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**Mini-Workshop: The mathematics of growth and remodelling of soft biological tissues**

Organised by

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ABSTRACT. Biology is becoming one of the most attractive fields of application of mathematics. The discoveries that have characterized the biological sciences in the last decades have become the most fertile matter for application of classical mathematical methods, while they offer a natural environment where new theoretical questions arise. Mathematical Biology has born many years ago and has developed along directions that now constitute its traditional background: population dynamics and reaction–diffusion equations. Nowadays Mathematical Biology is differentiating into several branches, essentially depending on the specific spatial scale size under consideration: molecular scale, i.e., DNA transcription, protein folding and cascades, cellular scale, i.e., motility, aggregation and morphogenesis, and macroscale, i.e., tissue mechanics. Currently one of the most attractive scientific topics is the mathematics of growth and remodelling of soft biological tissues. This area, located at the crossroads of biology, mathematics and continuum mechanics, concerns the statement and analysis of the equations that characterize the mechanics, growth and remodelling of systems like arteries, tumors and ligaments, studied at the macroscopic scale. These are open continuous systems that pose new challenging questions, which go beyond the standard mechanics that is traditionally devoted to closed systems. Past initiatives in Oberwolfach have been devoted to the interaction between biology and mathematics in a broad sense. The idea to this minisymposium is to bring together established researchers on this topic with newer entrants to the field and initiate discussion on established and novel approaches towards the mathematics of growth and remodelling of soft biological tissues.

## Introduction by the Organisers

One of the most challenging fields of applied mathematics and mechanics is the Mechanics of Biology, a well-recognized and rapidly-expanding subject that is a fundamentally interdisciplinary science. In contrast to engineering structures, living organisms show the remarkable ability to change not only their geometry, but also their internal architecture and their material properties in response to environmental changes. Mechanics of Biology provides a number of fascinating new areas of theoretical development, yet with clear applications, such as the functional adaptation of hard tissues, healing of fracture in bones, wound healing of the epidermis, regeneration of microdamaged muscles, general repair processes of the cardiovascular system and the wide area of cancer research related to tumour growth to name but a few.

Development of soft biological tissues is usually termed as growth and remodelling. Here, growth will imply changes in mass, while remodelling will be reserved for processes in which the tissue alters its microstructure while its mass remains constant. Biological tissues undergoing growth and remodelling involve the strong coupling of physical quantities and equations governing several distinct types of physics: mass transport, chemical reactions, mechanics, charge transport, and heat transport to name the most prominent ones. They therefore meet the definition of complex systems. Growth involves chemically- and physically-distinct species that exchange mass, momentum and energy among themselves and with external reservoirs. A growing tissue is therefore an open system. A remodelling tissue undergoes a change in its underlying geometric structure. In the language of continuum mechanics, it demonstrates an evolving reference configuration. Specific outstanding issues arising from this mathematical richness of soft tissue growth and remodelling are summarized in what follows.

### **Kinematics of growth**

Since hard tissues typically undergo small deformations and behave nearly elastically in the range of interest, the first rigorous mathematical models for biological tissues that were introduced in the mid 70s were restricted to growth of hard tissues such as bones. It was only in the mid 90s, that geometrically exact models for soft tissues were derived which also addressed the aspect of residual stress. The key idea draws upon the central idea of finite strain plasticity by decomposing the deformation gradient into an inelastic, growth tensor, and an elastic tensor. Both these tensors admit the interpretation of tangent maps. Similar to the kinematic decomposition employed in modelling plastic deformation, the elastic tensor is conjugate to the tissue stress via a potential defined by the strain energy density. The growth tensor, in loose analogy to the plastic strain, translates the growth/resorption of the solid phase or change in density of the fluid phase to kinematic terms. Much work remains to be done on defining the constitutive relation for the rate of the growth tensor and exploring its implications for the physics of growth. The local nature of the growth-elastic decomposition inherently leads to a residual stress. The presence of residual stress in a body poses

several questions. One regards stability and has been recently investigated by Ben Amar and Goriely [2005]. They analyze the stability of a grown neo-Hookean incompressible spherical shell under external pressure. The importance of residual stress is established by showing that under large anisotropic growth a spherical shell can become spontaneously unstable without any external loading.

### **Theory of open systems**

Growth and resorption of soft biological tissue such as muscles, arteries, ligaments, tendons and skin takes place as a result of volumetric mass sources and mass flux. This is in contrast to hard tissue which demonstrates only surface growth. The earliest models such as Cowin's [1976] theory of "adaptive elasticity" treated growth as a single species problem. This single species theory which is now recognized as open system thermodynamics allows for a local variation in mass. Mathematically, this variation manifests itself in additional source and flux terms in the balance of mass. The derivation of open system balance laws for mass, linear and angular momentum and energy then leads to the conclusion that the true stress, i.e., the Cauchy stress in the language of nonlinear mechanics, is unsymmetric due to the incorporation of a mass flux, see Epstein and Maugin [2000].

### **Growth laws**

The mathematical modelling of growth thus crucially depends on the choice of constitutive equations for the characteristic quantities, i.e., in this case the growth tensor and the mass source and flux. In a single species open system framework, guidelines for appropriate constitutive equations are provided by thermodynamical considerations. One typical analysis of the admissible growth laws on the basis of thermodynamic arguments is due to DiCarlo and Quiligotti [2002]. They state an a priori dissipative principle, involving standard forces and accretive forces, that has to be satisfied for any growth process. The exploitation of this inequality yields constitutive relationships that provide a direct coupling between stress and growth in terms of an Eshelby-like tensor. This approach has been further investigated by Ambrosi and Guana [2007], who demonstrate that suitable assumptions on the general model lead back to the one proposed by Taber and Eggers [1996] as a small strain limit.

### **Mixture theory**

Growth actually takes place as a result of reactions between numerous chemical species that also undergo transport with respect to the surrounding fluid medium. The corresponding mathematical models consist of reaction-diffusion equations for a minimal set of chemical species, a reaction-driven mass growth/resorption equation for the solid tissue phase and a transport equation for the interstitial fluid. This delineation of the equations assumes that the solid phase does not undergo transport, and that the interstitial fluid lacks sources and sinks. However, cell migration within a tissue is one phenomenon involving transport of what may be considered a "solid" cell phase. Likewise, interstitial fluid sources/sinks must be considered if lymph glands are present in the tissue. Both these exceptions are central to modelling of solid tumours. With regard to the models outlined in this paragraph, we note that diffusivities of some chemical species are known in water.

The kinetics of many reactions behind cancerous cell growth are also understood to some degree. However, the complexities of the mechanics have hindered a parallel advance of understanding of stress-driven fluid transport.

### **Constitutive equations in multispecies theories**

This last point on stress-driven fluid transport brings us to another critical issue: the coupling between the solid and fluid phases of soft tissue has a direct impact on the observed viscoelastic response of the tissue. Since fluid transport is driven by stress-gradients it is completely determined by the nature of this coupling. Soft tissue is “soft” because it is a composite material consisting of a porous, compliant, solid in whose interstitial spaces resides an incompressible fluid. Treatment of the coupled mechanics can draw from mathematical homogenization theory for composite materials. The simplest assumptions are the limiting cases: uniform deformation between the solid and fluid phases, or uniform stress between them. The former leads to an upper bound on the stiffness of the soft tissue, and the latter to a lower bound. More accurate models require an explicit treatment of the mechanics, a question that comes down to the interaction forces between solid and fluid phases. With a model for this force the individual linear momentum equations for the solid and fluid phases can be solved. Such a step increases the number of equations to be solved, but makes possible many gains: more accurate viscoelastic tissue response, stress-driven fluid transport, and since the reacting chemical species are advected by the fluid, more realistic growth models. Very little progress has, however, been made toward theoretical characterization of the solid-fluid interaction forces.

### **System stability and numerical stability**

A major class of growth models is based on the coupling of a number of partial differential equations for reaction-transport and momentum. For numerical efficiency it is common to adopt an operator splitting algorithm for solution of the coupled system of equations. Primitive variables are identified corresponding to each partial differential equation. The solution proceeds by solving each equation in turn while allowing the evolution of only some subset of the solution variables for each equation solved. In general, multi-pass algorithms must be used to ensure convergence to consistent sets of the solution variables. The alternative, a “monolithic” solution of the coupled equations proves too costly when the the number of coupled equations, or rather phenomena modelled, and system size increases. While operator-splitting techniques offer advantages of numerical efficiency, there arises a fundamental numerical issue related to stability: If uncontrolled growth is observed, is it a result of instabilities inherent in the equations, or of a spurious nature related to the numerical schemes employed? This issue has been addressed to some degree for other coupled phenomena such as thermomechanics and the more closely-related problem of flow through deformable porous media. However, the presence of reaction terms in the growth problem, and the kinematics of the rate of growth tensors, introduces a further element of complexity to this question of stability that has gone virtually unaddressed. The proposed workshop will serve as a forum for research addressing this specific question.

**Open problems**

The topic of soft tissue growth is an attractive interdisciplinary issue, challenging for its implications in applied mathematics, theoretical mechanics, theoretical biology and numerical mathematics. During this workshop, mainly during the days but even more enthusiastically during long nights, we discussed the following open mathematical issues that currently animate the discussion in the scientific community:

- the necessity of a multiplicative decomposition of the gradient of deformation, its uniqueness, its physical interpretation in simple model problems, its possible characterization by a lower dimensional form, e.g., spherical growth
- the proper use of the theory of mixtures with particular focus on the identification of the interaction terms
- the stability of grown states
- the introduction of thermodynamically admissible growth laws
- methods to hierarchically incorporate cellular scale information at a macroscopic spatial scale

Despite of all these tremendous developments, the mathematical aspects of the mechanics of biology today is a field still in its infancy. During this one week miniworkshop, the participants from different field critically discussed and helped to classify state-of-the-art models which capture the essence of mechanical and biological interactions. Some contributions focussed on appropriate computational simulation techniques to provide further insight into complex biomechanical phenomena and quantify basic dependencies and trends.

**Acknowledgements**

We would like to thank all the participants for coming to Oberwolfach, sharing with us their views on growths and remodelling, and contributing to lively discussions, which sometimes lasted into the middle of the night. Finally, we would like to acknowledge the support of the Oberwolfach team and the entire Mathematisches Forschungszentrum Oberwolfach without whose support this miniworkshop would not have been possible. We all enjoyed staying at your institute and hope to be able to return some day in the future.

Davide Ambrosi, Krishna Garikipati, Ellen Kuhl



## Mini-Workshop: The mathematics of growth and remodelling of soft biological tissues

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## Abstracts

### The theory of mixtures for growth and remodelling

DAVIDE AMBROSI

(joint work with Guido Vitale)

Volumetric growth is addressed in the literature in two different theoretical frameworks: the usual one-component continuum medium and the mixture theory. The former scenario is simpler and growth is included in the description as a volumetric mass source. Conversely, mass source takes the much more acceptable meaning of exchange between species in a mixture context. It is an open question whether the mixture theory is a more effective tool to investigate growth and remodeling of soft biological tissues. In the first part of our talk we have showed that both theories are unable to predict residual stress formation in its classical formulation, unless suitably enriched by some other descriptor.

