GROWTH AND REMODELING

Marcelo Epstein
Department of Mechanical and Manufacturing Engineering, University of Calgary, Canada

Keywords: adaptive elasticity, configurational mechanics, anelasticity, internal variables, Eshelby stress, Mandel stress, aging, damage, mixtures

Contents

Summary

The article begins with a brief description of some of the modeling challenges in the field of growth and remodeling, followed by a description of both continuous and discrete models of the growth of tumors, whereby the evolution law is derived fundamentally from the balance of mass supplemented with a constitutive law of diffusion. It then goes on to describe the first complete theory of growth and remodeling formulated within the framework of modern Continuum Mechanics, namely, the theory of adaptive elasticity. In this theory, residual stresses are ruled out by assuming that any new material created in the process of growth is accommodated in the available space provided by the pores of the bone matrix. The next paradigm is provided by the theory of anelastic evolution, which can be viewed as a particular case of the theory of internal state variables. The emergence of configurational forces, such as the Eshelby stress, is placed within this context. Some attention is then devoted to particular applications such as aging, trabecular bone, muscle tissue and plant growth. None of these topics is covered in depth. Finally, a brief section is included on the challenges presented by the modeling of surface growth.

1. Introduction

Although not limited exclusively to biological tissue, the theories of growth and remodeling have acquired their modern impetus from the need to understand and describe biological processes of increase or decrease of mass (*growth*), on the one hand, and processes whereby the material conditions and/or properties change over time and/or in response to the environment (*remodeling*), on the other hand. The boundary

between growth and remodeling, however, is at best fuzzy. Many processes of growth are accompanied by a need for the new material to occupy unavailable space, thereby leading possibly to the development of residual stresses or, at the very least, to a re-accommodation of the material particles at play. Moreover, a process of remodeling may entail just such a phenomenon without compromising the underlying chemical identity of the material or, more drastically, it may be accompanied by a true change of the material descriptors, such as the elastic constants, the refractive index, the brittleness or ductility properties, the electric and magnetic coefficients, and so on. It is customary to refer to these more radical processes as *aging*. In the case of growth too a distinction has to be drawn between *volumetric or bulk growth*, in which one may assume that (in a continuum model) the increase or decrease of mass takes place at each already existing particle (thus resulting in a mere increase or decrease of the mass density), and *surface growth*, which takes place by accretion of new material over the boundaries of the body (thus leading to a redefinition of the body itself). A simple mental picture of surface growth can be gathered from the case of a hollow sphere. In principle, surface growth on the internal boundary may lead to a closure of the hole. Such a dramatic topological change (from a hollow to a solid sphere) cannot take place in the case of volumetric growth. An excellent review of the whole field up to 1995, including both the biological foundations and the modeling aspects, can be found in (Taber, 1995). The present article is not a comprehensive review of the state of the art, but rather an account of various stages in the development of the theories of growth and remodeling. Thus, many important contributions have not been included. The emphasis is placed on the general lines of thought, rather than in the details of the applications. Moreover, the presentation emphasizes the modeling aspects rather than the physiological ones. One of the earliest treatments of theories of growth took place in the field of tumor growth, where it was recognized that the progress of a tumor is describable, at least in part, by means of a diffusion equation. Accordingly, the article is organized as follows: starting from tumor growth, it follows then chronologically with adaptive elasticity, anelastic theories, some particular theories and, finally, a short section on surface growth. The earliest attempts at a scientific theory of growth and remodeling go back to the end of the nineteenth century with the works of Roux (1881) and Wolff (1892) who, in different ways, were the first to hypothesize that there is a definite connection between mechanical stimuli and internal structure of biological tissue. Wolff, more specifically, assumed that bone trabeculae follow the lines of principal stress. These seminal ideas are still discussed today, and the power of electronic computation permits their implementation in an endless variety of contexts, from continuous optimization techniques to discrete implementation into cellular automata of events triggered by chemical signals at the microscopic level.

