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Review Paper

Continuum biomechanics of soft biological tissues

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Since its coming of age in the mid 1960s, continuum biomechanics has contributed much to our understanding of human health as well as to disease, injury, and their treatment. Nevertheless, biomechanics has yet to reach its full potential as a consistent contributor to the improvement of health-care delivery. Because of the inherent complexities of the microstructure and biomechanical behaviour of biological cells and tissues, there is a need for new theoretical frameworks to guide the design and interpretation of new classes of experiments. Because of continued advances in experimental technology, and the associated rapid increase in information on molecular and cellular contributions to behaviour at tissue and organ levels, there is a pressing need for mathematical models to synthesize and predict observations across multiple length- and time-scales. And because of the complex geometries and loading conditions, there is a need for new computational approaches to solve the boundary- and initial-value problems of clinical, industrial, and academic importance. Clearly, much remains to be done. The purpose of this paper is twofold: to review a few of the many achievements in the biomechanics of soft tissues and the tools that allowed them, but, more importantly, to identify some of the open problems that merit increased attention from those in applied mechanics, biomechanics, mathematics and mechanobiology.

Keywords: constitutive formulations; finite elasticity; viscoelasticity; mixture theory; mechanobiology; growth and remodelling

1. Introduction

Biomechanics is often defined as 'mechanics applied to biology' (Fung 1990), but it is actually much more. Proteins, cells, tissues, organs and organisms reveal an incredible spectrum of material structures and properties, which in turn govern their wonderfully diverse functions. As we learn more and more about the characteristics of living materials, we find that we must broaden our ideas on mathematical modelling and indeed even some of our basic postulates and concepts in mechanics. Hence, biomechanics is better defined as the development, extension and application

of mechanics for the purposes of understanding better physiology and pathophysiology as well as the diagnosis and treatment of disease and injury. That is, the overall goal of biomechanics is, and must remain, the general improvement of the human condition.

Much has been learned in biomechanics, particularly over the last 35 years, and there is now an extensive literature. We must build upon prior understanding and achievements, of course; thus there is a need to appreciate that which is in the literature. That said, we must also be careful not to be bound by past methods or concepts. New technologies are revealing much more detail about the fundamental building blocks of life—genes, proteins and cells—and new hypotheses and theories should build upon these new observations. The challenges, and likewise the promises, of biomechanics have never been greater.

2. Background

(*a*) *A brief history*

Although it is impossible to identify the true 'father of biomechanics', it is easy to suggest that biomechanics is as old as mechanics itself. For example (see Mason 1962), Leonardo da Vinci (1452–1519) was interested in a means by which man could fly and thus he studied the flight of birds. Applying biological principles to the study and design of engineering systems is called *bionics*, which remains an important approach within biomechanics, including new frontiers such as functional tissue engineering and prosthetics. Galileo Galilei (1564–1642) was interested in the strength of bones and suggested that bones are hollow for this affords maximum strength with minimum weight. Identification of principles of 'biological optimization' continues to hold great promise in unlocking some of nature's secrets. René Descartes (1596–1650) suggested a philosophic system whereby all material systems, including the human body (but not the soul), are simply machines ruled by the same mechanical laws, an idea that did much to promote and sustain biomechanical study. Among others, Giovani Borelli (1608–1679) embraced this idea and studied walking, running, jumping, the flight of birds, the swimming of fish and even the piston action of the heart within a mechanical framework. Robert Hooke (1635–1703), curator of experiments for The Royal Society, gave us the word cell, based on microscopic observations of the structure of cork as well as his famous law, 'as the force, so the extension'. The latter was based in large part on experiments on wire, but also biomechanical tests on '... hair, horns, silk, bones, sinews... and the like' (Timoshenko 1983). The first appointment of Leonard Euler (1707–1783) in the St Petersburg Academy was in the physiology branch, which facilitated his interest in biomechanical problems such as the propagation of pressure waves in arteries and sound waves in the ear (Bell 1986). Thomas Young (1773–1829) gave the 1808 Croonian Lecture before The Royal Society on the mechanical function of the heart and arteries; this paper illustrates well the need to combine theoretical ideas and experimental findings to understand the complexities of physiology and pathophysiology. Not one to ignore clinical applications, the physician Young also discussed the mechanics of blood letting.

