cdot d\xi, \tag{2.2}$$

where $\mathcal{C}(x_0,x)$ is an open line connecting points x_0 and x, Eq.(2.2) becomes

$$\partial_t f = D \nabla^2 f - (\Psi + \partial_t \lambda) f, \tag{2.3}$$

where

$$\Psi = \frac{1}{4D} \parallel v_d \parallel^2 + \frac{1}{2} \nabla \cdot v_d + A. \tag{2.4}$$

By requiring f to satisfy the initial condition $f(t_0, x) = f_0\delta(x - x_0)$ (δ is the Dirac's *delta* distribution centred at x_0), the formal solution to Eq.(2.3) is the *path integral* [10]

$$\mathcal{F}(t, x, t_0, x_0) = \int_{(t_0,x_0)}^{(t,x)} \mathcal{D}z \ \exp\left\{-\frac{1}{4D}\int_{t_0}^{t} \parallel \dot{z}(s) \parallel^2 ds - \right.$$

$$\left. \int_{t_0}^{t} [\Psi(s, z(s)) + \partial_t\lambda(s, z(s))]ds \right\}. \tag{2.5}$$

This quantity coincides with the Green's function associated with the differential equation (2.3). The symbol $\mathcal{D}z$ denotes the summation over all possible paths according to Wiener's measure [18,19], and z is the parameterisation of the generic path followed by the Brownian particle. By noting that $\lambda(t_0, x_0) = 0$, introducing the notation

$$\mathcal{H}(s, z(s), \dot{z}(s)) = \frac{1}{4D} \parallel \dot{z}(s) \parallel^2 + \Psi(s, z(s)), \tag{2.6}$$

and

$$H(t, t_0, z) = \int_{t_0}^{t} \mathcal{H}(s, z(s), \dot{z}(s))ds, \tag{2.7}$$

and applying Eqs.(2.2) and (2.5), it can be shown that the concentration of nutrients, $q(t, x)$, coincides with Green's function

$$\mathcal{Q}(t, x, t_0, x_0) = \int_{(t_0,x_0)}^{(t,x)} \mathcal{D}z \ \exp\{-H(t, t_0, z) + \right.$$

$$\left. \frac{1}{2D}\int_{t_0}^{t} v_d(s, z(s)) \cdot \dot{z}(s)ds \right\}. \tag{2.8}$$

Here, z is such that $x_0 = z(t_0)$ and $x = z(t)$, and the quantity

$$\mathcal{W}(t, t_0, z) = \exp\{-H(t, t_0, z) + \frac{1}{2D}\int_{t_0}^{t} v_d(s, z(s)) \cdot \dot{z}(s)ds\} \tag{2.9}$$

is the probability density functional for the particle to follow the specific trajectory, z.

If we postulate the existence of a characteristic time-scale such that the drift velocity, v_d, can be regarded as stationary with respect to the evolution of the Brownian particle, Eq.(2.8) can be rewritten as

$$\mathcal{Q}(t,x,t_0,x_0)=\int_{(t_0,x_0)}^{(t,x)}\mathcal{D}z\ \exp\{-H(t,t_0,z)+\frac{1}{2D}\int_{\Gamma(x_0,x)}v_d(y)\cdot dy\}, \tag{2.10}$$

where $\Gamma(x_0,x)$ is the generic path parameterised by z. The quantity $\mathcal{Q}(t,x,t_0,x_0)$ gives the probability density distribution for the Brownian particle released from x_0 at time t_0 to be found at x at time t. The *return* probability density distribution, i.e. the probability for the same particle to return to x_0 at a certain time $t>t_0$, can be found by computing Eq.(2.10) for $x=x_0$, and summing over all closed paths, C_t, passing through x, i.e.

$$\mathcal{Q}(t,x,t_0,x)=\int_{(t_0,x)}^{(t,x)}\mathcal{D}z\ \exp\{-H(t,t_0,z)+\frac{1}{2D}\int_{C_t}v_d(y)\cdot dy\}. \tag{2.11}$$

In this equation, the line integral on the right-hand-side is nonzero if, and only if, the drift velocity is such that $\omega_d=\nabla\times v_d\neq 0$. If we assume that this is the case, then the drift velocity contributes to the path integral (2.11) through the non-vanishing integral $\frac{1}{2D}\int_{C_t}v_d(y)\cdot dy$, and, consequently, affects the probability for the particle to be found at the same place from which it was emitted.