2. Modeling Challenges

The two extremes of modeling paradigms for growth and remodeling are represented by *discrete* and *continuous models*. In a discrete model, typified by but not restricted to *cellular automata*, the material background is lumped into a discrete collection of point-like *sites*, where all events take place. These sites interact with each other according to specific *rules* intended to represent the physical, chemical and mechanical laws. The rules may be very simple, but the complexity of the system, reflected in terms of the large number of sites at play, can result in a very flexible overall behavior able to

capture the essential features of the macroscopic phenomena. Among the merits of this approach is its ability to incorporate directly into the model a variety of criteria which are better understood in their raw nature as discrete events. Examples of this kind are: cell subdivision and transmission of information from the genes to the environment. On the other hand, other phenomena, such as the deformability of the medium and the expression of its thermo-mechanical properties, are not easy to implement in discrete systems without a considerable loss of fidelity. It is in this domain that continuous models have the upper hand. Accordingly, modern *Continuum Mechanics*, with its sophisticated blend of mathematical generality and a centuries-old tradition of success in particular theories of solids and fluids, is the preferred setting of most present-day models of growth and remodeling. In its standard formulation, however, Continuum Mechanics is not in itself sufficient to face the challenges posed by problems of growth and remodeling. Among the various reasons for this deficiency, three deserve particular mention. The first, and most obvious, reason is that one of the basic tenets of Continuum Mechanics is the law of *conservation of mass* (somewhat misleadingly called the *continuity equation* in fluid mechanics). This limitation is not too difficult to overcome by replacing the law of conservation by a law of *balance of mass*, whereby volumetric sources and surface fluxes of mass are admitted into the picture. Concomitant corrections have to be made to the other laws of balance (linear and angular momentum, energy and entropy). Such modifications are already available in the standard context in terms of the theory of *chemically reactive mixtures*. Indeed, focusing attention on one of the components of such a mixture alone, one obtains a correct version of the modified laws of balance alluded to above. The second challenge presented to standard Continuum Mechanics by the modeling of growth and remodeling is that the concept of *material body* as a fixed, invariable, collection of particles that manifests itself in space through configurations needs to be revised. Indeed, in a process of remodeling, changes are taking place in the body even in the absence of spatial deformation or motion. In a process of aging, for instance, the material properties are altered by the mere passage of time. The propagation of a crack may be triggered by the deformation, but results in a change of the body itself. Similar remarks apply to the propagation of phase boundaries, motion of dislocations, reorientation of the directions of anisotropy, and so on. In the last two decades, Continuum Mechanics has responded to this challenge by augmenting its scope to include the concept of *configurational* or *material forces* seen as the driving forces behind process of *material evolution*. Finally, a third challenge comes form the fact that (for instance, in cases of surface growth) not only the material characteristics of the body points evolve with time, but its very *topology* may evolve, as already mentioned above. This challenge is still open and we will briefly indicate later a possible line of attack.

3. The Growth of Tumors

The study of the growth of tumors can be considered as a field in its own right, functioning quite independently of the general trends prevailing in the field of growth and remodeling in general. Our interest in including it in this article is to encourage interaction between these fields and to emphasize the potential of discrete models for the numerical simulation of growth in general. Not all models of tumor growth are of the discrete type, but more attention has been devoted to discrete models in this field than in any other application of growth and remodeling. A comprehensive review of

both discrete and continuous models of avascular tumor growth is given by (Roose et al., 2007). Cancer develops in three successive phases: avascular, vascular and metastatic. Somewhat different techniques are used to model each of these phases, but the avascular phase forms the foundation. The *avascular phase* takes place initially when the *tumor spheroid*, as the tumor cell aggregate is called, is sustained by locally available nutrients (such as oxygen) only. The size of a tumor under these conditions is controlled by the natural dynamic balance between cell proliferation and cell death. In particular, the diffusion of the nutrients imposes a limit for tumor growth. It is generally hypothesized that, in order to continue growing, tumors recruit blood vessels from the surrounding tissues through a process known as *angiogenesis*, thus triggering the *vascular phase*.

3.1. Continuous Models

The most basic continuous models aim at predicting the time evolution of the tumor size from the equations of mass balance for each species of a chemically reacting mixture (see, e.g., Bowen (1969)). By discarding the balance of forces and energy, these models must implement an ad-hoc constitutive equation expressing the diffusive velocities in terms of the concentrations alone, such as Fick's law. In a mixture theory it is assumed that any spatial element of the mixture, no matter how small, is occupied by particles of all the n species. Denoting by $\mathbf{v}_\alpha$ and ρ_α the velocity and the mass density (per unit mixture volume) of the species α, the equations of mass balance are given by:

$$\frac{\partial \rho_\alpha}{\partial t} + \nabla \cdot \left(\rho_\alpha \mathbf{v}_\alpha \right) = \pi_\alpha \qquad \left(\alpha = 1, ..., n \right) \tag{1}$$