One possibility is to include the density of the solid component among the variables the free energy can depend on [2]. In our talk it has been shown that this generalization can actually account for the formation of residual stresses, provided explicit non-trivial dependence on the position and solid component density appears in the functional expression of the free energy:

$$(1) \quad \Psi^I = \Psi^I(\mathbf{F}, \rho_0^s, X) + \tilde{\Psi}^I(\rho_0^\beta), \quad \beta \neq s,$$

where  $\Psi^I$  is the free energy of the mixture,  $\mathbf{F}$  is the gradient of deformation of the solid component and  $\rho^s$  its density,  $X$  are the material coordinates and  $\rho_0^\beta$  the density of the  $\beta$ -th fluid component. At first order, functional derivative of the strain energy yields the Piola tensor

$$(2) \quad \bar{\mathbf{P}}^I = 2 \left( \frac{\partial^2 \Psi^I}{\partial \mathbf{F}^2} \right)_o (\mathbf{F} - \mathbf{1}) + 2 \left( \frac{\partial^2 \Psi^I}{\partial \mathbf{F} \partial \rho_0^s} \right)_o (\rho_0^s - \bar{\rho}_0^s).$$

How to obtain these constitutive informations from experiments remains to be explored.

An alternative approach is to introduce a multiplicative decomposition of the tensor gradient of deformation.

$$(3) \quad \mathbf{F} = \mathbf{F}_e \mathbf{G}$$

The tensor  $\mathbf{G}$  accounts for the growth of the solid component in the tissue [4]. This operation should be interpreted as the introduction of new degrees of freedom in the system and it therefore calls for a dimensionally correspondent balance law stated *a priori*, as duly prescribed by DiCarlo and Quiligotti [3]:

$$(4) \quad \mathbf{B} = \mathbf{C}$$

where  $\mathbf{B}$  and  $\mathbf{C}$  are the external and internal *remodeling forces*, respectively.

Authors who have adopted the Kroner–Lee multiplicative decomposition of the gradient of deformation have effectively predicted the mechanical behavior of residually stressed materials in a one-component framework and we have shown how

this choice can be applied to mixtures too, thus yielding thermodynamical restrictions to be satisfied. The accretive forces include and represent all the stimuli to growth (and resorption) that can have very different physical and biochemical origin; it is aim of ongoing investigation to unravel these mechanisms.

In our talk we have shown that a solid-fluid mixture description can exhibit inner aspects on the *dynamics* of growth, i.e. the biophysical forces that drive locally inhomogeneous growth, that remain somehow hidden in an abstract representation in a one-component framework. Some authors have pointed out the role of homeostasis as a target tension the system tends to by material re-organization [5, 1]. The presence of the chemical potential  $\mu$  in the evolution equation indicates a role of species concentration in driving growth: according to our calculations a simplest admissible growth law for a two-phases material  $(\ell, s)$  is

$$(5) \quad \dot{\mathbf{G}}\mathbf{G}^{-1} = \mathbf{C} + \mathbf{F}_r^T \frac{\partial \Psi^I}{\partial \mathbf{F}_r} + \rho_0^s \left[ \left( \mu^s + \frac{p}{\rho_T^s} \right) - \left( \mu^\ell + \frac{p}{\rho_T^\ell} \right) \right] \mathbf{1}.$$

where the superposed dot denotes differentiation in time,  $p$  is the pressure and  $\mu^\beta$  is the chemical potential of the  $\beta$ -th component.

Our main concern is that mixtures provide some more insight of inhomogeneous growth in terms of chemical equilibrium corresponding to non-homogeneous chemical distributions of species, an explanation in terms of basic physical mechanisms that one-component mechanics cannot capture. Equation (5) predicts that equilibrium occurs when the elastic tension and the imbalance of chemical potential are equal to the target  $\mathbf{C}$ . Although for a closed system, as the one under consideration, the Fickian dynamics tends to damp inhomogeneities in concentration according to a reaction-diffusion law of Fick type, the chemical potential imbalance can be sustained by non-movable species, as conjectured by Ateshian [2]. In such a case the growth dynamics drives the material reorganization necessary to satisfy the equilibrium in terms of residual mechanical stress: as  $\mathbf{F}_r = \mathbf{F}\mathbf{G}^{-1}$ , the evolution of the growth tensor  $\mathbf{G}$  tunes the first term at the right hand side of (5). until equilibrium is reached.

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## Growth of thin hypelastic soft tissues

MARTINE BEN AMAR

(joint work with Julien Dervaux)

Shape of plants and other living organisms is a crucial element of their biological functioning. Morphogenesis is the result of complex growth processes involving biological, chemical and physical factors at different temporal and spatial scales. Biological tissues are conventionally classified into two categories: hard tissues (e.g. bones or teeth) and soft tissues (e.g. muscles, arteries, tendons, skin), depending on their mechanical properties. Soft tissues, which typically exhibit anisotropic, nonlinear, inhomogeneous behaviors, are often subject to large stresses and strains. The theory of finite elasticity therefore forms an appropriate framework to describe their properties [1, 2, 3], in the absence of visco-elastic effects. Along these lines, much work has been done to establish constitutive relationships for specific biological materials such as the skin, blood vessels, lung, brain, liver and kidney [3, 4], although computing stresses and strains under applied external loads remains a difficult task.

Observation of biological tissues has revealed the existence of internal stresses, even in the absence of external loads. These *residual stresses* are induced by growth [2] and affect the geometrical properties of tissues. Soft tissues may undergo *volumetric growth* [5, 6] depending on space, orientation and the state of stress within the body. Growth is a complex process involving biochemical and physical reactions at many different length- and time-scales, that occur through cell division, cell enlargement, secretion of extra-cellular matrix or accretion at surfaces. The removal of mass is referred to as *atrophy* and occurs through cell death, cell shrinkage or resorption. Because of completely different time scales between relaxation via visco-elastic effects and the growth process itself which is assumed very slow, the total deformation of the body is only due to both change of mass and elastic deformations [7, 8, 9, 10, 11, 12].

Before (resp. after) the deformation, the body is in the *reference* (resp. *current*) *configuration* and the place of each material point is denoted by  $\mathbf{X}$  (resp.  $\mathbf{x}$ ). We define the *geometric deformation tensor* by  $\mathbf{F} = \partial\mathbf{x}/\partial\mathbf{X}$  to describe locally the *overall* deformation process. In order to model the growth process, we follow Rodriguez *et al* [13] in making the following three assumptions: *(i)* there exists a zero-stress reference state; *(ii)* the geometric deformation gradient  $\mathbf{F}$  admits a multiplicative decomposition of the form  $\mathbf{F} = \mathbf{A}\mathbf{G}$  where  $\mathbf{G}$  is a *growth tensor* describing the change in mass and  $\mathbf{A}$  an *elastic tensor* characterizing the reorganization of the body needed to ensure compatibility (no overlap) and integrity (no cavitation) of the body; *(iii)* the response function of the material depends only on the elastic part of the total deformation.

Despite its simplicity, Rodriguez theory is yet to be investigated, because of the complexity of finite elasticity although inhomogeneous and anisotropic growth has been studied in details in some simple geometry [14, 15]. Here we focus on growing thin samples subject to slow growth-induced finite displacements and we assume

that the sample has time to relax to its equilibrium shape. This reduction of dimensionality allows to derive the equilibrium equations whatever the constitutive laws of the tissues. Under appropriate scaling assumptions, the resulting equations are found to be an extension of the well known Föppl von Kármán (FvK) model, a powerful theory for buckling instabilities, that are widely diffused in nature, but which is also able to explain complex post-buckling phenomena such as crumpling. Experimentally, it has been shown that growth may affect curvature in various systems. In growing gels, both homogeneous growth under constraints [16] and free inhomogeneous growth [17] have been investigated. Thermal expansion, as well as desiccation, can also bend an elastic body and cause it to crumple as seen in dead leaves. In living tissues, viruses such as the Cotton Leaf Crumple Virus (CLCrV) modify the growth process and infected plants exhibit curled or crumpled leaves but buckling can also occur during normal development. Some mushrooms' or algae's caps may undergo symmetry breaking, and adopt an oscillatory or cup shape.

At the cellular level, a new milestone was reached with the discovery of the *CINCINNATA* gene whose local expression affects growth and curvatures of the *Antirrhinum* (snapdragon) leaf [18]. Complementary to the inhomogeneity of growth, anisotropy has been shown to be crucial in the generation of shape. Indeed "a key aspect of shape -petal asymmetry- in the petal lobe of *Antirrhinum* depends on the direction of growth rather than regional differences in growth rate" [19]. To investigate the effects of anisotropy, for which our formalism is well suited, we have studied the problem of a free elastic disk subject to homogeneous anisotropic growth. Consider a disc, of initial radius  $R_i$ , subject to anisotropic homogeneous growth, with free boundaries and no external loading. Referring to a cylindrical system of coordinates  $(R, \Theta, Z)$ , the growth tensor is diagonal and homogeneous:  $\mathbf{G} = \text{diag}(1 + g_1, 1 + g_2, 1)$  neglecting the thickening of the plate. If  $g_1$  and  $g_2$ , respectively the radial and circumferential components of the growth process, are equal, then growth is homogeneous and isotropic and no residual stress appears: the disk remains flat. The relevant control parameter is  $k = g_2 - g_1$ . The first case to consider is for  $k \ll H^2/R_i^2$  that induces an off-plane displacement  $\zeta$  much smaller than  $H$  and is outside the scope of the present theory. When  $k$  is of order  $H^2/R_i^2$ , which leads to  $\zeta \sim H$ , the bending and stretching contributions are of the same order and a linear stability analysis is performed. We look for a solution in which the in-plane fields (displacements  $U_R, U_\Theta$  and stresses  $\sigma_{RR}, \sigma_{R\Theta}$  and  $\sigma_{\Theta\Theta}$ ) are independent of  $\Theta$ . The off-plane displacement, however, can depend on  $\Theta$ . Since the disk is free, the boundary conditions imply that there is no tension or torque at the free edge and reads  $\sigma_{RR}(R_i) = \sigma_{R\Theta}(R_i) = 0$ . The only convergent solution that fulfills these boundary conditions, is  $\sigma_{RR} = \sigma_{R\Theta} = 0$  leading to  $U_R(R) = (2R/3)(g_2/2 + g_1)$ ,  $U_\Theta(R) = 0$  and a non-zero hoop stress  $\sigma_{\Theta\Theta} = (-2kY)/3$ . We assume a solution with discrete axial symmetry:  $\zeta(\rho, \Theta) = \xi(\rho) \cos(m\Theta)$  and find that the most unstable mode, occurring when growth is mainly circumferential with  $(\alpha = 6kR^2/H^2 > 0)$ , is characterized by  $m = 2$  -a saddle shape- with a threshold value of  $\alpha = 3.08$ .