3 Determination of the elastic and growth vorticity fluxes in a growing elastic continuum

Although the Theory of Mixtures [20,21] has been adopted by some scientists to model the mechanics of biological growth [22-25], for the sake of simplicity we assume here that all nutrients evolve within a monophasic continuum. For this specific case, the drift velocity, v_d, coincides with the velocity of the body, v [3,26].

We further assume that growth is isochoric, i.e. $\nabla\cdot v=0$ [11]. This assumption enables us to rewrite Ψ, as $\Psi=\frac{1}{4D}\parallel v\parallel^2+A$.

By denoting with $\chi(t,\cdot) : \mathcal{B}_R \to \mathcal{B}(t)$ the smooth motion which maps the reference configuration of the body $\mathcal{B}_R$, onto the portion of the three-dimensional Euclidean space E, occupied by the body at time t, $\mathcal{B}(t)$, the velocity field is such that $v(t,x) = (\partial_t \chi)(t,X)$, $\forall x \in \mathcal{B}(t)$, and $\forall X \in \mathcal{B}_R$. If v is assumed to be stationary with respect to the characteristic diffusion time-scale, the application of Stokes' Theorem to the line integral in Eq.(2.11) leads to the following expression

$$\frac{1}{2D}\int_{C(t)} v(x)\cdot dx = \frac{1}{2D}\int_{\Sigma(t)} (\omega\cdot n)(x)da = \frac{1}{2D}\int_{\Sigma_R} (\Omega\cdot N)(t,X)d\mathcal{A}, \tag{3.1}$$

where $\Sigma(t)$ is an open material surface contoured by the closed line $C(t)$, $\Sigma_R = \chi^{-1}(t,\Sigma(t))$ is the corresponding surface in $\mathcal{B}_R$, n and N are the unit vectors normal to $\Sigma(t)$ and Σ_R, respectively, the material vector $\Omega = JF^{-1}\hat{\omega}$ is the Piola transformation of $\hat{\omega} = \omega \circ \chi$ (from here on, the symbol "$\hat{}$" denotes the composition $\hat{\varphi}(t,\cdot) = \varphi(t,\cdot)\circ\chi(t,\cdot)$, for any physical quantity φ), and J is the determinant of the deformation gradient tensor, $F = \nabla_R \chi$ (the symbol ∇_R denotes differentiation with respect to referential coordinates).

By denoting with $L = \nabla v$, and $W = skew(L)$ the velocity gradient tensor, and the *spin* tensor, respectively, and using the linear application, $\tau : skew(E) \to E$, from the space of skew-symmetric tensors onto E, such that $\hat{\omega} = \tau(\hat{W})$ [27], Eq.(3.1) can be rearranged as

$$\frac{1}{2D}\int_{C(t)} v(x)\cdot dx = \frac{1}{2D}\int_{\Sigma_R} [JF^{-1}\tau(\hat{W})\cdot N](t,X)d\mathcal{A}. \tag{3.2}$$