These are but a few of the many examples of early studies in biomechanics. Although interest in biomechanics continued throughout the late 19th and early

20th centuries, it is suggested here that biomechanics did not truly emerge as a distinct field of study until the mid 1960s. Although historians will likely argue over the reasons for this, it is suggested that four nearly simultaneous advances gave birth to the field of modern biomechanics. Inasmuch as biological soft tissues exhibit an inherently nonlinear mechanical behaviour over finite strains, the field had to await the development of an appropriate theoretical framework. Biomechanics thus owes much to those who led the post World War II renaissance in nonlinear continuum mechanics, and in particular, finite elasticity, viscoelasticity and mixture theory. See Truesdell & Noll (1965) for an account of the nonlinear field theories, especially the historic developments from 1947 to 1965. Computers are essential in biomechanics for controlling experiments, reducing vast amounts of data, testing hypotheses via simulations and solving complex boundary- and initial-value problems. The development of the digital computer, and in particular the transistor-based machines of the 1960s, thus provided a technological advance that was needed for the growth of biomechanics. Paralleling this technological advance was the development of the finite-element method, introduced in 1956 based on prior mathematical advances and developed significantly throughout the 1960s to the point that Oden (1972) published a text on nonlinear finite-element methods that was suitable for tissue mechanics. And, finally, the 1960s marked the decade of exploration of the Moon. Clearly, one of the essential questions generated by the space race was: how will humans respond to the altered loads associated with space travel? This need for a predictive science that addresses the effects of mechanical loads on the body further solidified the need for a modern approach to biomechanics.

In summary then, we see that the birth of the modern field of biomechanics had to await the development of an appropriate theoretical foundation, an enabling technology, mathematical methods and heightened motivation. In addition to these four advances, it is not coincidental that the birth of biomechanics came on the heels of the birth of modern biology in the 1950s, which was due in large part to the discovery of the α-helix and β-sheet structures of proteins by L. C. Pauling and that of the double helix structure of DNA by J. D. Watson and F. H. C. Crick. Indeed, the 1950s also yielded seminal work on the triple-helix structure of collagen by G. N. Ramachandran and G. Kartha and A. Rich and F. H. C. Crick, and on the sliding filament cross-bridge hypothesis for muscle contraction by A. F. Huxley, two of the most important structural constituents in the body. As pointed out by Pauling (Marinacci 1995), we must recognize that theoretical physics and mathematics played a fundamental role in this revolution in biology; thus it is not surprising that continuum biomechanics, which seeks to synthesize biology and classical mechanics, would thereafter play a key role in both basic and applied research in the life sciences.†

Fundamental to the continued development of a field, of course, are professional societies, meetings and technical journals. For example, the scientific revolution in Europe in the 17th century was fostered greatly by an increased exchange of ideas, in part, through the founding of societies, such as The Royal Society of London in 1660, and the publication of their proceedings. With regard to biomechanics, the *Journal of Biomechanics* was founded in 1968, the ASME *Journal of Biomechanical*

† It is particularly interesting that Pauling attributes his consideration of a helical structure of protein to lectures at CalTech by mathematics professor H. Bateman, a mentor held in high regard by Truesdell (1984).

Engineering in 1977, *Computer Methods in Biomechanics and Biomedical Engineering* in 1998, and most recently *Biomechanics and Modeling in Mechanobiology* in 2002. These journals, and others such as the *Annals of Biomedical Engineering* and the *IEEE Transactions for Biomedical Engineering*, continue to promote the growth of biomechanics. In addition to earlier smaller meetings, such as the Symposium on Biorheology at Brown University in 1964 and the Symposium on Biomechanics and Related Bio-Engineering Topics at Strathclyde in 1964, it is important to note that the World Congress of Biomechanics began in 1990 via a meeting at San Diego, and has been followed by meetings in 1994 at Amsterdam, in 1998 at Sapporo and in 2002 at Calgary. These focused meetings, as well as symposia at many different technical meetings, have further promoted the exchange of ideas and thus contributed to the rapid growth of continuum biomechanics.