where t is the time variable, ∇ indicates the spatial divergence and π_α stands for the mass production, per unit mixture volume, associated with the species α (due to chemical reactions between the various species). Adding up the individual balance laws, we obtain, as expected, the conservation law:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot \left(\rho \mathbf{u} \right) = 0 \tag{2}$$

where:

$$\rho = \sum_{\alpha=1}^{n} \rho_\alpha \tag{3}$$

is the density of the mixture and:

$$\mathbf{u} = \frac{\sum_{\alpha=1}^{n} \rho_\alpha \mathbf{v}_\alpha}{\rho} \tag{4}$$

is the mean (barycentric) velocity of the mixture. The total mass production vanishes, since the chemical reactions are assumed to be (stoichiometrically) balanced. Introducing the *diffusive velocities*:

$$\mathbf{u}_\alpha = \mathbf{v}_\alpha - \mathbf{u} \qquad (\alpha = 1,...,n) \tag{5}$$

Equation (1) can be rewritten as:

$$\frac{\partial \rho_\alpha}{\partial t} + \nabla \cdot \left(\rho_\alpha \mathbf{u} \right) = -\nabla \cdot \left(\rho_\alpha \mathbf{u}_\alpha \right) + \pi_\alpha \qquad (\alpha = 1,...,n) \tag{6}$$

It is at this point that Fick's law of diffusion is introduced, namely:

$$\rho_\alpha \mathbf{u}_\alpha = -D_\alpha \nabla \rho_\alpha \qquad (\alpha = 1,...,n) \tag{7}$$

where D_α are positive definite tensors (or scalars) representing the *diffusivity* properties of each constituent of the mixture. Substituting into Eq. (6), we obtain the final form:

$$\frac{\partial \rho_\alpha}{\partial t} + \nabla \cdot \left(\rho_\alpha \mathbf{u} \right) = \nabla \cdot \left(D_\alpha \nabla \rho_\alpha \right) + \pi_\alpha \qquad (\alpha = 1,...,n) \tag{8}$$

We point out that in the usual presentation, where mixture theory is not used, it is argued that Eq. (1) contains only the mean velocity of each constituent around which there is a random motion. Under these conditions, the production term contains both the chemically induced mass supply and the diffusive term governed by Fick's law. These mass productions, clearly, do not need to add up to zero. Moreover, the final equations differ from Eq. (8) in that in the left-hand sides the mean mixture velocity is replaced by each constituent velocity. It is usually assumed, however, that all constituents have the same velocity and that they only differ by their respective random motions, thus arriving at Eq. (8) by a different, somewhat less rational, way. It is customary, in a chemical context, to express the various mass densities in Eq. (8) in terms of fixed molecular masses multiplied by the "number of particles" n_α of each species per unit mixture volume.

If the mean velocity $\mathbf{u}$ is known, and if the chemical reaction rates are expressed in terms of the concentrations, Eq. (8) becomes a system of diffusion equations to be solved for the density of each species. In practice, however, our interest lies in solving also for the velocity field. We observe that, even with the introduction of Fick's law for each constituent, the system of Eqs. (8) falls short in terms of number of equations versus number of unknown functions. To close the system, further assumptions are made, which are not always explicit or mutually consistent. The first assumption is that we are in the presence of a perfectly spherically symmetric problem, so that the only non-vanishing component of the mean velocity u is the radial one. The second assumption is that the total density ρ of the mixture is spatially and temporally constant. The third assumption is that the chemical productions are not perfectly balanced. To explain this better, let us assume that there exist just two components, which we denote

by L and D, for "live cells" and "dead cells", respectively. Although the increase of D cells is completely accounted for by the decrease in L cells, the increase of L cells is supplied externally by an unspecified source (not part of the mixture). Thus we have that the sum $\pi_{\mathrm{L}} + \pi_{\mathrm{D}}$ is always non-negative and seldom zero. Finally, we assume that the (scalar) coefficients of diffusivity in Fick's law are independent of each other and, in particular, that D_{D} vanishes. Finally, chemically inspired constitutive equations (see Casciari et al. (1992)) are supplied connecting the production with the velocity component. Since the density is assumed to be constant, an equation can be ultimately obtained and solved numerically for the increase of the radius of the spheroid as a function of time. Quite apart from some of the questionable theoretical features of the model, the complexity of the underlying phenomena is such that an accurate experimental substantiation of the constitutive assumptions is virtually impossible. This is the case, in fact, for most biomechanical models. More sophisticated continuum models of tumor growth exist (e.g., Greenspan (1975), Byrne and Chaplain (1996)) that incorporate mechanical constitutive equations, usually (but not necessarily, e.g. Roose et al. (2003)) in terms of an average pressure and a putative strain-energy function. These models permit to model a tumor that grows in a non-spherically symmetric fashion and remove some of the other limitations of the purely mass-balance-driven models.

