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

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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.

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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 interstial 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 "monolitihic" 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 grwoth 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.

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