We must remember, however, that biomechanics is part of a larger, multidisciplinary activity whose goal is to understand better the conditions of health as well as those of disease and injury. Consequently, biomechanics has and will continue to benefit greatly from developments in the basic life sciences, medical sciences, mathematics and materials science. Indeed, it would be hard to find an archival paper on biomechanics that does not refer to research in these allied fields and conversely it would be hard to find archival journals in these allied fields (e.g. the *American Journal of Physiology*, the *Biophysical Journal*, the American Heart Association's *Circulation Research,* the ASME *Journal of Applied Mechanics*, *The Journal of Orthopedic Research*, and so on) that do not contain papers on biomechanics.

(*b*) *Basic histology and cell biology*

It is axiomatic in mechanics that the response of a material to applied loads depends upon its internal constitution, that is, the distributions, orientations and interconnections of its microstructural components. Histology is defined as the study of the fine structure of tissues; it is thus fundamental to biomechanics. Similarly, cell biology is the study of how cells grow, move, function and communicate with their surroundings; it, too, is fundamental to biomechanics, particularly many of the open problems that face us today. Hence, let us briefly review some of the salient findings from histology and cell biology upon which biomechanics must continue to build.

Soft biological tissues exist in many different forms, each specialized to perform a specific function and each having a unique microstructure. Nonetheless, soft tissues are composed of the same basic constituents: cells and extracellular matrix. Cells are the fundamental structural and functional unit of tissues and organs. There are about 200 different types of cells in the human, which contain the same genetic information (genotype) but express different genes (phenotype) and thus serve different functions. The phenotype depends on both the genetic programming and the environment (epigenic factors). Of particular importance herein, diverse research over the last two decades has revealed that many types of cells (now collectively called mechanocytes) change their structure and function in response to even subtle changes in their mechanical environment. This observation has given rise to intense study, a sub-field now called *mechanobiology*, which is a perfect complement of biomechanics—each focuses on similar issues, just from different philosophic perspectives. For example, biomechanics relies on fundamental postulates to elucidate particular responses (i.e. by deduction), whereas mechanobiology seeks to glean from

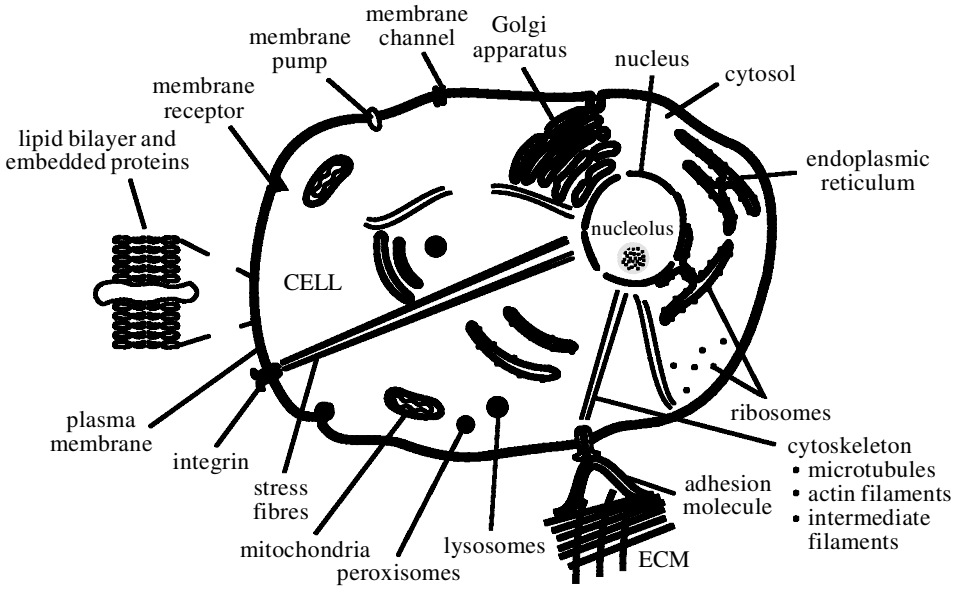

Figure 1. Schema of a typical cell, showing the cell membrane and its various receptors, the cytoplasm and the nucleus. Understanding the structure and properties of the cell and its constituents is essential in many areas of biomechanics. (Reproduced from Humphrey (2002) with permission.)