3.2. Discrete Models

In its most elementary version, a *cellular automaton* consists of a discrete number of fixed sites, each of which is in one of a discrete number of possible states, whose evolution in discrete time-steps is governed by a discrete set of rules of interaction of each site with its neighbors. The state of the system at any one time is completely determined by the state of the system at the immediately preceding time. A comprehensive picture of the capabilities of cellular automata in modeling complex systems can be found in Wolfram (1994). Thus, cellular automata are ideally suited for the description of the evolution of biological systems. In the case of the growth of tumors, a possible automaton rule may involve a probabilistic criterion, whereby a site occupied by a cancerous cell has a choice to either proliferate, or become quiescent, or die, or move to a neighboring site. The probability of each of these choices depends of the local state of the system, which, in addition to the presence of a cancerous cell at a site, may include the local concentration of nutrients and other factors (mechanical, chemical, etc.) deemed to be relevant. Qi et al. (1993), for instance, construct an automaton consisting of a square lattice divided into $n \times n$ equal compartments. Each cell is affected by only four neighbors, and it may be occupied by either a normal cell, a cancerous cell, a complex, a dead cancer cell, or an effector cell. The evolution of the automaton is then governed by 3 simple probabilistic rules, based on experimental evidence. Starting from an initial state for which there are 5 cancerous cells in the central compartment, and a normal cell and an effector cell in each compartment, Figure 1 shows the state of the tumor after about 100 steps, when it reaches its maximum size. The black compartments represent cancerous cells.

It is apparent that discrete models offer the advantage over continuous models of allowing for the transmission of signals, heterogeneity of cells and direct incorporation of relevant experimental information without the need to formulate precise physical

laws of balance. On the other hand, precisely because of this lack of a foundational physico-chemical underpinning, these models do not necessarily enhance the general understanding of the phenomena at hand. Each case stands on its own. Mixed models, involving a continuous substrate behaving according to the laws of Continuum Mechanics and a discrete model superimposed on it to represent the transmission of signals and other discrete phenomena, are very promising.

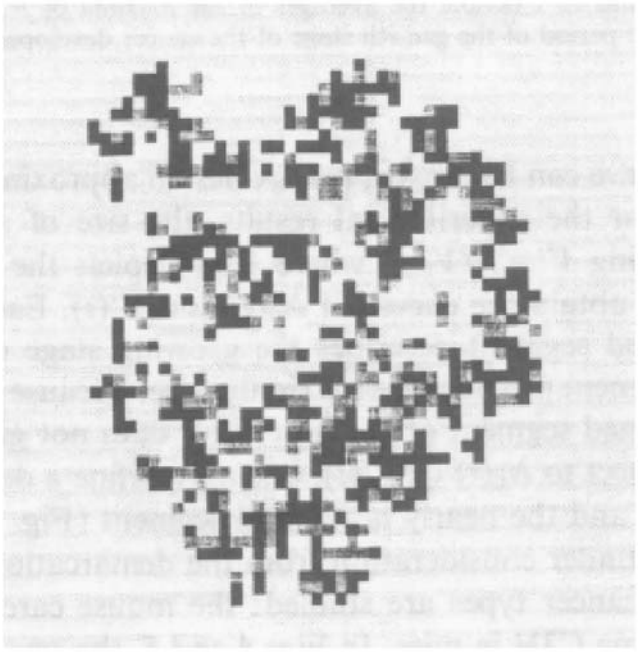

Figure 1. The predicted shape of a tumor. (From Qi et al. (1993), with permission from the Academic Press.)

