Morphoelasticity and mechano-transduction in living matter

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The emergence of shapes in living matter is the final result of a series of complex interactions relating the biochemical processes driving changes of microstructure to the macroscopic reorganization of the material architecture. Understanding the basic principles and the key mechanisms coordinating such a crosstalk at different length-scales is one of the main challenges in developmental biology. Moving from a biomechanical perspective, in this talk I will show how the combination of physical and mechanical theories/methods can foster understanding on the role played by the nonlinear elasticity in the formation of a specific pattern, with the aim to identify the key mechanical feedbacks regulating growth and remodeling in biological materials.

In continuum mechanics, a considerable amount of modeling research has been performed in the last decade to accommodate the evolution laws of mass variation inside a material, written as a volumetric change of bulk material or an accretion/resorption at a surface. A seminal idea has been borrowed from dislocation theory, assuming a separability principle between volumetric growth (i.e. smooth change in a single-phase material) and elastic deformation. Such a multiplicative decomposition hypothesis is the fundamental assumption of many morphoelastic theories, although encountering several limitations in biomechanical applications, often requiring a number of simplifications for providing analytical results of complex boundary value problems for biological materials (i.e. generally viscoelastic, anisotropic, incompressible bodies). Moreover, even if stress-driven growth processes can be taken into account, continuum theories of growth and remodeling often exclude *ab-initio* the possibility to include a diffusive mass flow inside the body, being not suitable to describe morphogenetic events where mass transport and chemo-mechanical coupling are of paramount importance.

In the first part, I will show how complex biological patterns can arise from the loss of elastic stability due to geometrical incompatibilities in the growth processes. In particular, I we will focus on the bifurcation analysis of soft growing materials, with the aim to investigate the influence both of growth rate and of external constraints (intended in terms of applied traction loads and/or spatial confinement). The cylindrical geometry is chosen to describe the grown pattern of multilayered tubular organs (e.g. airways, esophagus, intestine and blood vessels), where incompatible growth between the layers results in a complex transmural distribution of residual strains. Introducing a generating function to derive the implicit gradient form of displacement fields, the incompressibility constraint on the elastic deformation tensor is solved exactly using a canonical transformation. Therefore, a generic boundary value problem, with conservative applied volume forces and traction, can be completely transformed into a variational problem: the elastic solution is given by the value of the scalar generating function minimizing the total potential energy of the growing continuum, respecting the given boundary constraints. The variational formulation is able to provide a straightforward derivation of the linear stability analysis, which would otherwise require lengthy manipulations on the governing incremental equations. In addition, the use of a generating function allows accounting for the presence of local singularities in the elastic solution.
The proposed variational method is applied in the bifurcation analysis of few growth

problems of biomechanical interest. The theoretical results show that folding of the inner mucosal layer can appear in physiological growth conditions, even in absence of external loading. Furthermore, surface instability can occur at the outer boundary of a thin proliferating ring in contact with a soft inner core, as observed in the early development of skin cancers. The effects of external constraints, material properties and growth characteristics on the creation of a non-circular shapes are discussed in comparison with a wide variety of experimental studies. The theoretical predictions indicate that the transition towards a more complex pattern for soft materials is often initiated by a mechanical instability. Other than the mentioned clinical interest, a quantification of the effects of growth on the stability of soft materials is important for applications in bioengineering and in biomaterials.

In the second part, I will focus on the kinematic description and the main balance equations of a novel thermo-mechanical growth theory for a second-gradient continuum. The aim of such a modeling is to include the role of diffusing morphogens in the determination of spatial patterns of cell differentiation, providing a thermodynamically-based coupling for modeling the stress-driven feedback mechanisms that regulate growth and orchestrate shape during morphogenetic events. The viewpoint assumes that genes carry specific biochemical instructions for the creation of biological matter, while the biomechanical and biochemical interactions with the environment generate the pattern emergence. In the framework of a second gradient hyperelastic theory, the first single-phase continuum theory accounting both for volumetric growth and for mass transport phenomena is formulated. Mass changes are defined by a material isomorphism where growth processes act as local rearrangements of the material inhomogeneities: a first-order uniformity transplant determines the extent of volumetric growth, while a second-order transplant takes into account the curvature effects induced by a local differential deformation. The diffusion of biochemical species (e.g. morphogens, nutrients, migration signals) inside the biological matter is considered using the theory of configurations forces with internal variables. Mass transport phenomena are found to depend both on the first- and on the second-order material connections, and their driving forces can be written in terms of covariant material derivatives based on the two connections, reflecting in a purely geometrical manner the presence of a (first-order) torsion and a (second-order) curvature. The expression of remodeling evolution laws for first- and second-order material inhomogeneities is given, having a great importance for a consistent thermodynamical description of morphogenetic events. The proposed constitutive theory is applied for modeling the effects of an Eshelbian coupling on volumetric growth and mass transport in two biomechanical examples. First, the avascular development of a ductal carcinoma is considered, illustrating how both mechano-transduction and spatial limitation of nutrient diffusion can inhibit growth. Secondly, the proposed evolution equations of material inhomogeneities are used to analyze the remodeling laws driving homeostasis in blood vessels, both in healthy and in pathological conditions. The results indicate that diffusive mass fluxes play a fundamental role in the active regulations of homeostatic conditions, possibly being involved in the integral feedback mechanisms driving local growth rates. Finally, the biomechanical quantification of curvature-dependent effects on growth can help not only in understanding the growth patterns of cellular aggregates, but also has important applications for optimizing scaffolds in regenerative medicine and tissue engineering.