Current challenges in the mechanobiology of growth

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Alain Goriely, Václav Klika

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Introduction

As biological sciences become increasingly quantitative, there is a realization that mathematical sciences can play a central role in organizing fundamental ideas and provide a framework for analysis and understanding of key phenomena. In particular, in the last decade, biologists have become increasingly interested in various mechanical aspects of biological systems from the genetic to the organismal level. For instance, it has been acknowledged that biological growth and development has an important mechanical component that plays a role in both genetic programming as well as the regulation of physiological processes such as heart and arteries remodelling. However, a unified theory of the growth of elastic tissues that addresses the fundamental coupling between geometric quantities and physical and chemical fields is still lacking. A proper formulation relies on various branches of mathematics and mechanics (differential geometry, thermodynamics, non-linear elasticity) and the analysis of key problems uses the most advanced techniques in non-linear analysis, dynamical systems, and computational mathematics. These issues in the mathematical formulation of biological problems arise in many different fields and represent a truly multi-disciplinar endeavour for which mathematics has a unique window of opportunity to play an central organizing role.

Over the last two years, there has been a number of meetings on aspects of mechanical biology. Most of these meetings have been organized in the physics, engineering, or biological community (with the notable exception of a small meeting at Oberwolfach organized by one of the organizer in September 2008). What transpires from these meetings is that there are numerous common fundamental mathematical problems that either need to be resolved and whose solution need to be brought out to the general scientific community. In particular, there is a new generation of researchers at the interface between mathematics, mechanics, and biology who is emerging and defying the traditional discipline boundaries. The choice of participant lists reflects both the breadth of interest from various scientific communities and the interest of a new generation of scientists.

Resolved and current challenges

Bulk, surface, and boundary growth in continuum mechanics framework?

Formulation of a suitable framework for tissue growth has attracted a lot of attention in the last decade. However, there are different approaches to this problem and they are, in fact, quite distinct. Because the framework of continuum mechanics was build for non-growing bodies and thus a clear and non-evolving reference configuration.

Three types of growth can be distinguished (according to difficulties they have): volumetric, boundary, and surface growth. **Volumetric (or bulk) growth** can be characterized by evolution of mass corresponding to each material point but without adding any new ones. In this case, the whole classical theory of continuum mechanics can be applied since a fixed reference configuration may be used for a body undergoing deformation and growth, and further the field equations are essentially the same. To have growth in mass one has to drop the condition of mass conservation and replace it only with mass balance. This captures the fact that the system is considered open and that the model describes only some of the involved constituents in growth, only those who are essential for mechanical response of the tissue. These additional constituents causing the tissue to grow are assumed to perfuse freely throughout the body causing growth in the whole volume of the body. Mathematically, we have a manifold $\mathcal{M}$ of material particles on which we define mass related to material points through its balance equation. If we have source terms in this relation without condition for conservation of mass, we may describe the evolution of deforming and growing body by a homeomorphic mapping that does not change the topology of the considered body.

Surface or boundary growth are assuming that the body is growing only from surfaces and thus the newly created matter is concentrated at these surface (either inside or on the boundary of body). The clear distinction between surface and volume growth can be found in the classical paper (Skalak et al., 1982). Boundary growth is a special case of surface growth which has been recently distinguished and assumes that growth occurs only on the instantaneous body boundary or its part (Epstein, 2010). In both growth material is added to or resorbed from the body as growth progresses. As a consequence, there is nothing like a fixed reference configuration. This essential problem is related to the very fundamentals of continuum mechanics and has been approached differently in the scientific community. The most widely used methods are: the reference configuration to evolve during growth; a new parameter (time elapsed from birth) is added to each material point; treat the growing body as composition of two bodies (fix the reference configuration of the original body and introduce new reference configuration for the "added body" as needed); characterize growth by a residual stress that it is causing in the current unloaded body. See for example the paper by Goriely and Ben Amar where the growth in morphoelasticity is modelled in incremental way (Goriely and Ben Amar, 2007).

However, if we look at a highly localized growth such as tip growth in root hairs is, the growth occurs in some *volume* near the tip (keep in mind the difference in difficulties faced in each case), see Fig. 1.