many particular observations the underlying general mechanisms (i.e. by induction). Van der Meulen & Huiskes (2002) put it this way. They suggest that 'form follows function [which] follows form'. Hence, they suggest that biomechanics focuses on whether or how function follows form, whereas mechanobiology focuses on whether or how function determines form.

Figure 1 is a schema of a typical cell. It consists of a cell membrane, a cytoplasm (i.e. fluid-like cytosol, structural cytoskeleton and dispersed organelles), and a nucleus which contains the chromosomal DNA. The cell membrane consists primarily of a phospholipid bilayer with many embedded (transmembrane) proteins that serve a host of functions: channels, gates, receptors for target molecules and anchoring sites. In many cells, the structural integrity of the cell membrane is augmented by a sub-membranous cortical network or layer of actin filaments. Actin filaments, intermediate filaments and microtubules are the three primary structural proteins of the cytoskeleton. Specifically, actin filaments are *ca.* 5–9 nm in diameter and thought to be extensible and flexible; intermediate filaments are often described as rope-like structures *ca.* 10 nm in diameter that appear to play an important structural role throughout the cytoplasm; microtubules exist as long cylinders *ca.* 25 nm in diameter, and they appear to have a higher bending stiffness than the other two primary filaments. Janmey (1991) reported that actin filaments are stiffer in extension than microtubules, but that they rupture at a much lower extension (microtubules rupture at *ca.* 50% extension). He also reported that the intermediate filaments exhibit an intermediate extensional stiffness at lower extensions, but that they can sustain much larger extensions than the other two types of filaments while exhibiting a nonlinearly stiffening response (figure 2). In contrast to tradi-

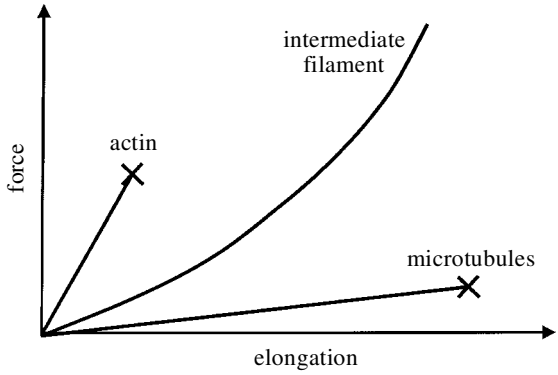

Figure 2. Schema of the mechanical behaviour of the three primary cytoskeletal proteins: actin, intermediate filaments and microtubules. We must remember, however, that the biological and mechanical function of these filaments depends both on their intrinsic properties and their interactions via a host of accessory proteins.

tional engineering materials, it must be noted that actin filaments and microtubules undergo a rapid assembly/disassembly, which is to say that they can continuously change their orientations, densities, cross-links and probably natural configurations in response to multiple stimuli. Moreover, as noted by Alberts *et al.* (1994), these three primary structural proteins cannot perform their functions without interactions with a host of accessory cytoskeletal proteins (e.g. actinin, myosin, talin), interactions that also change over time. This observation will prove important subsequently.

The various organelles within the cytoplasm play diverse roles. For example, mitochondria provide the cell with usable energy to perform its many functions. The smooth and rough endoplasmic reticulum are sites for the synthesis of proteins, lipids and steroids. The Golgi apparatus similarly plays a role in the synthesis of polysaccharides, but also in the modification, packaging and transport of various macromolecules. Finally, the lysosomes and perioxisomes are responsible for the hydrolytic degradation of various substances within the cell. The ability of a cell to produce and remove various substances within the confines of its cell membrane as well as within the extracellular matrix in which it resides is fundamental to much of its activity. As noted by many, the cell is the effector of changes within tissues and organs, many of which have biomechanical implications.