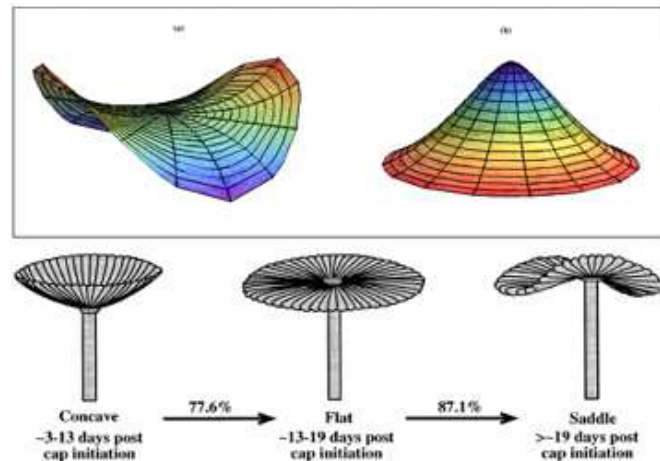


FIGURE 1. Top: The two first destabilized modes. (a) On the left  $k > 0$ , the disc adopts a saddle shape, with  $m = 2$ , at the threshold  $\alpha = 3.08$ . (b) On the right  $k < 0$  and the disc adopts an axially symmetric shape characterized by  $m = 0$ , at the threshold  $\alpha = -7.82$ . Bottom: shape changes in the *Acetabularia* algae, the figures indicate the fraction of algae that undergo the shape transition from an initial population of 85 plants, picture drawn from [20].

An axially symmetric solution, i.e.  $m = 0$ , appears when radial growth dominates ( $\alpha < 0$ ), at the threshold value  $\alpha = -7.82$ .

This simple model explains surprisingly well the changes of cap shape that the algae *Acetabularia acetabulum* undergoes during its development. Experiments performed in [20] show that radial growth occurs in the earliest stage of the development, which leads to a symmetric conical shape. At later stage however circumferential growth predominates to produce the saddle shape. For large deformations, those predictions can be easily checked by constructing a cone from a disc of paper in which a sector defined by two radii is withdrawn and then either replaced by a bigger one or just glued to close it. This simple demonstration illustrates the fact that singularities can arise from growth as observed in dead leaves or in the leaves infected by the CLCrV.

Using the formalism introduced by Rodriguez *et al*, we have developed a theory describing the behavior of thin elastic bodies subject to growth. By expliciting the sheet's small thickness, we showed all materials behave according to a generalized Hooke's law and the equilibrium equations generalize the FvK equations with growth. This extension describes a broad range of physical phenomena involving mass reorganization, from biological growth to thermal dilatation, as well as desiccation. Once observed in experiments, shape instabilities with well defined wavelength may give relevant informations on the growth process itself. The treatment presented in this letter also includes growth anisotropic effects. We have shown that anisotropic growth induces rich structures like curling and crumpling.

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## Elementary mechanics of muscular exercise

ANTONIO DICARLO

The mathematical theory of growth and remodelling of living tissues—either soft or hard—is still in its infancy, as unanimously acknowledged and amply testified during the miniworkshop. In these conditions, the lack of a well-founded and widely recognized axiomatic basis is only to be expected, and could even be regarded as a felicitous opportunity for the emergence of brand new ideas. However, this is no excuse for disregarding clean axiomatics nor for being opportunistic and sloppy in basic assumptions. At best, these are symptoms of a nasty infant disease we should fight against. To this end, I chose to discuss a very simple—but not too simple—macroscopic model of muscular exercise. Admittedly, nobody views muscle contraction—as opposed to muscle buildup—as an example of growth or remodelling. However, it is a fact that the very same formalism—which I call *material remodelling*—fitly covers both phenomena (and many others, either in living or non-living materials). At the same time, the utmost simplicity of the muscle model I consider makes the mathematical structure and the physical motivation of the underlying theory readily accessible.

*Prelude.* Let me invite you to an easy-to-do experiment: go to the gym, pick up a dumbbell, raise your forearm at ninety degrees with your upper arm, and hold on. Whoever has tried knows that an isometric exercise can be strenuous. However,

null work is being done: no motion, no power expended. How is it that a tough isometric workout implies no work? What's wrong? In actual fact, zillions of minuscule myosin heads have to move back and forth inside your biceps in order to keep your arm still under load. A decent model of muscular exercise, while eschewing all molecular details, should account for their net results on the gym scale. I consider the simplest macroscopic caricature of the muscular machinery able to mimic actin-myosin sliding and myosin action as independent mechanisms. Avoiding to lump them into a single effective mechanism is of the essence: in fact, the effort demanded by an isometric exercise and the energy apportionment required are simply cancelled in the lumping. Keeping track of the power expended separately by each mechanism, my model encompasses all regimes of muscular activity. In particular, it provides a non-null estimate of the energy required to perform an isometric exercise for a given amount of time.

*A two-bar model.* A whole skeletal muscle is modelled as a telescoping unit comprised of two straight bars, sliding into one another. Each bar is assumed to be uniformly tensed, and its present tension  $T_i(\tau)$  (with  $\tau$  the present time, and  $i = \mathbf{a}, \mathbf{p}$ ) to depend only on the present stretch  $\lambda_i(\tau)$ :

$$T_i(\tau) = \widehat{T}_i(\lambda_i(\tau)),$$

the stretch being defined as the ratio between the *actual* and the *relaxed* length of the bar, both strictly positive:

$$\lambda_i(\tau) := \ell_i(\tau)/\ell_i^*(\tau) > 0.$$

Both response functions

$$\widehat{T}_i : ]0, +\infty[ \rightarrow \mathbb{R}$$

are assumed to be one-to-one and monotonously increasing, with inverses

$$\widehat{\lambda}_i := \widehat{T}_i^{-1}.$$

Be it noted that  $\widehat{T}_i(1) = 0 \Leftrightarrow \widehat{\lambda}_i(0) = 1$ . Labels  $\mathbf{a}, \mathbf{p}$  stand for *active* and *passive*, respectively: while the  $\mathbf{a}$ -bar is susceptible of remodelling, *i.e.*, its relaxed length may actually evolve in time,  $\ell_{\mathbf{p}}^*$  is assumed to be constant: for all time  $\tau$ ,

$$\ell_{\mathbf{p}}^*(\tau) = \ell_0 \quad \Rightarrow \quad \dot{\ell}_{\mathbf{p}}^* = 0$$

(a superposed dot denotes differentiation with respect to time). The overall length of the two-bar unit at time  $\tau$  is given by

$$L(\tau) = \ell_{\mathbf{a}}(\tau) + \ell_{\mathbf{p}}(\tau) - s(\tau),$$

where  $s(\tau)$  measures the present *overlap* between the two bars. The above assumptions are clearly inspired by the way actin and myosin filaments are organized in sarcomeres and myofibrils. A quote from Andrew F. Huxley [1] is to the point:

Length changes in muscle take place by relative sliding of two overlapping sets of filaments, composed respectively of myosin and actin. Tension is generated in the overlap regions by cross-bridges

formed by the heads of myosin molecules, which attach to an adjacent actin filament, exert force and detach. Attachment ends when a molecule of ATP binds to the myosin head.

In conclusion we have to deal with 4 DOFs overall, the evolution of the muscle during an exercise being parameterized by the *extended motion*

$$(1) \quad \tau \mapsto (\ell_a(\tau), \ell_p(\tau), s(\tau), \ell_a^*(\tau)).$$

The governing equations are obtained following the uniform procedure set forth in [2]. The equations corresponding to the first three DOFs in (1) are standard, while the fourth is not.

*Power and balance.* The total power expended is assumed to be given by the sum

$$(2) \quad \left( R^o \dot{\ell}_a^* + F \dot{L} \right) + \left( R^i \dot{\ell}_a^* + C \dot{s} - T_a \dot{\ell}_a - T_p \dot{\ell}_p \right),$$

where parentheses group the *outer* and the *inner* contribution, in this order. In (2)  $F$  is the (standard) force applied to the muscle ends by the tendons;  $R^o$  and  $R^i$  are the outer and inner *remodelling forces*,  $R^o$  representing the essential interaction with the chemical degrees of freedom, which are left out—but not ignored!—by the model;  $C$  is the (standard) force exchanged between the two bars, which—as established by the assumptions in (2)—are connected in series.

The principle of virtual power yields the 4 balance equations:

$$(3) \quad T_a = T_p = C = F,$$

$$(4) \quad R^o + R^i = 0.$$

*Energetics.* The free energy is assumed to be the sum of the elastic energies of the two bars—the energy apportion from biochemical sources being accounted for by the outer remodelling force  $R^o$ :

$$\Psi(\tau) = \widehat{\Psi}_a(\lambda_a(\tau)) + \widehat{\Psi}_p(\lambda_p(\tau)).$$

A *dissipation principle* [2, 3] is enforced, requiring that the power dissipated—defined as the difference between the power expended along a motion and the time derivative of the free energy—should be non-negative:

$$(5) \quad -\left( R^i \dot{\ell}_a^* + C \dot{s} - T_a \dot{\ell}_a - T_p \dot{\ell}_p \right) - \dot{\Psi} \geq 0.$$

A distinguished set of constitutive assumptions satisfying identically inequality (5) is the following (a prime denotes differentiation):

$$(6) \quad \widehat{T}_i = \widehat{\Psi}'_i,$$

$$(7) \quad C = -(1/M)\dot{s} \quad (\text{with } M > 0),$$

$$(8) \quad R^i = \lambda_a \widehat{T}_a(\lambda_a) - D \dot{\ell}_a^* \quad (\text{with } D > 0).$$

Note that the additive structure of the right side of (8) is a necessary consequence of the dissipation principle postulated. In particular, the energetic term  $\lambda_a \widehat{T}_a(\lambda_a) = \lambda_a \widehat{\Psi}'_a(\lambda_a)$  is the pertinent *Eshelby coupling* between hyperelasticity and remodelling of the  $\mathbf{a}$ -bar.



*Evolution equations.* Substitution of eqs. (6–8) into (3) and (4) yields the equations determining the time rates of the overlap  $s$  and of the relaxed length of the a-bar  $\ell_a^*$ :

$$\begin{aligned}\dot{s} &= -MF, \\ D \dot{\ell}_a^* &= \widehat{\lambda}_a(F)F + R^\circ,\end{aligned}$$

plus the rate-independent balances  $\widehat{T}_a(\lambda_a) = \widehat{T}_p(\lambda_p) = F$ .

*Biochemical power expended.* It is readily seen that in an *isometric* ( $\dot{L} = 0$ ) and *isotonic* ( $\dot{F} = 0$ ) exercise the outer power coincides with the power expended by the outer remodelling force and is non-null (unless  $F = 0$ ):

$$R^\circ \dot{\ell}_a^* = \left(1 + DM / (\widehat{\lambda}_a(F))^2\right) MF^2.$$

Note that  $\widehat{\lambda}_a(F) = 1 + \mathcal{O}(F)$ . Hence,  $R^\circ \dot{\ell}_a^* = (1 + DM)MF^2 + DM^2 \mathcal{O}(F^4)$ . Consider, however, that there is no reason why the mobility  $M$  and the resistance (or inverse mobility)  $D$  should not depend on  $F$ .

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### Mathematical modelling of solid tumor growth

KRISHNA GARIKIPATI

(joint work with Harish Narayanan, Karl Grosh, Ellen M. Arruda)

The classical view of growth in biology is that of a problem of geometry. This was the approach of D’Arcy Thompson [1] who was most interested in the form of horns, tusks, antlers, shells, and other structures. This view of growth was adopted by Skalak [2] who made very effective use of kinematics as developed in continuum mechanics to compute, via growth velocities and velocities of generating cells, the forms of biological structures that Thompson described.