Hereafter, we assume that the multiplicative decomposition $F = F_{el}G$ holds true. This decomposition is based on the introduction of an *elastically released configuration*, $\mathcal{B}_G$, which is obtained by applying the linear map G, to the tangent space, $T_X\mathcal{B}_R$, of $\mathcal{B}_R$, for any $X \in \mathcal{B}_R$ [28]. In $\mathcal{B}_G$, each material point of the elastic body is assumed to attain a stress-free state (see Ref.[16], and references therein). Here, F_{el} and G are two smooth, but not necessarily integrable, tensor fields which measure the elastic deformation, and the anelastic effects related to growth, respectively. In the following, G will represent the growth tensor. Basing on

the introduced composition, the velocity gradient reads $\hat{L} \equiv (\partial_t F)F^{-1} = L_{el} + \Lambda_G$, where $L_{el} = (\partial_t F_{el})F_{el}^{-1}$, $\Lambda_G = F_{el}L_G F_{el}^{-1}$, and $L_G = (\partial_t G)G^{-1}$ (L_G represents the growth velocity gradient). Accordingly, the global spin tensor $\hat{W}$ writes as the sum of an elastic term and a term due to growth, respectively. More specifically, $\hat{W} = W_{el} + W_G$, where $W_{el} = skew(L_{el})$ and $W_G = skew(\Lambda_G)$.

By taking into account the additive decomposition for $\hat{W}$, Eq.(3.2) becomes

$$\int_{C_t} v(x) \cdot dx = \int_{\Sigma_R} [JF^{-1}\tau(W_{el}) \cdot N](t, X)d\mathcal{A} + \\ + \int_{\Sigma_R} [J(F^{-1})\tau(W_G) \cdot N](t, X)d\mathcal{A}. \tag{3.3}$$

Equation (3.3) states that the global vorticity flux of the system, Φ, can be written as

$$\Phi = \int_{C_t} v(x) \cdot dx = \Phi_{el} + \Phi_G, \tag{3.4}$$

where the elastic and growth vorticity fluxes are defined by

$$\Phi_{el} = \int_{\Sigma_R} [JF^{-1}\tau(W_{el}) \cdot N](t, X)d\mathcal{A},$$

$$\Phi_G = \int_{\Sigma_R} [JF^{-1}\tau(W_G) \cdot N](t, X)d\mathcal{A}, \tag{3.5}$$

respectively. Note that the condition $\Phi_G \neq 0$ is satisfied if, and only if, $W_G = skew(\Lambda_G) \neq 0$.

Remark

For biphasic mixtures, nutrients are carried by the fluid-phase. In this case, the drift velocity, v_f, coincides with the fluid-phase velocity such that

$$v_f(t, x) = v_S(t, x) + F_S(t, X)w_f(t, X), \tag{3.6}$$

where v_S is the porous solid velocity, F_S is the solid-phase deformation gradient tensor, and w_f is the *filtration velocity* [22]. By substituting Eq.(3.6) into Eq.(3.3), we note that there might be another source of vorticity due to w_f. Since the filtration velocity can be expressed as the

product of the fluid-phase *permeability tensor* $\mathcal{P}$, and the thermodynamic driving force $\Im$ [23,25] (this is a generalization of Darcy's law for a fluid filtrating through a porous solid medium), the vorticity produced by w_f is essentially due to the form of the constitutive law, rather than the generation of material inhomogeneities. For this reason, considering a mono-phasic system is not associated with any loss of generality.

4 The role of vorticity on the source of mass

In the presence of growth, the local form of the mass balance law in the reference configuration of the body, $\mathcal{B}_R$, is given by [4]

$$\partial_t \rho_R = \Gamma_R - \nabla_R \cdot M, \tag{4.1}$$

where $\rho_R = J\hat{\rho}$, $\Gamma_R = J\hat{\Gamma}$, and $M = JF^{-1}\hat{m}$ are the Piola transformations of the mass density $\hat{\rho}$, the mass source $\hat{\Gamma}$, and the mass flux vector $\hat{m}$, respectively.