4. The Theory of Adaptive Elasticity

4.1. Introduction

Although the earliest theories of tumor growth were developed in the 1960s (e.g. Burton (1966)), when Continuum Mechanics in general and the theories of mixtures in particular were already flourishing, and in spite of the impressive predictive power of some of the models, the field of tumor growth seems to have remained for a long time in a stage of imprecise formulation. The first impetus toward a fully fledged thermomechanical theory of growth based on a complete and rigorous expression of the underlying physical and mathematical laws took place only in the next decade in the field of bone growth. Without a doubt, the pioneering work in this field is the seminal article by Cowin and Hegedus (1976a) under the name of the theory of *adaptive elasticity*. The main assumptions of the theory are as follows: (i) bone is a considered as an elastic porous matrix (made of extracellular material) whose pores are filled with a liquid perfusant; (ii) the slow chemical reactions (mediated by the bone cells) responsible for growth and remodeling are controlled by the state of strain of the matrix; (iii) the addition or removal of solid mass resulting from the chemical reactions takes place exclusively at the expense of the porosity, thus causing no residual stresses; (iv)

the porosity is included as one of the kinematic variables of the theory; (v) the balance equations are formulated on the basis of the solid phase alone (namely, the matrix), which is an open system immersed in an isothermal perfusant bath. Some of the features of the model are illustrated schematically in Figure 2.

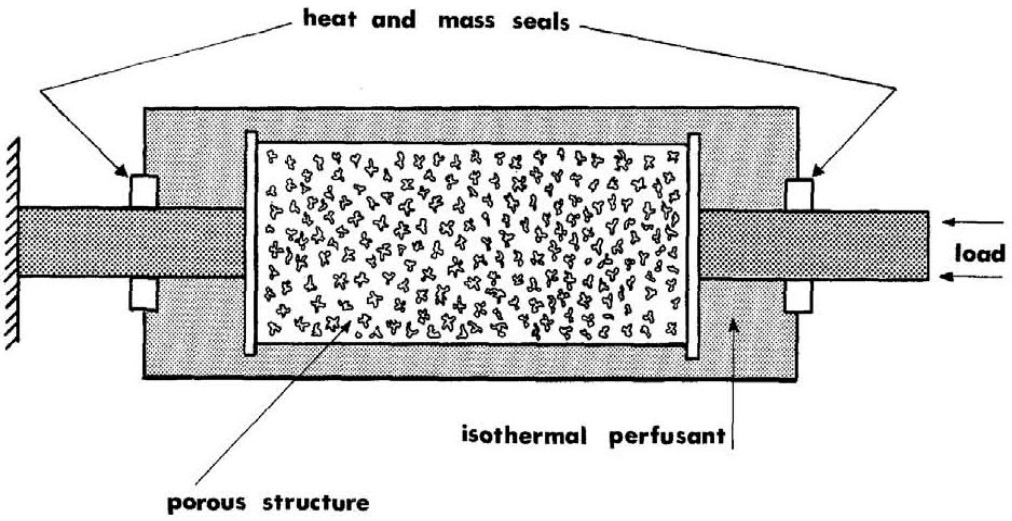

Figure 2. Schematic diagram of the model. (From Cowin and Hegedus (1976a), with permission from Springer.)

Since the addition (growth) or removal of material (resorption) take place exclusively at the pores, the total volume occupied by the bone in an (assumed to exist) stress-free configuration at constant temperature remains invariable.

4.2. Field Equations

Denoting by γ the density of the matrix material and by ϕ the porosity, the effective density ρ of the porous structure is given by:

$$\rho = \gamma(1-\phi) \tag{9}$$

A crucial part of a growth theory is the incorporation of a distributed mass source *c* measuring the mass produced per unit time and per unit spatial volume. The local Eulerian form of the balance of mass can then be written in terms of the (spatial) velocity field **v** as:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = c \tag{10}$$

This equation is identical in form and meaning to Eq. (1) for the balance of mass of a single component of a mixture, as discussed in the case of tumor growth. But, whereas in the former context the entire theory was based on equations of this type alone, in the theory of adaptive elasticity (as indeed also in later theories of tumor growth) this equation is coupled with other equations of thermomechanical balance. These equations

-

-

-

Bibliography

Alford P.W., Humphrey J.D. and Taber L.A. (2008), Growth and remodeling in a thick-walled artery model: effects of spatial variations in wall constituents, *Biomechanics and Modeling in Mechanobiology* 7, 245–262. [The mixture concept of Humphrey and Rajagopal (2002) is applied to the arterial wall].

Bowen R.M. (1969), The thermochemistry of a reacting mixture of elastic materials with diffusion, *Archive for Rational Mechanics and Analysis* 34, 97-127. [This is one of several important papers by this authority on the theory of chemically reacting mixtures].