The extracellular matrix (ECM) serves many functions: it endows a tissue with strength and resilience and thereby maintains its shape; it serves as a biologically active scaffolding on which cells can migrate or adhere; it helps to regulate the phenotype of the cells; it serves as an anchor for many substances including growth factors, proteases and inhibitors of such; and finally, it provides an aqueous environment for the diffusion of nutrients, ions, hormones and metabolites between the cell and the capillary network. In many respects, therefore, it is the ECM that regulates cell shape, orientation, movement and overall function. It is the cells (e.g. fibroblasts), however, that fashion and maintain the ECM—hence, a strong symbiotic relationship.

The ECM consists primarily of proteins (e.g. collagens, elastin, fibronectin), glycosaminoglycans (GAGs) and bound and unbound water (Fawcett 1986; Alberts *et*

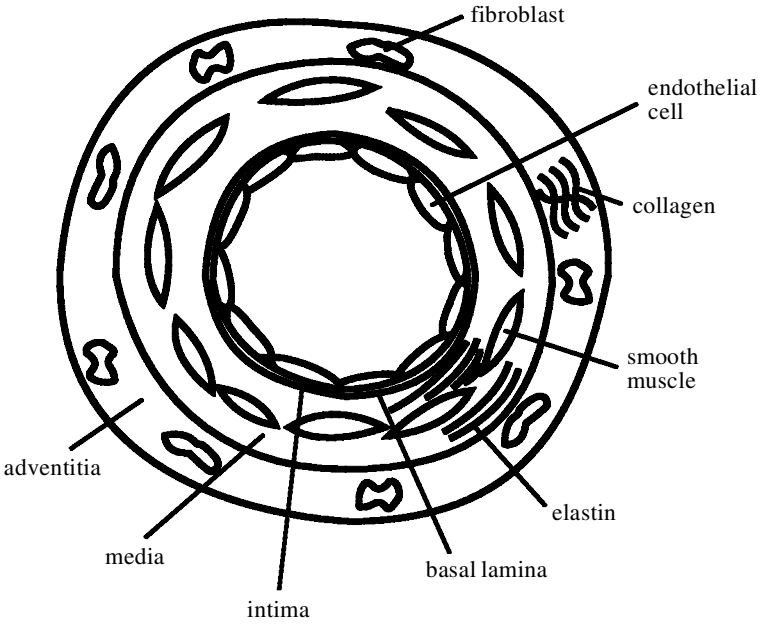

Figure 3. Schematic of the cross-section of a typical artery showing the three primary cell types (endothelial, smooth muscle and fibroblasts) as well as the primary extracellular proteins (elastin and collagen). Like the artery, many soft tissues are heterogeneous, and it appears that as we include more and more of the intrinsic complexities we find greater homogeneity in the computed stress fields. That is, simplicity appears to arise from complexity; hence we must be careful not to over-idealize our constitutive and computational models.

al. 1994). Whereas the glycosaminoglycan heparan sulfate decorates the luminal surface of the endothelial cells that line all blood vessels, and thereby promotes blood flow by inhibiting blood clots, the GAGs are often covalently bound to protein cores within the ECM, thus forming extracellular proteoglycans that have diverse functions. From the perspective of mechanics, the three primary structural constituents of the ECM are typically collagen (the most abundant protein in the body), elastin (the most elastic and chemically stable protein) and the proteoglycans (which often sequester significant water as well as growth factors, proteases, etc.). Figure 3 shows, for example, a cross-section of an artery whereby the elastin, collagens and primary cells are evident. Like the cytoskeletal proteins, most extracellular constituents turnover continuously, albeit some very slowly. For example, collagen in the peridontal ligament appears to have a half-life of the order of days, whereas that in the vasculature may have a normal half-life of months. In response to altered loads, disease or injury, however, the rates of synthesis and degradation of collagen can increase manyfold to effect a rapid response.