A quite different view prevails in modern biology, where growth means an increase in mass [3]. This is the view adopted in my talk. Notably, there is a robust debate ongoing in biology, spurred by recent work on the growth of organisms by [4]. These authors considered the “energy usage”, measured by metabolic rates, of organisms to model growth. They proposed a law of the form

$$(1) \quad \underbrace{B}_{\propto m^{3/4}} = \underbrace{N_c B_c}_{\propto m} + \underbrace{E_c \frac{dN_c}{dt}}_{\propto \frac{dm}{dt}}.$$

Here the left-hand side is the total metabolic rate, which they argued is proportional to the mass raised to the  $3/4$  power. The first term on the right-hand side is the rate of energy consumption required to maintain the critical functions of the organism, and is proportional to the mass. The last term is the energy consumed for growth, and is proportional to the rate of change of mass. With this law West and co-workers were able to match the growth data of biological organisms across 27 orders of magnitude in mass—from molecules, through sub-cellular organelles and cells, to the largest animals and plants [5]. Their model has come to be called a universal law. It has, of course, attracted its share of criticism, mainly directed at the  $3/4$  power, which the authors justified on the basis of the scaling of the terminal vasculature in organisms.

The current continuum mechanical treatment of growth marries these views of changes in form and mass. It has produced a large body of work: [6], [7], [9], [10], [11], [12], [8], to name just a few. This approach has exposed the continuum field theoretic nature of growth at macroscopic scales. There remain some open problems and controversies, which other participants in this workshop will discuss. I want to take a different approach. After summarizing the mathematical formulation, I ask what use it is.

For this purpose I will consider tumor growth as the model problem. The equations are

$$\begin{aligned} \frac{\partial \rho^m}{\partial t} + \nabla \cdot (\rho^m \mathbf{v}^m) - \pi^m &= 0 \\ \frac{\partial \rho^c}{\partial t} + \nabla \cdot (\rho^c \mathbf{v}^c) - \pi^c &= 0 \\ \rho^s \frac{\partial \mathbf{v}^s}{\partial t} + \mathbf{v}^s \cdot \nabla \mathbf{v}^s &= \nabla \cdot \boldsymbol{\sigma} + \rho^s (\mathbf{q}^s + \mathbf{g}) \\ \frac{\partial \rho^f}{\partial t} + \nabla \cdot (\rho^f \mathbf{v}^f) &= 0 \\ \rho^f \frac{\partial \mathbf{v}^f}{\partial t} + \mathbf{v}^f \cdot \nabla \mathbf{v}^f &= \nabla p + \rho^f (\mathbf{q}^f + \mathbf{g}), \\ \frac{\partial \rho^n}{\partial t} + \nabla \cdot (\rho^n \mathbf{v}^n) - \pi^n &= 0 \end{aligned}$$

where m is the extra-cellular matrix; s is the solid (extra-cellular matrix + cells); c is the cells; f is the fluid; and n represents chemical species such as enzymes, nutrients, by-products and others. Additionally,  $\rho$  represents concentrations,  $\mathbf{v}$  represents velocities,  $\boldsymbol{\sigma}$  is the stress in the solid,  $p$  is the fluid pressure,  $\mathbf{q}$  represents interaction body forces between solid and fluid phases,  $\mathbf{g}$  represents external body forces, and  $\pi$  represents mass sources.

Using this set of equations, complemented by constitutive relations, the growth of soft tissue tumors can be modelled in some detail. The figure below shows the horizontal displacement contours and displacement vectors of a tumor after 100 days of growth. Included in this computation are the hyperelastic solid phase; cells that proliferate, migrate under haptotaxis and diffusion, apply passive and

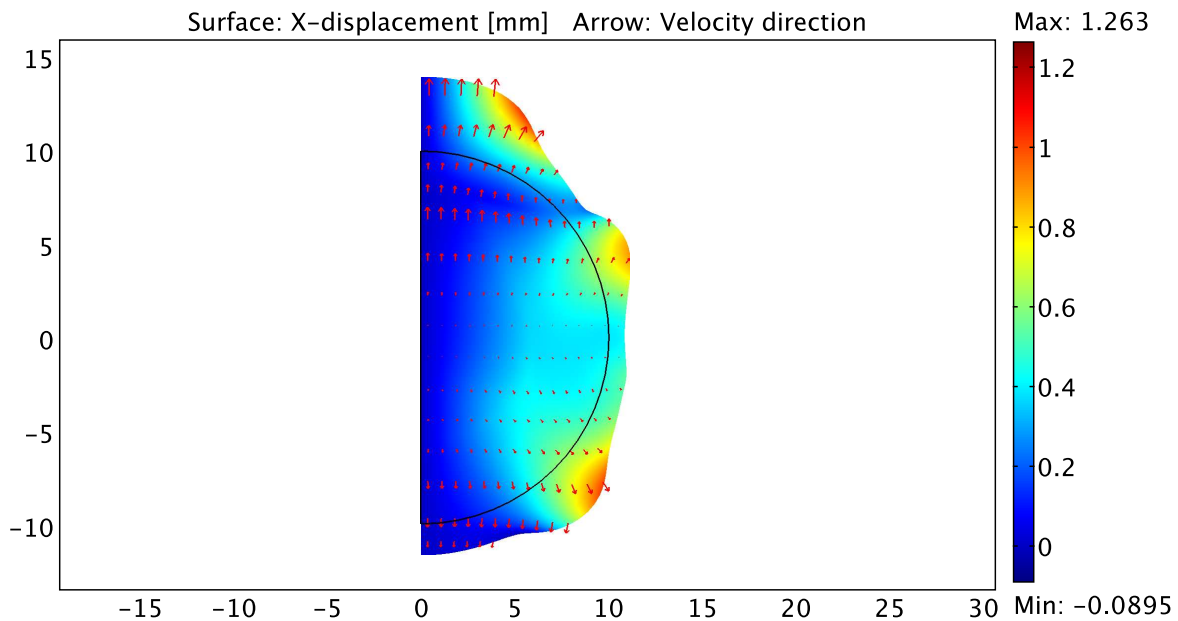


FIGURE 1. Constrained growing tumor

active stress on the extra-cellular matrix; and chemical species representing the nutrition for cells, enzymes and by-products. The fluid phase and viscoelasticity were not included in the computation because their effects are not relevant over the large time scale involved (100 days). On the right the tumor encounters soft contact, meant to model a neighboring organ imposing a constraint on its growth in that direction.

Such computations can be useful to test the complex growth dynamics of tumors, the effect of drug doses and protocols, mechanical effects on vasculature and so on.

There also are some emerging possibilities that these models will shed greater light on the details of energy usage in growing tumors.

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## Analysis of growth and diffusion dynamics in biological materials

ALFIO GRILLO

(joint work with Gabriel Wittum, Gaetano Giaquinta, Milan V. Mićunović)

We study a growing biological tissue as an open biphasic mixture whose phases undergo exchange interactions. We assume that both the solid- and fluid-phase are composed of several constituents allowed to be transferred from one phase to the other. Because of growth and exchange, or transfer, source terms must be accounted for in balance laws. We relate the source terms which are relevant for our purposes with thermodynamic quantities defined at the pore scale of the tissue. This procedure, carried out through the Theory of Homogenization [1], aims to give growth a pore scale justification. Particular attention is given to the exploitation of the Clausius-Duhem inequality and the kinematics of growth. Since the mixture under investigation has to satisfy restrictions, we provide a modified Clausius-Duhem inequality that, following Liu's theorem, accounts for constraints through the Lagrange multiplier technique [2][3]. Constraints, and related Lagrange multipliers, are also introduced in the definition of Helmholtz free energy densities in order to include constitutive laws for solid- and fluid-phase mass densities less strict than incompressibility. We perform an analysis of our constrained Clausius-Duhem inequality in the neighborhood of thermodynamic equilibrium. This enables us to obtain Onsager relations that generalize some results found in the literature about a thermodynamically consistent procedure for determining an evolution law for growth and mass transfer. We show that the driving mechanism for mass transfer and growth is related to a generalized Eshelby-like tensor, which accounts for chemical potential. For example, we find that the *inhomogeneity velocity "gradient"* due to mass transfer can be given the

expression

$$(1) \quad \mathbf{L}_S^{\text{tr}} = \mathbb{M} : \left\{ (G_F - G_S) \mathbf{I}_N - \left[ \left( A_F \mathbf{I}_N - \mathbf{b}_F \right) - \left( A_S \mathbf{I}_N - \mathbf{b}_S \right) \right] \right\},$$

where  $\mathbf{I}_N$  is identity in the *natural configuration*,  $G_F$  and  $G_S$  are Gibbs free energy densities of the fluid- and solid-phase, respectively, and second order tensors  $\mathbf{b}_F$  and  $\mathbf{b}_S$  are Eshelby-like stress tensors defined by

$$(2) \quad \mathbf{b}_F := A_F \mathbf{I}_N - \sum_{\beta=0}^{N-1} C_{\beta F} \frac{\partial A_F}{\partial C_{\beta F}} \mathbf{I}_N,$$

$$(3) \quad \mathbf{b}_S := A_S \mathbf{I}_N - \sum_{\beta=0}^{N-1} C_{\beta S} \frac{\partial A_S}{\partial C_{\beta S}} \mathbf{I}_N - \mathbf{F}_S^{\text{el}} \cdot \frac{\partial A_S}{\partial \mathbf{F}_S^{\text{el}}}.$$

In Equations (2) and (3),  $C_{\beta F}$  and  $C_{\beta S}$  denote the mass fractions of the  $\beta$ -th constituent present in the fluid- and solid-phase, respectively,  $A_F$  and  $A_S$  are Helmholtz free energy densities, and  $\mathbf{F}_S^{\text{el}}$  is the elastic part of deformation experienced by the solid-phase. The terms

$$(4) \quad \frac{\partial A_F}{\partial C_{\beta F}} =: \tilde{\mu}_{\beta F} \quad \text{and} \quad \frac{\partial A_S}{\partial C_{\beta S}} =: \tilde{\mu}_{\beta S}$$

are said to be “reactive chemical potentials”, and are identified with the quantities  $\tilde{\mu}_{\beta F} := \mu_{\beta F} - \mu_{NF}$  and  $\tilde{\mu}_{\beta S} := \mu_{\beta S} - \mu_{NS}$ , with  $\mu_{NS}$  and  $\mu_{NF}$  absolute chemical potentials of constituent  $N$  in the solid- and fluid-phase, respectively.

In our opinion, Equation (1) seems in agreement with other previous theories (cf., for example, [4]).