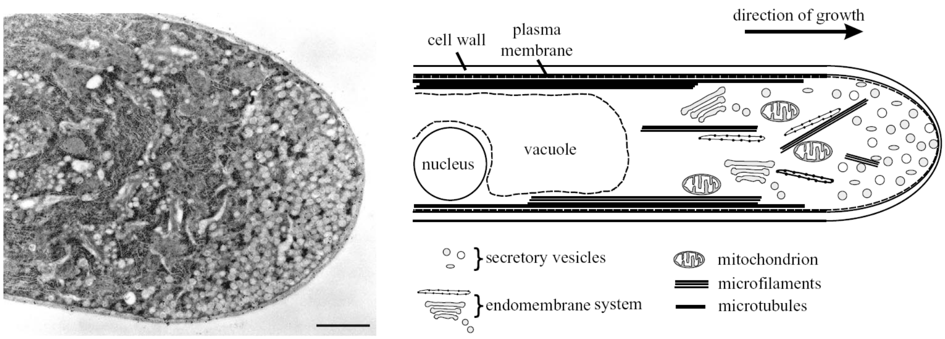

Figure 1: Example of quite concentrated growth - tip growth of root hairs cells (Carol and Dolan, 2002). Is it surface or volumetric growth case?

Multiplicative decomposition

The multiplicative decomposition of the deformation gradient $\mathbf{F} = \nabla\chi$ into an elastic part $\mathbf{F}^e$ and a growth tensor $\mathbf{F}^g$ (the growth tensor as a representation for a volumetric growth was developed by Skalak et al. (Skalak et al., 1982)) proposed by Rodriguez and co-workers (Rodriguez et al., 1994) is the most widely model used (see Fig. 2).

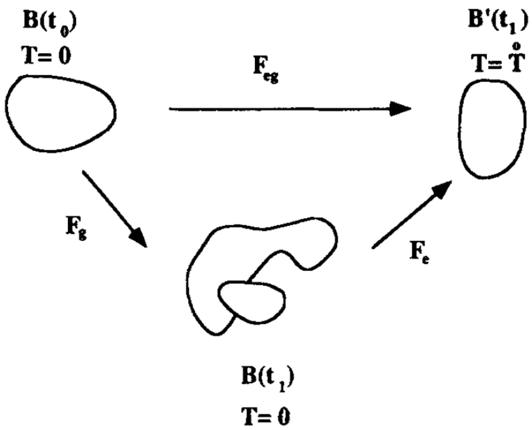

Figure 2: Typical consideration in tissue growth with multiplicative decomposition. Adapted from (Rodriguez et al., 1994)

In growth kinematics, the important issue is to describe the evolution of the growing body when external loads are removed. The multiplicative decomposition does not bring any insight into this experimentally inaccessible configuration. The evolution equation for the growth tensor has to be based directly on the underlying biological processes which are exactly those, who are being neglected in the open system consideration. The framework to be built has to be capable of incorporating these effects - one possibility may be the usage of mixture theory approach, e.g. (Humphrey and Rajagopal, 2002).

The following simple observation reveals some of the limitations of the multiplicative decomposition: due to the multiplicative character it is assumed that the displacement at each material point can be decomposed into two subsequent events - one related to growth and the other to deformation. And because all the properties of the material at a given material point are characterized by (averaged) quantities specified only at these material points, the newly formed material cannot have different material properties than the original material at the given point (this can be easily followed at least in the volumetric case). Thus, multiplicative decomposition cannot be used in the case when the newly formed tissue is deposited with a different stress than the already existing material, at different velocity or when ageing of the tissue is of relevance.

Moreover, even when using a detailed mixture theory there still seems to be need of using multiplicative decomposition to combine the effects of growth and elastic deformation.

Mixture theory or multiplicative decomposition?

Apart from multiplicative decomposition, mixture theory is the most widely used approach. It seems to be more natural since growth and remodelling are a consequence of chemical reactions. And even mechanosensing and mechanotransduction events involve chemical reactions. Mixture theory is taking advantage of continuum theory which is used to describe deformation of each individual constituent and of the mixture as a whole but is also capable of capturing the chemical reactions among constituents and thus providing more details about the growth process itself. If one compares it to the kinematic description using multiplicative decomposition, one finds that mixture theory is ideally suited for the purposes of modelling growth of deforming body/tissue when the evolution of separate constituents are known.