In summary, there is a need in biomechanics to understand both the biological and mechanical characteristics of the cells and extracellular matrix that comprise a tissue or organ of interest and how these constituents interact and turnover in response to normal or altered stimuli. For more detail on the biology, the interested reader is referred to textbooks of histology (e.g. Fawcett 1986), cell biology (e.g. Alberts *et al*. 1994) and physiology of the specific system of interest (e.g. Milnor (1990) for the

cardiovascular system), each of which, like a medical dictionary, must be on every biomechanicist's bookshelf.

(*c*) *General characteristic behaviours*

Like continuum mechanics, continuum biomechanics consists of three general areas of study: identification of fundamental concepts, postulates and principles; formulation of constitutive relations that describe material behaviour; and solution of initial–boundary-value problems of academic, industrial and clinical importance. Fortunately, as anticipated by Descartes and others, soft tissues respect the basic postulates of mechanics (e.g. conservation of mass, momentum and energy), and basic concepts such as stress, strain and entropic elasticity apply as well. Hence, much of biomechanics focuses first on the formulation of reliable constitutive relations and then on the solution of initial–boundary-value problems. We shall review some specific constitutive approaches in § 3 below and motivate the need to solve associated initial–boundary-value problems in § 2 *d*.

That the formulation of appropriate constitutive relations has long been of central importance in biomechanics is revealed, in part, by the following quote from Fung (1973): 'we see that the greatest need lies in the direction of collecting data in multiaxial loading conditions and formulating a theory for the general rheological behavior of living tissues when stresses and strains vary with time in an arbitrary manner.' There are, in general, five basic steps in the formulation of a constitutive relation:

(i) delineation of general characteristics of interest;

(ii) establishing an appropriate theoretical framework for quantification;

(iii) identification of specific functional forms of the constitutive relations;

(iv) calculation of the values of the associated material parameters; and

(v) evaluation of the predictive capability of the final relation.

A former student suggested that these five steps are remembered easily with the aid of the acrostic *DEICE*.

Let us consider here some of the general characteristic behaviours exhibited by soft tissues. As noted above, it has long been known that biological soft tissues behave very differently from traditional engineering materials such as metals, wood and concrete. In an 1847 paper, M. G. Wertheim presented force–elongation data for various tissues, including arteries and veins, which led him to conclude that soft tissues do not obey Hooke's law (i.e. a linear relation between Cauchy stress and a linearized measure of strain). Roy (1880) came to a similar conclusion; indeed, this paper is a must read for any student of cardiovascular mechanics. For example, Roy observed that arteries exhibit an anisotropic response, an 'elastic after-action' or creep, which signifies a viscoelastic character, and a thermoelastic behaviour similar to rubber. He additionally showed that the material properties of arteries differ with radial location within the wall (a local heterogeneity) and along the vascular tree (i.e. a regional heterogeneity), that they change with exercise, age, disease and time post-mortem, and even that they differ with gender. That is, most soft tissues exhibit

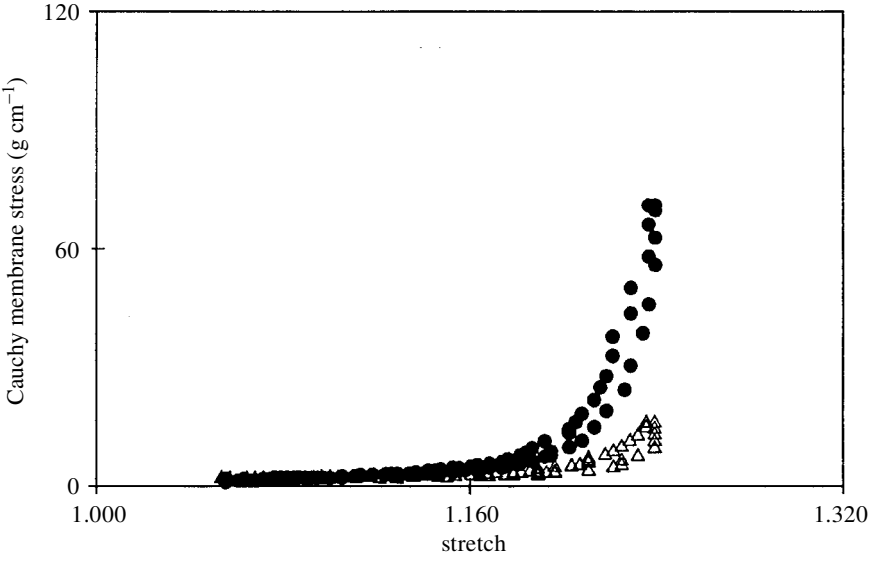

Figure 4. Typical stress–stretch data for soft tissues. Shown is the nonlinear, anisotropic response of excised epicardium, a collagenous membrane that covers the heart.