By virtue of the decomposition $F = F_{el}G$, the determinant of the deformation gradient tensor can be written as $J = J_{el}J_G$ (where $J_G = \det(G)$), and the referential mass density becomes $\rho_R = J_{el}J_G\hat{\rho}$. By introducing the quantity $\rho_G = J_{el}\hat{\rho}$, we obtain that $\rho_R = J_G\rho_G$. Since the process of growth is assumed to "bring" $\mathcal{B}_R$ into $\mathcal{B}_G$, ρ_G cannot depend on time [3,4]. Consequently, the time derivative of ρ_R must be entirely compensated for by the time variation of J_G. Since $\partial_t J_G = J_G tr(L_G)$, we find that [3,4]

$$\partial_t \rho_R = tr(L_G)\rho_R. \tag{4.2}$$

If the mass flux vector, M, is assumed to be identically zero (this condition is automatically satisfied within a first-order constitutive framework [4]), the substitution of Eq.(4.2) into Eq.(4.1) yields [3,4]

$$\Gamma_R = tr(L_G)\rho_R. \tag{4.3}$$

By denoting with $L_G^{(h)}$ and $L_G^{(d)}$ the hydrostatic and deviatoric part of the growth velocity gradient, respectively, Eq.(4.3) can be rearranged as $\Gamma_R = tr(L_G^{(h)})\rho_R$. This remark infers that, even though growth is

anisotropic, only $L_G^{(h)}$ contributes to Eq.(4.3), while $L_G^{(d)}$ has no influence on the mass source, Γ_R. This is consistent with the suggested assumption on the mass source as long as the action of chemical agents is disregarded. The growth tensor G can be then considered as an internal variable [16] that depends on mechanical factors only similarly to the case of the transplant operator K^{-1} introduced in Ref. [4,29]. For example, within a first-order thermo-mechanical constitutive theory, Epstein and Maugin [4] showed how uniformity and material invariance requirements led to the evolution equation

$$\mathbf{R}(L_G, b_G, C_{el}, \partial_t C_{el}) = 0, \tag{4.4}$$

where $C_{el} = F_{el}^T F_{el}$, $b_G = J_G^{-1} G b G^{-1}$, and b is the Eshelby tensor, i.e., the driving force acting on the material inhomogeneities generated by growth [30].

However, when biochemical aspects of growth are included, the concentration of chemical substances must be given in Eq.(4.4). If we further assume that the evolution law is given by a set of equations, which define the components of the growth velocity gradient L_G as functionals of the mechanical and chemical variables, we may write

$$L^{\alpha}_{G_\beta} = \mathcal{L}^{\alpha}_{G_\beta}(\eta, C_{el}, \partial_t C_{el}, b_G, \hat{q}), \tag{4.5}$$

where $L^{\alpha}_{G_\beta}$ are the components of L_G in $\mathcal{B}_G$, $\hat{q}(t, X) = q(t, x)$ is the concentration of nutrients, and $\eta : \mathcal{I} \times \mathcal{B}_R \to \mathcal{I} \times \mathcal{B}_R$ is the identity map ($\mathcal{I}$ is an interval of time), i.e. $\eta(t, X) = (t, X)$.

By substituting Eq.(4.5) into Eq.(4.4), and introducing the functional $\mathcal{T}_G = tr(\mathcal{L}_G)$, Eqs.(4.2) and (4.3) become

$$\partial_t \rho_R = \Gamma_R = \mathcal{T}_G(\eta, C_{el}, \partial_t C_{el}, b_G, \hat{q})\rho_R. \tag{4.6}$$

Equation (4.6) prescribes that the mass source is determined by the concentration of nutrients, q, and the mechanical variables, C_{el} and b_G. Moreover, since q is coupled with the body velocity, v, through the drift term, qv, the source of mass is also influenced indirectly by the body dynamics.

By virtue of Eqs.(2.11) and (3.5), and the identity $q(t, x) = \mathcal{Q}(t, x, t_0, x)$, we can rewrite Eq.(4.6) as

$$\partial_t \rho_R = \Gamma_R = \mathcal{T}_G(\eta, C_{el}, \partial_t C_{el}, b_G, \hat{\mathcal{Q}})\rho_R, \tag{4.7}$$

where

$$\mathcal{Q}(t,x,t_0,x)=\int_{(t_0,x)}^{(t,x)}\mathcal{D}z\left[e^{-H_0(t,t_0,z)+\frac{1}{2D}\Phi_G}\right],$$