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### Growth, optimization and configurational forces

ANDERS KLARBRING

(joint work with Bo Torstenfelt)

In order to obtain a simplified model of growth mechanics we consider the standard linear elastic stiffness equation of a discrete or discretized structure:

$$(1) \quad \mathbf{F} = \mathbf{K}(\boldsymbol{\rho})\mathbf{u}.$$

Here  $\mathbf{u}$  is the vector of nodal displacements and  $\mathbf{F}$  is the corresponding force vector. The symmetric positive semi-definite stiffness matrix  $\mathbf{K}(\boldsymbol{\rho})$  depends on a vector  $\boldsymbol{\rho} = (\rho_1, \dots, \rho_n)^T$  of configurational variables such that

$$\mathbf{K}(\boldsymbol{\rho}) = \sum_{i=1}^n \mathbf{K}_i(\rho_i), \quad \mathbf{K}_i(\rho_i) = g_i(\rho_i) \tilde{\mathbf{K}}_i$$

where  $n$  is the number of elements in the structure,  $\mathbf{K}_i(\rho_i)$  is an element stiffness matrix and  $\tilde{\mathbf{K}}_i$  is such a matrix for a unit value of the function  $g_i(\rho_i) \geq 0$ . As a particular case of this function we study the one used in the bone remodeling formulation of Harrigan and Hamilton [1]:  $g_i(\rho_i) = \rho_i^p$ , where  $p = n/m$ ,  $\rho_i^{1/m}$  represents the density of the material and the constant  $n$  describes how the stiffness relates to this density. It turns out experimentally that  $n$  is closed to the value 3.

A hypothesis of optimum bone structure leads to considering the following optimization problem:

$$(\mathcal{G}) \quad \min_{\boldsymbol{\rho} \in K} f(\boldsymbol{\rho}), \quad f(\boldsymbol{\rho}) = \frac{1}{2} \mathbf{F}^T \mathbf{u}(\boldsymbol{\rho}) + \mu \sum_{i=1}^n a_i \rho_i,$$

where  $K$  is a set of admissible configurational variable, including a constraint giving positive values. It is assumed that  $\mathbf{K}(\boldsymbol{\rho})$  is nonsingular for all  $\boldsymbol{\rho} \in K$ , so that the displacement can be seen as a function of the configuration, i.e.,  $\mathbf{u} = \mathbf{u}(\boldsymbol{\rho}) = \mathbf{K}(\boldsymbol{\rho})^{-1} \mathbf{F}$ . The first term in  $f(\boldsymbol{\rho})$  is known as the compliance and, by (1), equals the strain energy. The last term can be interpreted as a cost of material, where  $\mu$  is a constant regulating the relative importance of the two terms of  $f(\boldsymbol{\rho})$ , and the constants  $a_i$  represent the costs for individual elements.

An indirect but from several point of views very useful approach to solving and analyzing  $(\mathcal{G})$  is to consider a gradient flow (dynamical system, ODE, neurodynamical) reformulation of the problem: Let  $\boldsymbol{\rho}$  be a function of a time-like variable  $t$  and solve, for some initial condition, the ordinary differential equation

$$(2) \quad \dot{\boldsymbol{\rho}} = \lambda \Pi_K(\boldsymbol{\rho}, -\nabla f(\boldsymbol{\rho})).$$

Here  $\lambda$  is a positive constant, a superposed dot indicates a derivative with respect to  $t$  and  $\Pi_K(\boldsymbol{\rho}, -\nabla f(\boldsymbol{\rho}))$  is the Euclidean projection of  $-\nabla f(\boldsymbol{\rho})$  on the tangent cone of  $K$  at  $\boldsymbol{\rho}$ .

Problem  $(\mathcal{G})$  and the ordinary differential equation (2) are connected by the fact that if the Hessian  $\nabla^2 f(\boldsymbol{\rho})$  is positive definite at a stationary point  $\boldsymbol{\rho}$  of  $(\mathcal{G})$ , then every solution of (2) that starts sufficiently close to  $\boldsymbol{\rho}$  will converge (exponentially) towards it. A slight extension of a result by Svanberg [2] shows that  $(\mathcal{G})$  is a convex problem for  $n \leq m$ , meaning that for such values, solution curves of (2) will always converge to a solution of  $(\mathcal{G})$ . The condition  $n \leq m$  was also found by Harrigan and Hamilton [1]. In fact, they found that this condition is also necessary for convexity. They interpret it as one of stability for the evolution equation.

Disregarding the constraint  $\boldsymbol{\rho} \in K$ , it can be shown that (2) reads

$$(3) \quad \frac{1}{\lambda} \dot{\rho}_i = \frac{1}{2} \mathbf{u}^T \frac{d\mathbf{K}_i(\rho_i)}{d\rho_i} \mathbf{u} - \mu a_i,$$

and we conclude that growth is positive if

$$p\rho_i^{(p-1)}\frac{1}{2}\mathbf{u}^T\tilde{\mathbf{K}}_i\mathbf{u} > \mu a_i.$$

**Algorithm:** We suggest a simple Euler-type numerical algorithm for the solution of equation (2), see [3]. Given a solution  $\boldsymbol{\rho}(t)$  at time  $t$ , we want to calculate the solution at time  $t + \Delta t$ . By an explicit time discretization of equation (2) we calculate test values  $\hat{\rho}_i(t + \Delta t)$  from

$$(4) \quad \frac{\hat{\rho}_i(t + \Delta t) - \rho_i(t)}{\Delta t} = -\lambda \frac{\partial f(\boldsymbol{\rho}(t))}{\partial \rho_i}.$$

After such a test value is calculated, we make a projection onto the constraint set  $K$  in order to obtain  $\rho_i(t + \Delta t)$ . The gradient of  $f$  can be calculated as

$$\frac{\partial f(\boldsymbol{\rho}(t))}{\partial \rho_i} = \mu a_i - e_i(\boldsymbol{\rho}(t)), \quad e_i(\boldsymbol{\rho}) = p\rho_i^{(p-1)}\frac{1}{2}\mathbf{u}^T\tilde{\mathbf{K}}_i\mathbf{u}.$$

Thus, formula (4) reads

$$(5) \quad \frac{\hat{\rho}_i(t + \Delta t) - \rho_i(t)}{\Delta t} = \lambda[e_i(\boldsymbol{\rho}(t)) - \mu a_i].$$

The optimality criteria algorithm of structural optimization, see [4], is an algorithm for solving directly the optimization problem ( $\mathcal{G}$ ). Thus, there is no explicit reference to an evolution of configurational variables in this algorithm. Nevertheless, a sequence of iterates from this algorithm is frequently interpreted in an evolutionary sense and it would be interesting to compare such a sequence of iterates to the sequence obtained when solving the gradient flow problem (2) by the above Euler-type method. In the optimality criteria algorithm, when an iterate  $\boldsymbol{\rho}^n$  is known, the next iterate is obtained by first calculating the test value

$$(6) \quad \hat{\rho}_i^{n+1} = \left(\frac{e_i(\boldsymbol{\rho})}{\mu a_i}\right)^\beta \rho_i^n,$$

and then doing a projection onto  $K$ . The constant  $\beta$  is usually referred to as a damping coefficient.

In order to compare (5) and (6) we note that the latter can be rewritten as

$$(7) \quad \hat{\rho}_i^{n+1} = \left(1 + \frac{e_i(\boldsymbol{\rho}) - \mu a_i}{\mu a_i}\right)^\beta \rho_i^n \\ = \left\{1 + \frac{\beta}{\mu a_i}(e_i(\boldsymbol{\rho}) - \mu a_i) + O\left[\left(\frac{e_i(\boldsymbol{\rho}) - \mu a_i}{\mu a_i}\right)^2\right]\right\} \beta \rho_i^n,$$

which can be compared with (5). If  $\hat{\rho}_i^{n+1} = \hat{\rho}_i(t + \Delta t)$  and  $\hat{\rho}_i^n = \hat{\rho}_i(t)$ , (7) and (5) coincide to the first order if  $\rho_i(t)\beta = \Delta t\lambda\mu a_i$ . This condition can generally not be satisfied simultaneously for all  $i$  and  $t$ , and, even though (5) and (6) should converge to the same solution, it becomes difficult to interpret non-convergent iterates of the optimality criteria method as states of the evolution at a particular time instant: something that is obviously possible in the Euler method. At the

talk in Oberwolfach numerical solutions based on the optimality criteria algorithm were presented.

**Thermodynamics:** We like to investigate the thermodynamics of a time evolution of the system. To that end we disregard the constraint  $\boldsymbol{\rho} \in K$ . Changes of the displacement produces the power  $\mathbf{F}^T \dot{\mathbf{u}}$ , where a superposed dot means time derivative, and where the force  $\mathbf{F}$  represents the mechanical environment. Similarly, changes in the configurational variable  $\boldsymbol{\rho}$  produce the power  $\mathbf{r}^T \dot{\boldsymbol{\rho}}$ , where  $\mathbf{r}$  is an external configurational force representing the biochemical environmental impact on growth. Note also that in most problems of biological growth the time scale for changes in the biochemical environment is much larger than that of the mechanical environment. Therefore, the force  $\mathbf{F}$  should usually be regarded as an average load.

The free energy of the structure is taken as

$$(8) \quad \Psi = \frac{1}{2} \mathbf{u}^T \mathbf{K}(\boldsymbol{\rho}) \mathbf{u} + \Theta(\boldsymbol{\rho}),$$

where the first term is the strain energy and the second term represents a part of the internal energy that is purely associated with changes in  $\boldsymbol{\rho}$ . We expect that  $\partial\Theta/\partial\rho_i > 0$ .

The following dissipation inequality, representing a mechanical version of the second law of thermodynamics, is assumed to hold:

$$(9) \quad \dot{\Psi} \leq \mathbf{F}^T \dot{\mathbf{u}} + \mathbf{r}^T \dot{\boldsymbol{\rho}}.$$

Inserting (8) into (9) gives

$$(10) \quad (\mathbf{F} - \mathbf{K}(\boldsymbol{\rho})\mathbf{u})^T \dot{\mathbf{u}} + \sum_{i=1}^n \left[ r_i - \frac{\partial\Theta(\boldsymbol{\rho})}{\partial\rho_i} - \frac{1}{2} \mathbf{u}^T \frac{d\mathbf{K}_i(\rho_i)}{d\rho_i} \mathbf{u} \right] \dot{\rho}_i \geq 0,$$

where we have used the symmetry of  $\mathbf{K}(\boldsymbol{\rho})$ . The first term of (10) vanishes due to (1). If we assume that  $r_i$  has a local character in its depends on the configurational variable, i.e.,  $r_i$  is a function of  $\mathbf{u}$ ,  $\rho_i$  and  $\dot{\rho}_i$ , then (10) holds for all evolutions if and only if

$$(11) \quad r_i - \frac{\partial\Theta(\boldsymbol{\rho})}{\partial\rho_i} - \frac{1}{2} \mathbf{u}^T \frac{d\mathbf{K}_i(\rho_i)}{d\rho_i} \mathbf{u} = c_i \dot{\rho}_i,$$

for some functions  $c_i = c_i(\mathbf{u}, \rho_i, \dot{\rho}_i) \geq 0$ .

For given functions  $\mathbf{F}$ ,  $\mathbf{K}$ ,  $\mathbf{r}$  and  $c$ , equations (1) and (11) represent a system of evolution equations for  $\mathbf{u}$  and  $\boldsymbol{\rho}$ . An essential difficulty is the choice of the configurational force  $\mathbf{r}$ . Comparison with a gradient flow formulation gives such a choice. By letting  $c_i = 1/\lambda$  and comparing (11) and (3) we obtain

$$r_i = \mathbf{u}^T \frac{d\mathbf{K}_i(\rho_i)}{d\rho_i} \mathbf{u} - \mu a_i + \partial\Theta(\boldsymbol{\rho})/\partial\rho_i.$$

The last term on the left hand side of (11) represents a sort of specific strain energy. We note that  $\tilde{r}_i = r_i - \partial\Theta(\boldsymbol{\rho})/\partial\rho_i$  represents a constitutive target function for this mechanical entity and that this interpretation is a consequence of thermodynamics (the dissipation inequality) and not an arbitrary assumption. To take



a constant value for  $\tilde{r}_i$  would correspond to the idea of homeostasis, used, e.g., in soft tissue mechanics of arteries where circumferential and axial stresses approach distributions that are constant across the thickness of the arterial wall.