a nonlinear, inelastic, heterogeneous, anisotropic character that varies from point to point, from time to time and from individual to individual. Figure 4, for example, shows data from the author's laboratory that illustrate the nonlinear, anisotropic, heterogeneous behaviour of a typical soft tissue (from the wall of the heart). More on this in § 3.

That some of these characteristic behaviours are similar to those exhibited by elastomers and that this is because of the long-chain, cross-linked polymeric structure of both classes of materials, allowed advances in rubber and tissue elasticity to proceed hand in hand in the early to mid 20th century (see the excellent discussion in Treloar (1975, ch. 1)). Indeed, many advances in soft-tissue mechanics have come from building upon advances in rubber elasticity. Not all characteristic behaviours are shared between these two classes of materials, however. Most notably, many rubber-like materials exhibit an isotropy with respect to their unloaded natural configuration, whereas most soft tissues exhibit an anisotropy—transverse isotropy by tendons and ligaments, cylindrical orthotropy by arteries, and complex symmetries by planar tissues such as skin and pericardium. Soft-tissue and rubber-like behaviour also differ in other fundamental ways. Osborne (1909) showed, for example, that inflated rubber balloons exhibit a limit point instability whereas the urinary bladder does not (it exhibits a monotonically increasing pressure–radius relation), an observation that went unremarked upon for many years, but is relevant to recent research on the natural history of aneurysms. Aneurysms are focal dilatations of the arterial wall that likely result from imbalances in the local degradation and synthesis of collagen in the extracellular matrix (Humphrey & Canham 2000).

In summary, soft tissues exhibit complex characteristic behaviours, many of which are shared. Yet, the different behaviours commensurate with the different functions of individual tissues demand a close examination during the first step in any constitutive formulation.

(d) R&D applications

As noted by Fung (1990), 'Biomechanics aims to explain the mechanics of life and living. From molecules to organisms, everything must obey the laws of mechanics.' It is not hard to imagine, therefore, that biomechanics has a vital role to play in research and development: from the design of a vehicle with improved crashworthiness, to the design of a wheelchair; from the design of a left ventricular assist device to aid a failing heart, to the design of an intraocular implant to improve vision; from predicting which diagnosed aneurysm is at risk of rupture, to identifying the failure strength of an anterior cruciate ligament in an elite athlete, which must be protected during training and competition; from designing an artificial heart valve that must open and close over 30 million times per year, to designing a biologically coated intravascular stent device to prevent restenosis; from using computer-aided modelling to guide plastic surgery, to designing catheters that induce less denudation damage; from designing a mechanical ventilator to support patients in respiratory distress, to specifying rehabilitation schedules that promote tissue healing; from quantifying brain properties that enable robotic-assisted surgery, to designing improved procedures in surgical specialties; and, finally, from the engineering of tissue for surgical replacement, to the development of an improved interpretation of ultrasound images and hundreds of applications in between. Although each of these examples may appear very technical and impersonal, we must also remember that each represents a great opportunity to affect people one family at a time. Given that we tend to be motivated by past accomplishments, current needs or future promise, in continuum biomechanics the ultimate motivation must remain clear: to improve health-care delivery.