Burton A.C. (1966), Rate of growth of solid tumours as a problem of diffusion, *Growth* 30, 157–176. [This is one of the earliest mathematical formulations of biological growth].

Byrne H.M. and Chaplain M.A.J. (1996), Modelling the role of cell-cell adhesion in the growth and development of carcinomas, *Mathematical and Computer Modelling* 24, 1–17. [See critical discussion in Roose et al. (2007)].

Carter D. R., Fyhrie D. P. and Whalen R. T. (1987), Trabecular bone density and loading history: regulation of connective tissue biology by mechanical energy, *Journal of Biomechanics* 20, 785-794. [An extension of the paper by Fyhrie and Carter (1986)].

Casciari J.J., Sotirchos S.V. and Sutherland R.M. (1990), Nutrient concentration and pH gradients in multicellular tumor spheroids and their effects on growth and metabolism, Paper 192c, Proceedings of the AICHE Annual Meeting, Chicago. [See critical discussion in Roose et al. (2007)].

Chaboche J.L. (1987), Continuum damage mechanics: present state and future trends, *Nuclear Engineering and Design* 105, 19-33. [This is a review paper by one of the important contributors in this field].

Coleman B.D. and Gurtin M.E. (1967), Thermodynamics with internal state variables, *J. of Chemical Physics* 47, 597-613. [This is one of the foundational and pioneering papers in this area].

Chudnovsky A. and Preston S. (2006), 4-D geometrical modeling of material aging , *Int. J. of Geometric Methods in Modern Physics* 3, 1529-1558. [This paper presents a novel approach to aging using rather sophisticated mathematics].

Cowin S.C. (2001), The false premise of Wolff's law, in *Bone Mechanics Handbook*, 2nd edition (ed. S.C. Cowin), CRC Press. [An interesting and provocative analysis and criticism of the underpinnings of Wolff's law].

Cowin S.C. and Hegedus D.H (1976a), Bone remodeling I: Theory of adaptive elasticity, *J. Elasticity* 6, 313-326. [The first complete and rigorous theory of growth and remodeling based on the tenets of Continuum Mechanics].

Cowin S.C. and Hegedus D.H (1976b), Bone remodeling II: Small strain adaptive elasticity, *J. Elasticity* 6, 337-352. [The authors present a specialization of the results of the previous paper with a discussion of interesting examples].

DiCarlo A. (2005), Surface and bulk growth unified, in *Mechanics of Material Forces* (ed. P. Steinmann and G.A. Maugin), Springer, 53-64. [The idea of growth concentrated on a vanishingly thin lamina is developed].

DiCarlo A., Naili S., Quiligotti S and Teresi L. (2005), Modeling bone remodeling, *Proceedings of the ComsolMultiphysics Conference* (ed. J.M. Petit and J. Daluz), Paris, 31-36. [This short paper presents the rotational remodeling case with realistic data of bone].

DiCarlo A. and Quiligotti S. (2002) Growth and balance, *Mechanics Research Communications* 29, 449-456. [The authors propose the consideration of an independent equation of remodeling couples]. Epstein M. (2009), The split between remodeling and aging, *Int. J. of Non-Linear Mechanics* 44, 604-609. [It is found that the two types of processes can be clearly separated only for certain symmetry groups].

Epstein M., Burton D. and Tucker R. (2006), Relativistic anelasticity, *Classical and Quantum Gravity* 23, 3545-3571. [The idea of anelastic evolution is extended to the context of General Relativity in terms of a body-time manifold].

Epstein M. and Elżanowski M. (2007), *Material inhomogeneities and their evolution*, Springer. [This monograph presents a geometric theory of continuous distributions of inhomogeneities and their evolution in time].

Epstein M. and Goriely A. (2012), Self-diffusion in remodeling and growth, *Zeitschrift für Angewandte Mathematik und Physik* 63, 339-355. [In this paper, the issue of self-diffusion is tackled within a single-species formulation with the introduction of an additional kinematic variable].

Epstein M. and Maugin G.A. (2000), Thermomechanics of volumetric growth in uniform bodies, *International Journal of Plasticity* 16, 951-978. [The basis of first- and second-order growth theories and the role of the Ehelby stress are presented].

Eshelby J. D. (1951), The force on an elastic singularity, *Philosophical Transactions of the Royal Society of London* **A244**, 87-112. [A classical paper that pioneers the notion of configurational or material forces in Continuum mechanics].