and

$$H_0(t,t_0,z)=H(t,t_0,z)-\frac{1}{2D}\Phi_{el}.$$

In order to estimate the effect of Φ_G on Γ_R, we write $\mathcal{Q}(t,x,t_0,x)$ as

$$\mathcal{Q}(t,x,t_0,x)=\int_{(t_0,x)}^{(t,x)}\mathcal{D}z\ \left[e^{-H_0(t,t_0,z)}e^{\frac{1}{2D}\Phi_G}\right]=$$

$$\int_{(t_0,x)}^{(t,x)}\mathcal{D}z\ e^{-H_0(t,t_0,z)}+\int_{(t_0,x)}^{(t,x)}\mathcal{D}z\ \left\{e^{-H_0(t,t_0,z)}\left[e^{\frac{1}{2D}\Phi_G}-1\right]\right\}=$$

$$\mathcal{Q}_0(t,x,t_0,x)+\mathcal{Q}_1(t,x,t_0,x), \tag{4.8}$$

where

$$\mathcal{Q}_0(t,x,t_0,x)=\int_{(t_0,x)}^{(t,x)}\mathcal{D}z e^{-H_0(t,t_0,z)},$$

and

$$\mathcal{Q}_1(t,x,t_0,x)=\int_{(t_0,x)}^{(t,x)}\mathcal{D}z\{e^{-H_0(t,t_0,z)}[e^{\frac{1}{2D}\Phi_G}-1]\}.$$

By performing the Taylor expansion

$$\mathcal{T}_G(\eta,C_{el},\partial_t C_{el},b_G,\hat{\mathcal{Q}})=\mathcal{T}_G(\eta,C_{el},\partial_t C_{el},b_G,\hat{\mathcal{Q}}_0)+$$

$$+\sum\nolimits_{n=1}^{\infty}\frac{1}{n!}\left[\frac{\partial^n\mathcal{T}_G}{\partial\hat{\mathcal{Q}}^n}(\eta,C_{el},\partial_t C_{el},b_G,\hat{\mathcal{Q}}_0)\right](\hat{\mathcal{Q}}_1)^n, \tag{4.9}$$

and introducing the notation

$$\mathcal{T}_G(\eta, C_{el}, \partial_t C_{el}, b_G, \hat{\mathcal{Q}}) = T_G, \quad \mathcal{T}_G(\eta, C_{el}, \partial_t C_{el}, b_G, \hat{\mathcal{Q}}_0) = T_G^{(0)},$$

and

$$\sum\nolimits_{n=1}^{\infty} \frac{1}{n!}[\frac{\partial^n \mathcal{T}_G}{\partial \hat{\mathcal{Q}}^n}(\eta, C_{el}, \partial_t C_{el}, b_G, \hat{\mathcal{Q}}_0)](\hat{\mathcal{Q}}_1)^n = T_G^{(1)},$$

Eq.(4.7) becomes

$$\partial_t \rho_R = \Gamma_R = [T_G^{(0)} + T_G^{(1)}]\rho_R. \tag{4.10}$$

The integration of Eq.(4.10) permits to express the source of mass as

$$\Gamma_R(t,X) = [T_G^{(0)}(t,X) + T_G^{(1)}(t,X)]e^{\int_0^t T_G^{(0)}(s,X)ds} e^{\int_0^t T_G^{(1)}(s,X)ds} \rho_R(0,X) =$$

$$= T_G^{(0)}(t,X) e^{\int_0^t T_G^{(0)}(s,X)ds} \rho_R(0,X) \left[1 + \frac{T_G^{(1)}(t,X)}{T_G^{(0)}(t,X)}\right] e^{\int_0^t T_G^{(1)}(s,X)ds}. \tag{4.11}$$