Passive remodelling, i.e.,  $\mathbf{r} = \mathbf{0}$ , when the growth process does not interact energetically with the biochemical environment, is of special concern. We note that if  $\partial\Theta/\partial\rho_i > 0$ , the spontaneous evolution that occurs in the structure is towards lower values of  $\rho_i$ , i.e., towards lower density of the bone.

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### **A cell-based continuum mechanics approach towards ventricular growth and remodeling**

ELLEN KUHL

(joint work with Serdar Göktepe, Markus Böl, Oscar Abilez)

Heart disease is the primary cause of death in industrialized nations, claiming more than 16 million lives world wide each year. A leading cause of congestive heart failure is myocardial infarction, caused by the loss of blood supply in the myocardial wall. As a result, the functional units of the myocardium, the cardiomyocytes, lose their contractile property, die, and induce changes in form and function of the entire heart.

Within this presentation, we explore both short term and long term changes of cardiac physiology in response to myocardial infarction. Short term changes affect the cardiac conduction system of the heart, see, e.g., [4, 5]. They may result in uncoordinated self-excitation caused by re-entrant spiral waves which re-excite the tissue in an unphysiological way as illustrated in figure 1. Long term changes involve altered material properties and changes in ventricular size in the form adaptive growth and remodeling, see, e.g., [6, 8]. These changes help to maintain cardiac output at a physiological level as demonstrated in figure 2. We present our first attempts to model cardiac electrophysiology on the short time scale and cardiac growth and remodeling on the long time scale with the help of finite element based hierarchical whole heart models. Potential paths for verification and validation of the computational model will be illustrated in terms of animal infarct models based on non-invasive microCT, invasive fluoroscopic marker technologies, see [7], and ECG data, see figure 3. We conclude by discussing novel passive sup-

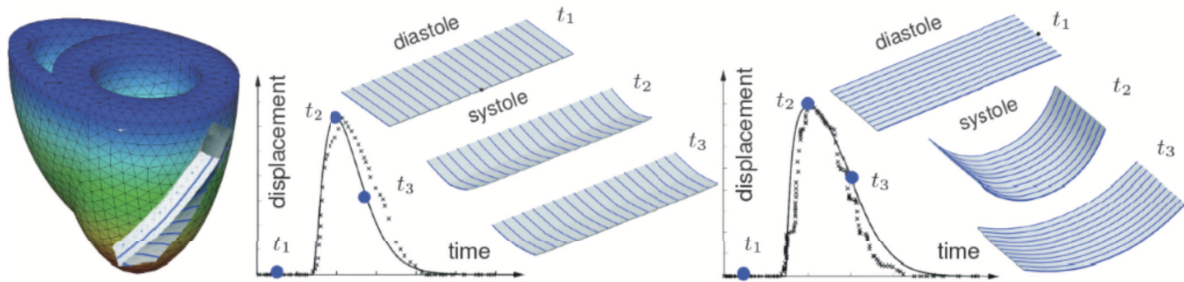


FIGURE 1. Virtual implantation of tissue engineered vascular grafts onto the damaged myocardium (left). Synchronously contracting neonatal rat ventricular cardiomyocytes seeded on polydimethylsiloxane (PDMS) base layer, see [3], and multiscale finite element simulation of actively contracting fibers seeded on a polymeric substrate, as described in detail in [2].

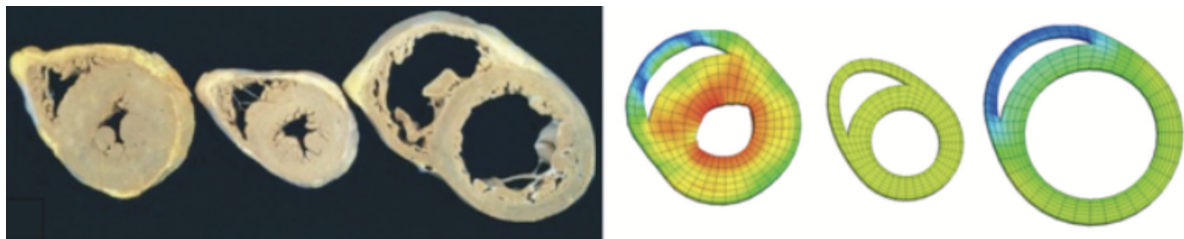


FIGURE 2. Patient-specific electrocardiogram based on generalized FitzHugh-Nagumo equations for excitable media. Human heart (left) and its finite element discretization (middle), see [4]. Nonlinear finite element simulation of excited human heart (middle). *In silico* EKG generated from projection of heart vector (right).

port devices and stem-cell based technologies as potential treatment strategies to restore cardiac function after myocardial infarction.

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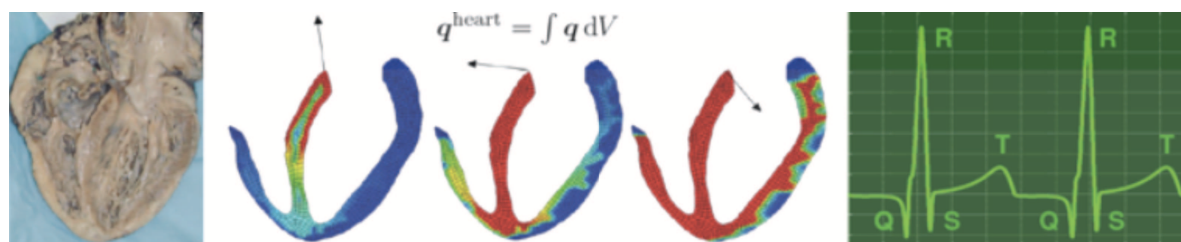


FIGURE 3. Ventricular growth and remodeling. Pressure overload-induced hypertrophy in response to aortic stenosis, normal heart, and volume overload-induced dilation in response to myocardial infarction. Sections (left), see [1], and finite element simulations based on multiplicative growth model with microscopically-motivated growth laws (right).

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### Growth and remodelling of soft biological tissues – Modelling approaches and computational aspects

ANDREAS MENZEL

(joint work with Magnus Harrysson, Victor Alastrué)

Soft biological tissues possess various types of microstructures on different levels of observation. The interplay of mechanical, biological, and chemical effects results in physical phenomena – such as growth and remodelling – directly observable on a macroscopic scale. Commonly one distinguishes between surface and bulk growth, which may affect mass and volume of the material body considered, and remodelling effects that render the mechanical properties of the material to change or rather adapt to the local loading conditions.

The formulations discussed in this contribution solely account for mechanical effects and, moreover, are embedded into the theory of open systems so that all balance and constitutive equation reduce to the description of one single solid phase. Key aspects of appropriate modelling approaches for bulk growth and remodelling are (i) the incorporation of initial or adaptation-induced residual stresses, (ii) a sound description of the material's anisotropic properties within a finite deformation context, and (iii) the adaptation of the anisotropic material properties such that the reorientation of macroscopic fibre families or rather turnover is captured.

From a multi-scale computational modelling perspective one may either introduce so-called structural tensors directly on the macro-level or determine the

macroscopic material properties based on an appropriate homogenisation scheme. The three approaches discussed in this contribution follow these lines.

*Structural tensors:* One the hand, use of the nowadays well-established multiplicative decomposition of the deformation gradient into a growth-related contribution and an elastic part is adopted. The growth term allows to incorporate residual stresses and is assumed to be, in general, non-spherical such that anisotropic growth is recaptured. On the other hand, the elastic properties are also considered to be anisotropic. To be specific, two symmetric structural tensors of rank one are incorporated as additional arguments into the strain energy function as reflecting orthotropic response. Furthermore, the general format of the growth tensor is reduced to be symmetric – two principal directions additionally being assumed to coincide with the elastic anisotropy directions as used for the definition of the structural tensors. The adaptation process itself comes into the picture by means of evolution equations for the eigenvalues of the growth tensor and a reorientation formulation of its principal direction (which, furthermore, directly includes the elastic properties via the structural tensors within the strain energy function). While the saturation-type evolution of the growth eigenvalues is driven by their energetically conjugate thermodynamical forces, a deformation-driven formulation is chosen for the fibre reorientation.

*ODF-based structural tensors:* Orientation distribution functions (ODF) provide an excellent framework to account for the dispersion of fibres. Their second moment contribution as integrated over the orientation space takes the interpretation as a generalised structural tensor. This quantity may either reflect a spherical, uni-axial, or biaxial distribution. As elaborated above, this generalised structural tensor is incorporated into the strain energy function, which enables to account for the material's anisotropic properties. Moreover, the adaptation process is represented by means of an evolution equation of this structural tensor, which itself depends of the corresponding fourth order moment tensor. The particular model proposed is based on two mechanically equivalent fibre families with the distributions of both being assumed to be characterised by a von Mises ODF.

*ODF-based micro-sphere model:* To further extend the ODF-based approach towards a computational multi-scale modelling approach, an affine micro-sphere model is adopted. In other words, the local deformation, as represented by the deformation gradient, is projected onto particularly chosen directions on the unit-sphere such that the related scalar-valued stretch can be used for simple one-dimensional constitutive relations. The corresponding stress quantity on the macro-level is then obtained by straightforward integration with respect to the underlying unit-sphere. Furthermore, the individual integration direction are weighted by an ODF so that anisotropic material properties are accounted for on this micro-level. By

analogy with the previous formulation, two von Mises-type ODFs are combined such that macroscopically orthotropic response is captured. The particular example investigated refers to the composite structure of an artery under internal pressure. It thereby turns out that the incorporation of initial residual stresses is of cardinal importance. This additional inhomogeneous stress contribution was determined by means of the deformation state related to the so-called opening angle experiment, and its incorporation obviously reduces the maximum stress level within the vascular tissue.

One of the advantages of the ODF-based micro-sphere model consists in the application or rather reduction to simple one-dimensional constitutive models. The particular one used in this contribution is the well-established worm-like chain model. In this regard, it seems to be of particular interest to (i) combine the ODF-based micro-sphere model with a remodelling formulation and to (ii) account for effects as active contraction or aging by means of appropriate evolution equations or rather modifications of the physically motivated parameters that determine the worm-like chain model.

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### **Collaborative computational frameworks and the growth problem**

HARISH NARAYANAN

(joint work with Krishna Garikipati, Anders Logg)

Growth in biological tissue is a direct outcome of cascades of complex, intracellular, biochemical reactions involving numerous species, their diffusion across cell membranes, and transport through the extracellular matrix. Both reaction and transport are influenced by mechanics in a number of ways, and much of our

modelling work thus far [1, 2] has been aimed at gaining a deeper understanding of the biophysical bases underlying these influences.