Fung Y.C. (1991), What are residual stresses doing in our blood vessels? *Annals Biomedical Engineering* **19**, 237-249. [In this lecture, the author presents his original ideas about arterial remodeling, including his law of mass growth].

Fung Y.C. and Liu S.Q. (1989), Change of residual strains in arteries due to hypertrophy caused by aortic constriction, *Circulation Research* 65, 1340-1349. [Evidence for residual stress in arteries is shown by means of the opening angle experiment].

Fyhrie D. P. and Carter D. R. (1986), A unifying principle relating stress to trabecular bone morphology, *Journal of Orthopaedic Research* 4, 304-317. [Bone is assumed to be a self-optimizing material to predict trabecular orientation and apparent density].

Galilei G. (1638), *Discorsi e dimostrazioni matematiche intorno a due nuove scienze attenenti alla mecanica e i movimenti locali*, Elsevier, Leiden. [During the second day of these dialogues, Galileo discusses the impossibility of enlarging a structure proportionally while preserving its strength and uses the size of animal bones as an example].

Garikipati K., Arruda E. M., Grosh K., Narayanan H. and Calve S. (2004), A continuum treatment of growth in biological tissue: The coupling of mass transport and mechanics, *Journal of the Mechanics and Physics of Solids* 52, 1595-1625.[In this major paper, the formulation incorporates several species and the issue of mass flux is subsumed in the diffusion of nutrients within the matrix].

Greenspan H.P. (1975), On the growth and stability of cell cultures and solid tumors, *J. Theoretical Biology* 56 229–242. [See critical discussion in Roose et al. (2007)].

Hamant O., Heisler M., Jonsson H., Krupinski P., Uyttewaal M., Bokov P., Corson F., Sahlin P., Boudaoud A., Meyerowitz E., Couder Y. and Traas J. (2008), Developmental Patterning by Mechanical Signals in Arabidopsis, *Science* 322, 1650–1655. [Evidence is shown of the alignment of microtubules with the maximum principal stress direction in plants].

Han H. C. and Fung Y. C. (1991), Residual strains in porcine and canine trachea, *Journal of Biomechanics* 24, 307-315. [Experimental evidence for the existence of residual stresses in tubular biological structures other than arteries is presented].

Huiskes R., Ruimerman R., van Lenthe G.H. and Janssen J.D. (2000), Effects of mechanical forces on maintenance and adaptation of form in trabecular bone, *Nature* 405, 704-706. [This highly cited paper contains impressive numerical predictions for bone remodeling].

Humphrey J.D. (2002), *Cardiovascular Solid Mechanics*, Springer. [This book contains a comprehensive treatment of the cardiovascular system within the framework of modern Continuum Mechanics].

Humphrey J.D. and Rajagopal K. (2002), A constrained mixture model for growth and remodeling of soft tissues, *Mathematical Models and Methods in Applied Sciences* 12, 407-430. [An extension is presented of the anelastic idea to a multi-component mixture].

Kachanov L.M. (1986), *Introduction to continuum damage mechanics*, Nijhoff, Dordrecht. [This book presents the theory of continuum damage mechanics by one of its founders].

Kuhl E. and Steinmann P. (2003), Mass- and volume-specific views on thermodynamics of open systems, *Proceedings of the Royal Society of London* A459, 2547-2568. [In this detailed analysis of open systems, mass flux is included in the formulation].

Maugin G.A. and Muschik W. (1994), Thermodynamics with internal variables, *J. Non-equilibrium Thermodynamics* 19, 217-289. [A comprehensive review of this area, it consists of two parts dealing, respectively, with general concepts and with applications].

Noll W. (1967), Materially uniform bodies with inhomogeneities, *Archive for Rational Mechanics and Analysis* 27, 1-32. [This paper served to launch a geometrically rigorous inhomogeneity theory based exclusively on the macroscopic constitutive equation of a body].

Qi A.-S., Zheng X., Du C.Y. and An B.S. (1993), A cellular automaton model of cancerous growth, J. Theoretical Biology 161, 1–12. [This paper presents a simple and clearly described model that typifies the main features of cellular automata].

Rodriguez E.K., Hoger A. and McCulloch A.D. (1994), Stress-dependent finite growth in soft elastic tissues, *J. Biomechanics* 27, 455-467. [The first paper to suggest the use of the anelastic theory to growth and remodeling].