By denoting with $\Gamma_R^{(0)}(t,X)$ the source of mass in the absence of the inhomogeneity-vorticity-flux, we obtain

$$\Gamma_R^{(0)}(t,X) = T_G^{(0)}(t,X) e^{\int_0^t T_G^{(0)}(s,X)ds} \rho_R(0,X), \tag{4.12}$$

and Eq.(4.11) can therefore be rewritten as

$$\Gamma_R(t,X) = \Gamma_R^{(0)}(t,X) \left[1 + \frac{T_G^{(1)}(t,X)}{T_G^{(0)}(t,X)}\right] e^{\int_0^t T_G^{(1)}(s,X)ds}. \tag{4.13}$$

This result can be manipulated to obtain the dimensionless expression

$$\frac{\Gamma_R(t,X) - \Gamma_R^{(0)}(t,X)}{\Gamma_R^{(0)}(t,X)} = \left[1 + \frac{T_G^{(1)}(t,X)}{T_G^{(0)}(t,X)}\right] e^{\int_0^t T_G^{(1)}(s,X)ds} - 1. \tag{4.14}$$

This formula expresses the *normalized* variation of the mass source in the presence of the inhomogeneity-vorticity-flux, i.e., it singles out the contribution of the anisotropy of the growth tensor to $\Gamma_R(t,X)$.

Although Eq.(4.14) shows how anisotropic growth may enhance the intensity of the mass source acting within the body, it should be noted that the kinematic constraint $\Gamma_R = tr(L_G)\rho_R$ is not violated because the constraint derives from the general theory of growth kinematics which merely requires that the mass source magnitude must be coherently varying with the magnitude of $\partial_t J_G = tr(L_G)$. Therefore, we conclude that the mass source is instantaneously rearranged as new inhomogeneities evolve in the system.

We note that, in the limit $\frac{1}{2D}\Phi_G << 1$, $\mathcal{Q}(t, x, t_0, x)$ (cfr. Eq.(4.8)) can be approximated by the first-order expression

$$\mathcal{Q}(t, x, t_0, x) \approx \int_{(t_0,x)}^{(t,x)} \mathcal{D}z \ \left[e^{-H_0(t,t_0,z)}(1 + \frac{1}{2D}\Phi_G) \right] =$$

$$= \int_{(t_0,x)}^{(t,x)} \mathcal{D}z \ e^{-H_0(t,t_0,z)} + \int_{(t_0,x)}^{(t,x)} \mathcal{D}z \ \left[e^{-H_0(t,t_0,z)} \frac{1}{2D}\Phi_G \right]. \qquad (4.15)$$

Since, in the absence of Φ_G, $\mathcal{W}_0(t, t_0, z) = e^{-H_0(t,t_0,z)}$ is the probability density functional of nutrients, and $\mathcal{Q}_0(t, x, t_0, x) = \int_{(t_0,x)}^{(t,x)} \mathcal{D}z \ \mathcal{W}(t, t_0, z)$ is the corresponding *return* probability density distribution, the quantity

$$\mathcal{R}(t, t_0, x) = \left\langle \frac{1}{2D}\Phi_G(t, t_0, x) \right\rangle = \frac{1}{2D} \int_{(t_0,x)}^{(t,x)} \mathcal{D}z \ \left[\mathcal{W}(t, t_0, z)\Phi_G \right], \quad (4.16)$$

can be taken as the *average* of Φ_G (with respect to $\mathcal{W}_0(t, t_0, z)$) *over all paths*, and can be identified with the correlation function of the inhomogeneity–vorticity–flux. Therefore, we can give $\mathcal{Q}(t, x, t_0, x)$ the approximate expression

$$\mathcal{Q}(t, x, t_0, x) = \mathcal{Q}_0(t, x, t_0, x) + \mathcal{R}(t, t_0, x), \qquad (4.17)$$

and Eq.(4.14) becomes

$$\frac{\Gamma_R(t, X) - \Gamma_R^{(0)}(t, X)}{\Gamma_R^{(0)}(t, X)} =$$

$$\left[1 + \frac{\Xi(t, X)\hat{\mathcal{R}}(t, t_0, X)}{T_G^{(0)}(t, X)} \right] e^{\int_0^t \Xi(t,X)\hat{\mathcal{R}}(t,t_0,X)ds} - 1, \qquad (4.18)$$