When treated as a continuum (usually in the context of mixture theory [3] to accommodate multiple interacting species, as in our previous work), a formal axiomatic treatment can be used to derive a general set of governing equations which specify how the mass, momenta and energy of each constituent species of the tissue evolve with time. These relations do provide a great deal of insight into the general behaviour of growing tissue treated as mixtures, the nature of the coupling between different physics and, with the incorporation of additional axiomatic principles (such as the Clausius-Duhem inequality), provide hints for constitutive specification.

Even so, when attempting to tailor a general continuum field formulation for a specific tissue growth problem, several basic modelling choices need to be made, which include:

- Determining which species need to be incorporated (collagen, proteoglycans, different kinds of cells, extra-cellular fluid, sugars, proteins . . .)
- Appropriate constitutive relationships for the stress response of load-bearing species
- Specific models used for the various biochemical reactions,
- Determination of realistic boundary conditions
- Judicious introduction of additional constraints (such as tissue saturation)

When attempting to address some of these fundamental questions, it often proves useful to experiment *in silico*; constructing simple test cases to help shape ideas. This requires a computational framework that is not only efficient, but functions at a sufficiently high level so that it can evolve easily with our understanding of the problem.

In this context, the **FEniCS** project (a collaborative project for the automation of computational mathematical modelling based on the finite element method [4]) serves as an appropriate foundation to construct a computational tool kit specifically tailored to the needs of the tissue growth modelling community. Since it allows researchers to pose their problems directly in terms of the weak forms of the partial differential equations arising from the theory, it allows them to focus on higher-level modelling questions and not be hindered by specific implementation issues. As preparatory steps for implementing a common, robust computational tool kit for the growth problem, several relevant improvements to core **FEniCS** components are currently actively being worked upon, including automated symbolic linearisation of classes of nonlinear forms, improved support for finite deformation and fluid-structure interaction, and adaptive mesh refinement/enrichment toward (goal-oriented) error control.

These enhancements will better help the creation of a common computational infrastructure customised for modelling growth. Since it is an open source project, anyone is free to obtain, use, study and extend the code. This will allow researchers and students to both contribute their own expertise, as well as learn from others, enhancing common understanding of the problem.

Such a computational framework would furnish a powerful tool that can easily be tailored to answer specific questions ranging from those pertinent to viscoelastic aspects of the mechanical response of growing tendons under different loading conditions, to quantitative investigations of the efficacy of drugs based on how they are administered, to understanding the cellular processes associated with tumour growth.

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### **Configurational forces: are they needed?**

PAOLO PODIO-GUIDUGLI

(joint work with Frederic Francois Dechamps)

Attention for foundational issues is and has always been for the few, especially so in times like those we live, when the “how?” sells much better than the “why?”. I myself have always kept alive my basic-training habit of asking the latter question.

For one thing, it seems to me that many of the present-day users of configurational mechanics – in as disparate fields as plant morphology, solid/solid phase transitions, defect dynamics, structure optimization, growth and remodeling of animal tissues, etc. etc. – have forgotten (given that they ever knew) that the citizenship in the realm of mechanics of configurational forces consistent with their balances has been strongly questioned by many until a few years ago. Therefore, I have chosen to resume an argument I concocted long ago (and published only more recently [1]), an argument that makes evident that, in the absence of configurational forces, the physically reasonable assumption that tangential surface accretion ( $\equiv$  tangential mass addition at a body’s periphery) should require no contact working leads to untenable consequences.

There was no time to touch on some related representation issues for both contact and distance configurational forces, dealt with in [1]; the interested reader may also wish to take a quick look at [2], where I show that, even within a variational framework with its intrinsic limitations in scope, configurational force systems do capture certain physical circumstances that standard force systems do not directly account for.

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**Tumours as elasto-visco-plastic growing bodies**

LUIGI PREZIOSI

(joint work with Davide Ambrosi)

Most research on solid tumour growth historically focuses on the interplay between the biochemical factors that promote or inhibit growth (e.g., nutrients and growth factors), influence motility (e.g., chemoattractants), induce environmental changes (e.g., tumour angiogenic factors and metalloproteinases). Mechanical effects have been neglected for a long time, until recent experiments have shown that they play a relevant role both at the onset of tumour growth through the process of contact inhibition and along its development because of the importance of the mechanical interactions with the surrounding tissues.

As most biological tissues, tumours can be modeled as a mixture of many components that can be grouped in three main categories: cells, extracellular matrix, and liquid.

In the framework of mixture theory the basic mathematical model can then be written as a set of mass balance equations and force balance equations with inertia neglected. Actually, also the contributions due to the presence of the extracellular liquid can be neglected, so that the basic system writes as

$$\begin{aligned} \frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) &= \Gamma_\alpha, & \alpha \in C \cup \{m\} \\ \nabla \cdot (\phi_\alpha \mathbf{T}_\alpha) + \sum_{\beta \neq \alpha, m} \mathbf{m}_{\alpha\beta} + \mathbf{m}_{\alpha m} &= \mathbf{0}, & \alpha \in C \\ \nabla \cdot (\phi_m \mathbf{T}_m) - \sum_{\alpha \neq m} \mathbf{m}_{\alpha m} &= \mathbf{0} \end{aligned}$$

where  $\phi_\alpha$  and  $\mathbf{v}_\alpha$  are the volume ratio and the velocity of the  $\alpha$ -th constituent, respectively.  $C$  is the set of cell indices taken into consideration and  $m$  refers to the ECM. The equations above requires the identification of the growth term  $\Gamma_\alpha$ , of the constitutive equation for the stress tensors  $\mathbf{T}_\alpha$ , and of the interaction forces  $\mathbf{m}_{\alpha\beta}$ .

A possible strategy to identify these relations is to consider experiments on adhesion at a cellular level. Cells adhere each other via cadherin junctions and to the extra-cellular matrix via integrin junctions. Some experiments performed to measure the strength of the adhesive bonds of different types of cells [2, 3, 8] show the existence of a characteristic strength of a bond, that is, if an ensemble of cells



is subject to a sufficiently high tension, locally some bonds break and some others form.

From these experiments it can be inferred that in principle any cell-cell or cell-ECM interaction is characterized by a threshold of the strength of the microscopic interaction force that can be sustained by the constituents considered in the interaction. Above this threshold detachment and relative motion between the constituents occur.

In particular, the mechanism of cell attachment–detachment becomes relevant during growth under an external load, when duplicating cells are able to displace their neighbours only if the energy needed is available.

Of course, one of the key issue is to upscale the cell-scale measurements above to macroscopic constitutive equations. Following the idea proposed in [1, 6, 7], we introduce for any constituent  $\alpha$  a multiplicative decomposition and consider the deformation gradient as split in the contributions due to pure growth  $\mathbf{G}^\alpha$ , to plastic cell reorganization  $\mathbf{F}_p^\alpha$  and to elastic deformation  $\mathbf{F}_n^\alpha$ , i.e.,

$$\mathbf{F}^\alpha = \mathbf{F}_n^\alpha \mathbf{F}_p^\alpha \mathbf{G}^\alpha.$$

This splitting is suggested also by the observation that growth occurs on a time scale much longer (hours up to days) than deformation.

In fact, the deformation gradient indicates how the body is deforming locally going from the initial (reference) configuration  $K_0^\alpha$  to the current configuration  $K_t^\alpha$ . An imaginary intermediate configuration  $K_n^\alpha$  is then introduced assuming that a point of the body can relieve its state of stress while relaxing the continuity requirement, i.e. the integrity of the body. It then locally relaxes to a stress-free configuration. The atlas of these pointwise configurations forms what we define natural configuration with respect to  $K_t^\alpha$ . Since it will change with time due to growth and cell re-arrangement, it is also called evolving natural configuration. One can then again consider the map from  $K_0$  to  $K_n$  as composed of two parts: the first one related to growth/death processes (therefore to mass variations in the volume element), the second one due to internal reorganisation, which implies re-arranging of the adhesion links among the cells, without change of mass in the volume element.

The role of the constitutive models is then to identify how the contributions due to growth and plastic reorganization evolve in time and how to describe the elastic component of the stress constitutive equation.

The constitutive equation for the stress takes a very convenient form in the limit case of small deformation with respect to the evolving natural configuration, that is typically true in the growth of tumour cell aggregates, because for larger stress, the natural configuration evolves, due to cell reorganization. One can then write

$$\lambda_\alpha \dot{\mathbf{T}}'_\alpha + \left[ 1 - \frac{\tau_\alpha}{f(\mathbf{T}'_\alpha)} \right]_+ \mathbf{T}'_\alpha = 2\eta_\alpha \left( \mathbf{D}_\alpha - \frac{1}{3} \text{tr} \mathbf{D}_\alpha \mathbf{I} \right),$$

where  $\mathbf{D}_\alpha$  is the rate of strain tensor,  $[\cdot]_+$  stands for the positive part of the argument,  $\lambda_\alpha$  is called cell re-arrangement time, and  $\tau_\alpha$  is a yield stress. The function  $f$  is a frame invariant measure of the stress.

We observe that the term containing the yield stress plays the role of a stress relaxation term that switches on just when the stress is above the yield value. Otherwise, for  $\tilde{f}(\mathbf{T}'_\alpha) < \tau_\alpha$ , it gives back the constitutive equation for an elastic solid.

As in classical viscoelasticity,  $\lambda_\alpha$  identifies the characteristic time needed to relax the stress to the yield value (not the null one, as in Maxwell fluids). It is then easy to realise that for processes with characteristic times much larger than  $\lambda_\alpha$  and stresses much larger than  $\tau_\alpha$  (i.e.,  $\tilde{f} \gg \tau_\alpha$ ) the model behaves like the viscous models commonly used in the literature on cancer modeling.

In transient phenomena for times much larger than the cell re-arrangement time the natural configuration has evolved relaxing the stress, leaving the material in a state of stress living at most on the yield surface.

It can be proved that this constitutive model is able to describe both the experiments by Forgacz and coworkers [4, 8], who perform a uniaxial test on a cell aggregate, and by Verdier and coworkers [5], who perform a shear test on a dense suspension of cells.

Following a similar reasoning for heterotypic cellular interaction and for cell-ECM interaction we propose the following model for the interaction forces

$$\lambda_{\alpha\beta} \dot{\mathbf{m}}_{\alpha\beta} + \left( 1 - \frac{\sigma_{\alpha\beta}}{|\mathbf{m}_{\alpha\beta}|} \right)_+ \mathbf{m}_{\alpha\beta} = \mathbf{M}_{\alpha\beta}(\mathbf{v}_\beta - \mathbf{v}_\alpha),$$

where the  $\mathbf{M}_{\alpha\beta}$ 's depend in turn nonlinearly on the volume ratios.

If  $\lambda_{\alpha\beta} = 0$  the model extends the one proposed in [7] for cell-ECM interactions also to all the heterotypic cellular interactions. In particular, the model states that if  $|\mathbf{m}_{\alpha\beta}| < \sigma_{\alpha\beta}$  then the interaction is not strong enough and the two constituents remain attached. Conversely, if  $|\mathbf{m}_{\alpha\beta}| \geq \sigma_{\alpha\beta}$  they detach.

Notice that the model above allows a configuration without relative motion ( $\mathbf{v}_\alpha \neq \mathbf{v}_\beta$ ) with non vanishing  $\mathbf{m}_{\alpha\beta}$  with  $|\mathbf{m}_{\alpha\beta}| < \sigma_{\alpha\beta}$ . This means, for instance, that the tissue can be at rest but have a moderate residual stress among the constituents.