Roose T., Chapman S.J. and Maini, P.K. (2007), Mathematical Models of Avascular Tumor Growth, *SIAM Review* 49, 179-208. [Although limited to the avascular type, this review article provides a comprehensive coverage of modeling techniques in general and of cellular automata in particular].

Roose T., Netti P.A., Munn L.L., Boucher Y. and Jain R.K. (2003), Solid stress generated by spheroid growth estimated using a linear poroelasticity model, *Microvascular Research* 66, 204–212. [See critical discussion in Roose et al. (2007)].

Roux W. (1881), *Der Kampf der Teile im Organismus*, Engelmann, Leipzig. [Before Wolff, Roux had proposed that bone remodeling is the result of a self regulating mechanism at the cell level, a remarkably modern idea].

Ruimerman R. and Huiskes R. (2005), Development of a unifying theory for mechanical adaptation and maintenance of trabecular bone, *Theoretical Issues in Ergonomics Science* 6, 225–238. [This paper presents an improved version of Huiskes et al. (2005)].

Ruimerman R., Hilbers P., van Rietbergen B. and Huiskes R. (2005), A theoretical framework for strain-related trabecular bone maintenance and adaptation, *Journal of Biomechanics* 38, 931-941. [Further numerical simulations are presented based on the theory of Huiskes et al. (2005)].

Segev R. (1997), On symmetrically growing bodies, *Extracta Mathematicae* 12, 261-271. [The author presents a differential-geometric treatment of growing bodies in which both cases of bodies with and without identifiable particles are considered].

Segev R. and Epstein M. (1996), On theories of growing bodies, in *Contemporary Research in the Mechanics and Mathematics of Materials* (ed. R.C. Batra and M.F. Beatty), CIMNE, Barcelona, 119-130. [The notion of material manifold as distinct from the growing body manifold is introduced an applied to various examples of volumetric and surface growth].

Segev R. and Rodnay G. (2001), Worldlines and body points associated with an extensive property, *Int. J. Nonlinear Mechanics* 38, 1-9. [The balance of an extensive property is used to construct the material structure of a body, whereby material points are identified with worldliness].

Skalak R., Dasgupta G., Moss M., Otten E., Dullemeijer P. and Vilmann H. (1982), Analytical Description of Growth, *J. Theoretical Biology* 94, 555-577. [This is a seminal paper in the history of modeling of growth].

Taber L.A. (1995), Biomechanics of Growth, Remodeling and Morphogenesis, *Applied Mechanics Reviews* 48, 487-545. [This excellent review article is highly recommended for the scope and depth of coverage of the state of the art].

Taber L.A. (1998), Biomechanical growth laws for muscle tissue, *J. Theoretical Biology* 193, 201-213. [The author presents a unified theory of growth of both striated and smooth muscle].

Taber L.A. (2009), Towards a unified theory for morphomechanics, *Philosophical Transactions Royal Society A* 367, 3555–3583. [Ideas of the theory of growth and remodeling are applied to the embryo level to explain morphogenetic events].

Wolff J. (1892), *Das Gesetz der Transformation der Knochen*, A. Hirshwald, Berlin. [Wolff's law as originally formulated. An English translation exists, published by Springer].

Wolfram S. (1994), *Cellular Automata and Complexity*, Addison-Wesley. [This book contains a series of collected papers by one of the strongest proponents and advocates of cellular automata].

Biographical Sketch

Marcelo Epstein obtained his first degree in Engineering from the University of Buenos Aires and went on to graduate as MSc and PhD (1972) from the Technion (Israel Institute of Technology). Since 1976 he has been at the University of Calgary, where he now holds the position of University Professor of Rational Mechanics. His main interest is in both the foundational and the applied aspects of Continuum Mechanics, a field in which he has published extensively in international journals. He is the co-author (with W. Herzog) of a book on skeletal muscle mechanics (Wiley, 1997) and (with M. Elżanowski) of a monograph on the geometric theory of continuous distributions of defects and their evolution (Springer, 2007). He is also the author of two books on the geometrical language of Continuum Mechanics (Cambridge University Press, 2010) and on the elements of Continuum Biomechanics (Wiley, 2012). He also holds a degree in Classical Studies and teaches a course in the Latin of Science at the Faculty of Humanities in Calgary. He is a Fellow of the American Academy of Mechanics and a recipient of the Cancam Medal (2009) for his contributions to Applied Mechanics.