where $\frac{\partial \mathcal{T}_G}{\partial \hat{\mathcal{Q}}}(\eta, C_{el}, \partial_t C_{el}, b_G, \hat{\mathcal{Q}}_0) = \Xi$. By virtue of Eq.(4.18), we conclude that, in the limit $\frac{1}{2D}\Phi_G << 1$, the first-order non-dimensional expression of the inhomogeneity-induced mass source "modulation" is *driven* by the time correlation function of the inhomogeneity-vorticity-flux.

5 Conclusions

We showed how, in the presence of anisotropic growth, the source of mass acting within a tissue, Γ_R, is "modulated" by Φ_G: the vorticity flux due to the production of material inhomogeneities (cfr. Eq.(4.14)). Such a modulation occurs through the rearrangement of the source of mass as new material is anisotropically inserted into the tissue. This result may be interpreted as a "self-interaction" between material inhomogeneities and the source that produced them. In order to observe this effect, we enlisted the concentration of nutrients, q, among the variables which determine Γ_R (cfr. Eq.(4.6)), and showed how the availability of these substances is enhanced by the presence of the non-vanishing spin tensor, $\hat{W}$ (cfr. Section 2). Since $\hat{W}$ can be written as $\hat{W} = W_{el} + W_G$ (cfr. Section 3), the global vorticity of the system consists of an elastic contribution, W_{el}, and a contribution due to growth, W_G. The presence of the latter term can be explained by realizing that the material inhomogeneities produced by anisotropic growth act as a *source* of vorticity for the system.

We believe that the study of the interactions between the motion of nutrients (modelled as Brownian particles) and the tissue dynamics may lead to some interesting analogies with Solid State Physics (e.g., the Theory of Berry's phases as treated in [31,32]). For example, Brownian particles "feel" the vorticity flux, Φ_G, as a potential which tends to deflect their trajectories by imprinting a rotational motion. This behaviour is remnant of the effect exerted by defects on electronic dynamics in solids. Moreover, the result reported in Eq.(4.14) seems to evoke the phenomenon of "mass renormalization", i.e. the effect which is encountered in Solid State Physics when the "fully-dressed" Green's function for a particle propagating in a solid medium can be expressed in terms of a "self-energy" part (e.g., cfr. [33]).

The physical picture presented in this paper can also be described in terms of material symmetries [34]. In particular, by interpreting growth as the "breaking" of the body material symmetries [35], and retrieving the material balance laws with a Noether-like approach [35,36], the production of vorticity can be related to the unbalance of material angular momentum due to the generation of anisotropy.

If the body is assumed to be isotropic prior to growth, then the anisotropy of the growth tensor, G, *breaks* the body's rotational symmetry and brings it into an anisotropic "state". If, however, the body is anisotropic at the start, then its "degree" of anisotropy is changed by growth. In both cases, this process is reflected by the presence of the flux Φ_G, and implies a rearrangement of the mass source as shown in Eq.(4.14).

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Submitted on May 2005, revised on September 2005.

Uloga materijalnih nesavršenosti u biološkom rastu

UDK 531.01

Istražuje se uticaj materijalnih nesavršenosti usled anizotropnog rasta na izvor mase koji deluje unutar rastućeg živog tkiva. Za ovo je potrebno da proučimo medjudejstvo ovih materijalnih nesavršenosti i hemijskih agenata rastvorenih unutar tkiva. U tu svrhu koristimo neke ideje i metode iz fizike kondenzovane materije (recimo tehniku inegrala zavisnog od puta koja se primenjuje u modeliranju Braunovskih procesa) te ih primenjujemo na opis zapreminskog rasta koji se koristi u mehanici kontinuuma. Autori smatraju da ovakav pristup može ostvariti novo fizičko sagledavanje medjudejstava makroskopske dinamike živih sistema i razvoja podsistema koji biološke procese aktiviraju.