In order to better understand the meaning of the first term in the equation for  $m_{\alpha\beta}$ , consider again the case  $|\mathbf{m}_{\alpha\beta}| < \sigma_{\alpha\beta}$ , so that the term with the positive part of the parenthesis drops. In this case, even at rest a residual interaction force acts between the constituents due to the different natural configurations they would like to tend to.

Focusing on the interaction between cell and ECM, modeling it as

$$\sigma_{\alpha m} = \frac{\hat{\sigma}_{\alpha m} \phi_\alpha m}{m_* - m}, \quad \text{with } m_* < 1,$$

implies that cells can not pass through regions where the ECM is denser than  $m_*$ . The presence of such terms in modelling tumour growth is fundamental because it allows to consider the case of cell compartmentalization by ECM barriers or basal

membranes, and therefore to better describe the process of tumour encapsulation, membrane remodelling and rupture due to the joint action of mechanical cues and metalloproteases.

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**Patterns and numbers on growing shells**

PATRICK SHIPMAN

(joint work with Alan C. Newell, Régis Chirat)

Patterns of ridges or spots are ubiquitous in nature, arising as sand ripples, fingerprints, geological and cloud formations, and in the camouflouge of tigers and leopards. In recent work, we have studied patterns that arise from growth in plants [4, 6, 7, 8, 9] and mollusks [1]. In plants, the arrangement of structures such as leaves, bracts on a pine cone, or florets of composite flowers is referred to as *phyllotaxis* (*phyllo* from the Greek word for *leaf* and *taxis* from the Greek word for *arrangement*). It has long been observed that phyllotactic patterns can be classified into just a few types and that the arrangement of *phylla* arising on plants as different as sunflowers (in which case the *phylla* are the florets and underlying bracts that make up a sunflower head) and many cacti (in which case the *phylla* are the aeroles that support spines) are identical. In the sunflower pattern, *phylla* are arranged in families of spirals that meet at the center of the plant; for a typical plant, the numbers of spirals in each family lie in the Fibonacci sequence 1, 1, 2, 3, 5, 8, 13, . . . . In another pattern, observed commonly on columnar cacti, *phylla* are arranged along undulating ridges that radiate out from the center of the plant. In extreme cases, this pattern becomes one of true ridges, so that like those in sand ripples or fingerprints, the plant surface can be described locally as

a periodic function. A similar competition between ridges and undulating ridges appears in mollusk shells.

What physical or chemical mechanisms are behind the formation of these patterns? and why is it that only a few patterns, in many ways similar to those observed elsewhere in nature and in laboratory experiments, dominate in both plants and mollusks?

Let's begin with phyllotaxis. Underlying the genesis of phyllotactic patterns is a rich interaction of biophysical and chemical mechanisms whose respective roles are only beginning to be understood. On the one hand, Paul Green and colleagues in the 1990s correlated the regions of compressive stress on a plant shoot to regions where the phyllotactic patterns are formed and demonstrated through experiments that mechanical forces influence pattern choice. On the other hand, experimental work in the past five years has revealed how an instability involving the diffusion and transport against diffusion of the growth hormone auxin plays a central role in plant development. Auxin essentially acts to promote growth, so that a nonhomogeneous distribution of auxin results in nonhomogeneous growth. We have developed a model for the interaction between mechanics and auxin within the framework of the Föppl-von Kármán-Donnell (FvKD) shell equations. The plant is thought of as a thin shell (the plant's outer skin, its *tunica*) on an elastic foundation (the plant's squishy corpus). Differential growth, partially due to nonhomogeneous auxin concentration, gives rise to stresses in the tunica, which may then buckle. In our most recent model [8], the elastic energy that is minimized by this buckling is a functional  $\mathfrak{E}(w, F, g)$  of the shell deformation  $w$ , a potential  $F$  for the in-plane stress tensor, and a growth function  $g$  related to auxin concentration. The variations of  $\mathfrak{E}$  with respect to  $w$  and  $F$  yield the FvKD equations

$$(1) \quad w_t + \nabla^4 w + P\nabla^2 w - [F, w] + \kappa w + \gamma w^3 = 0,$$

$$(2) \quad \nabla^4 F + \nabla^2 g + \frac{1}{2}[w, w] = 0,$$

which are then completed by an equation (derived as a continuum approximation of a discrete model proposed by Jönsson, *et. al.* [5]) governing the auxin concentration distribution. In (1,2), the bracket is defined by  $[F, w] = F_{xx}w_{yy} + F_{yy}w_{xx} - 2F_{xy}w_{xy}$  (where subscripts denote derivatives).

The key observation in analyzing these equations is that the energy is minimized on configurations for which, written in polar coordinates,

$$(3) \quad w(r, \theta) = \sum A_\nu(r) \cos(\vec{k}_\nu(r) \cdot (r, \theta)) = \sum A_\nu(r) \cos(l_\nu(r)r + m_\nu\theta),$$

consists of *triads* of periodic deformations, meaning that the wavevectors  $\vec{k}_\nu = (l_\nu, m_\nu)$  form a Fibonacci-like sequence with  $\vec{k}_\nu + \vec{k}_{\nu+1} = \vec{k}_{\nu+2}$ . Note that the angular wavenumbers  $m_\nu$  are integers and lie in the Fibonacci sequence. The analysis relies on reducing the problem to solving differential equations for the *order parameters*, namely the wavevectors  $\vec{k}_j$  and amplitudes  $A_\nu$ , which parameterize the space of possible patterns. For a fixed value of  $r$ , the order parameter

equations for the amplitudes  $A_\nu$  read

$$(4) \quad \frac{\partial A_\nu}{\partial t} = \sigma(\vec{k}_\nu)A_\nu + \sum \tau(\vec{k}_\nu, \vec{k}_p, \vec{k}_q)A_p^*A_q^* + \text{quartic terms},$$

where the cubic term is summed over all triads of wavevectors such that  $\pm\vec{k}_p \pm \vec{k}_q = \vec{k}_\nu$ . In form, this system of equations is generic in that it governs bifurcations from rotationally symmetric states to states with say,  $D_4$  (squares) or  $D_6$  (hexagons) symmetry. The details of the microscopic mechanisms lie in the coefficients  $\sigma, \tau$ , and these coefficients determine the optimal choice of wavevector sequence  $\vec{k}_\nu$ . Depending on  $r$ , solutions with  $D_4$  or  $D_6$  symmetry may be preferred, or neither symmetry may be compatible with the boundary conditions. However, a continuous symmetry can be expressed in the existence of functions  $\mathcal{A}$  and  $\mathcal{L}$  such that

$$A_\nu(r) \simeq \mathcal{A}\left(\frac{r}{m_\nu}\right), \quad l_\nu(r) \simeq \mathcal{L}\left(\frac{r}{m_\nu}\right).$$

The functions  $\mathcal{A}$  and  $\mathcal{L}$  can be calculated from the PDE model by numerically solving the amplitude equations (4), in which case the exact forms of  $\mathcal{A}$  and  $\mathcal{L}$  depend on the coefficients  $\sigma$  and  $\tau$ . In [9], we further show how functions  $\mathcal{A}$  and  $\mathcal{L}$  can be derived starting not with a PDE model, but rather by making reference to a global invariance condition which demands that the lattice determined by the wavevectors  $\vec{k}_\nu$  vary as little as possible with  $r$ . In particular, the sequence  $l_\nu$  is related to the sequence  $m_\nu$  by  $\frac{l_{\nu+1}}{l_\nu} = \lim_{\nu \rightarrow \infty} \frac{m_\nu}{m_{\nu+1}}$ . Classical theorems on the continued fraction expansions and the approximation of irrational numbers, such as  $\frac{l_{\nu+1}}{l_\nu}$ , by rational numbers, such as  $\frac{m_\nu}{m_{\nu+1}}$ , come into play.

The situation with mollusks is somewhat similar. In [1] we describe how differential growth in the mantle that excretes the material that hardens into the mollusk shell can give rise to patterns of ridges, undulating ridges, or lattices of bumps. But, in contrast to plant patterns (which form in a disk), mollusk patterns form at edges of growing shells and result from an interaction between soft surface growth (the growing mantle) and hard surface growth (the shell that is being excreted). The kinematics of shell formation has been modeled by Skalak and Hoger [10], but we suggest that various three-dimensional deformations of the basic shell shapes result from the interaction with the growing mantle.

Martine Ben Amar and colleagues [2] have studied other problems of growing shells using the Föppl-von Kármán equations, and the Oberwolfach workshop provided an opportunity to think more about the structure of these equations and the consequences of growth in two-dimensional bodies. What questions concerning growth in general are suggested by these examples? One question involves the interaction of energy-minimizing gradient systems (such as the FvKD equations) and chemical systems which are often not gradient. Indeed, our continuum approximation of the discrete auxin-based model of Jönsson, *et. al.* [5] reveals that this model is not gradient. It is no surprise, therefore, that simulations with this model do not generally result in stable patterns. It is not to be expected that chemical systems are gradient, but since the patterns observed in plants

are so regular, one wonders if a chemical-based patterning mechanism could be stabilized upon feedback with a biophysical mechanism. Another question is motivated by a calculation in [3], where we show how the buckling pattern resulting from a nonuniform stress state in a plate can be modified by the presence of soft modes. These are modes which are neutral (in that their linear growth rate is 0 at the buckling threshold) but which, through nonlinear interactions with the active (positive linear growth rate) modes, can become players in determining the energy-minimizing state. Might soft modes play a role in some growing shells, where spatially nonuniform stress states are to be expected?

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### Mathematical modeling and simulation of rotational tissue cultures

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(joint work with Raymond Chan, Juan J.L. Velázquez)

Rotational tissue cultures are relevant for high throughput drug testing systems in regenerative medicine. A petri dish, which contains growth medium and dispersed embryonic cells, is located on a gyratory shaker. The specificities of the rotation affect the fluid flow in the petri dish and thus the motion of the cells. Without any movement of the petri dish, the cells generally form a mono-layer at the bottom and grow in a disorganized manner. However, under a specific rotation of the petri dish, the cells finally form several 3-dimensional spheroids. Details about these experimental methods can be found in [1] and [2].

To understand the role the fluid dynamics play in this reaggregation and structure forming process, an experimental model system was set up. Microscopic beads

were put into the culture dish and rotated under the same conditions as the cellular systems. This experiment is assumed to serve well as a model system for the cell-based fluid dynamics under consideration. Clustering of beads could be observed only for certain rotation speeds. For other speeds further interesting patterns and phase transitions occurred. To confirm the hypothesis that mechanical aggregation plays a key role in the initial clustering of the beads, a mathematical model for the fluid dynamics was derived and numerically analyzed. The basis are the incompressible Navier-Stokes Equations with fictitious body forces added, resulting from the rotation of the petri dish. A dimensional analysis was performed and the model was reduced to a shallow water type of problem by regular perturbation techniques. The main assumption is, that the Reynolds number in horizontal direction is much larger than in vertical direction. The qualitative behavior of the mathematical model compares well to the aggregation behavior of the beads observed in the experiment. Further details about the mathematical model, its simulation and visualization are given in [3]

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