But there are some drawbacks related to this approach. First of all, mixture theory approach is not really an alternative to multiplicative decomposition. It only provides more details about the interactions among constituents and one has to relate growth with tissue response. This is again done in most cases through multiplicative decomposition. Further, mixture theory can be developed in very general setting including interface jump conditions between phases (see for instance (Eringen and Ingram, 1965; Atkin, 1976; Drew, 1983)), diffusion of constituents relatively to each other, chemical reactions (e.g the classical paper (Bowen, 1969) or even emergence of residual stresses (e.g. (Ateshian, 2007; Ambrosi et al., 2010)). However, to apply this theory to concrete problem always leads to many substantial assumptions and restrictions that enable to solve the problem numerically, not mentioning the desire to have analytical solution to compare with some know results or behaviour. Classical example of constrained mixture theory is (Rao et al., 2003) and probably the most complex application (at least that we are aware of) of mixture theory of non-reacting species to concrete problem can be found in (O'Dea et al., 2010). Next, the classical problem with mixture theory is the definition of relevant boundary conditions for a given problem. Usually, we do not usually have a detailed knowledge of the problem and interactions among substances that would instruct us how to describe boundary conditions for each constituent, for example how should be the external load distributed among constituents? The notion of partial pressures is not of much help in this regard.

Revising classical mixture theory? However, classical mixture theory which is based on rational thermodynamics may need revision. Here, we follow some notes from two papers on this topic by Hansen and his co-workers (Hansen et al., 1991; Hansen, 1989) which for some reason did not attract much attention. In his first paper, Hansen points out that he used weighting of individual constituent contributions to obtain mixture variables is of crucial importance and should not be based on mass fraction in general. He proposes a correction called *volume fraction mixture theory* (especially for definition of mixture velocity) which is physically more appealing and shows on an example of simple two-phase mixture which can be analytically solved that the re-examined theory provides correct results whereas the classical one fails (Hansen, 1989). In the second paper, Hansen summarizes the principles of mixture theory as put forth by Truesdell (Hansen et al., 1991):

1. All properties of the mixture must be mathematical consequences of the properties of the constituents.
2. So as to describe the motion of a constituent, we may virtually isolate it from the rest of the mixture, provided we allow properly for the actions of other constituents upon it.
3. The motion of the mixture is governed by the same equations as a single body.

Of particular interest is the third principle as it leads to fundamentally different restrictions for the supply terms in governing equations representing constituent interactions. They revise this principle: "... the summed balance equations are not required to reduce to those of a single continuum". This point of view is adopted on the grounds that mixture theory represents a generalization to the mechanics of a continuous medium. Hence, there is no reason to force the governing equations for a diffusing mixture to be the same as those governing a single continuum. *Rather the field equations* *for a continuum should represent a special case of the mixture relations.*". Moreover, they compared both theories with results from the kinetic theory of gas mixtures where the volume fraction theory is consistent with it while the classical theory is not.

This clearly suggest that behaviour of the mixture is governed only by summing the behaviour of each of its constituent without imposing any constraints on this summation. But what really is the importance of used weighting? And is there any need for definition of mixture variables at all? This should be subject of further research, i.e. comparing these two mixture theories (and probably some others as well, e.g. multiphase flow models) on some example of tissue growth to demonstrate the importance of the used approach and if needed proposing some further modifications.

Conclusions and perspectives

From all the above mentioned issues and problems faced when establishing mathematical foundations for tissue growth we would like to highlight outstanding issues. The first key challenge is to find a way to derive evolution equation for growth tensor $\mathbf{F}^g$ needed in both multiplicative decomposition or mixture approach. Further, information from mechanosensing and mechanotransduction should be used to understand the coupling between mechanical and chemical processes. This last point is essential in order to derive a consistent framework for tissue growth where this coupling is fundamental. Some insight may be gained using thermodynamics, see for example the work of Kuhl's group (Goktepe et al., 2010) or for general consideration about coupling of mechanical and chemical phenomena (Klika, 2010; Klika and Maršík, 2009). However, postulating phenomenological laws will be most probably needed in a first step to model the the complexity of biological systems.

It is clear that mixture theory allows for more detailed information about the interactions among constituents, however it remains unclear how one can exploit the knowledge of concrete interaction terms appearing in the balance of mass. Even though the process of mass addition and removal (source terms in mass balance equation) is clearly connected to growth, it is still not clear how the evolution of the different component relate to the the evolution of the growth tensor $\mathbf{F}^g$.

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