3. Theoretical frameworks

Constitutive relations describe the response of a material to applied loads, which depends of course on the internal constitution of the material. Ultimately, we desire relations that quantify such responses based on fine-details of the structure of a protein, cell, tissue or organ and their interactions. Because of the incredible complexity of both the ultrastructure and microstructure of these materials, however, we continue to rely primarily on phenomenological descriptors of the behaviours of interest, descriptors that are often motivated by only a limited knowledge of the underlying structure. Here, therefore, we emphasize that constitutive relations describe the behaviour of a material under conditions of interest, not the material itself. That is, although we would prefer an equation that describes the behaviour of a particular material under all conditions (e.g. water in its solid, liquid and gaseous phases depending on the local temperature and pressure), we can generally expect to identify relations that hold only under specific conditions of interest. Hence, although tissues may be best classified as mixture-composites that exhibit inelastic behaviours, under particular conditions of interest it may be sufficient to model their behaviour within the context of an elasticity or viscoelasticity theory rather than, for example, a full mixture theory. For this reason, let us briefly review six different theoretical frameworks that have found considerable utility in the continuum biomechanics of soft tissues.

(*a*) *Finite elasticity*

Although M. G. Wertheim, C. S. Roy and others showed in the 19th century that soft-tissue behaviour is generally nonlinear over finite strains, the simplicity of and familiarity with the linearized theory of elasticity has tempted many to employ it inappropriately. Indeed, in 1967 Fung wrote, 'The main difficulty lies in the customary use of infinitesimal elasticity to the media [tissues] which normally exhibit finite deformations.' Employing the theory of finite elasticity to quantify soft-tissue behaviour was thus the first major advance in the biomechanics of these tissues, and our field owes much to R. S. Rivlin, L. R. G. Treloar, A. E. Green, A. J. M. Spencer, J. L. Ericksen and others who in the late 1940s through the mid 1960s established the foundations of this discipline, which were suitable for textbook presentation in Truesdell & Noll (1965) and Green & Adkins (1970) that supported the birth and early growth of biomechanics.

The interested student should read the papers by Fung (1967, 1973), which represent early efforts to place soft-tissue biomechanics within this framework of finite elasticity. In particular, Fung reported data from uniaxial tests on excised strips of mesentery, a thin collagenous membrane in the abdomen. Similar to the data in figure 4 on the epicardium, results from these tests revealed a strongly nonlinear relationship between stress and stretch, with extreme tissue compliance at the lower stretches. Moreover, the data revealed that although the tissue exhibited creep its response under cyclic loading was relatively insensitive to strain rate and it was repeatable after a few initial 'preconditioning' cycles, characteristics that later led Fung to coin the term *pseudoelasticity*. Fung also showed that if one plotted the stiffness (i.e. $\mathrm{d}P_{11}/\mathrm{d}\lambda$, where P_{11} is the uniaxial first Piola–Kirchhoff stress and λ a stretch ratio) versus the stress itself, one obtains a near linear relationship: $\mathrm{d}P_{11}/\mathrm{d}\lambda = \alpha + \beta P_{11}$, where α and β are material parameters. This relation (a first-order ordinary differential equation) immediately suggests an exponential stress–stretch relation. During the period 1967 to 1983, Fung developed and refined a theory of an exponential stress–strain behaviour of soft tissues that essentially resulted from one bold postulate. Given the experimentally revealed one-dimensional exponential relationship between the first Piola–Kirchhoff stress and stretch, Fung postulated the existence of a three-dimensional (3D) pseudostrain energy function $W = c(\mathrm{e}^Q - 1)$, where Q is a function of the Green strain tensor $\boldsymbol{E} = (\boldsymbol{F}^{\mathrm{T}} \cdot \boldsymbol{F} - \boldsymbol{I})/2$, with $\boldsymbol{F}$ the deformation gradient tensor, and c is a material parameter. This, in turn, suggested an exponential relationship between the second Piola–Kirchhoff stress tensor $\boldsymbol{S}$ and the Green strain tensor, namely

$$\boldsymbol{S} = \frac{\partial W}{\partial \boldsymbol{E}} = c\mathrm{e}^Q \frac{\partial Q}{\partial \boldsymbol{E}}, \tag{3.1}$$

from which the Cauchy stress tensor $\boldsymbol{t}$ is determined easily: $J\boldsymbol{t} = \boldsymbol{F} \cdot \boldsymbol{S} \cdot \boldsymbol{F}^{\mathrm{T}}$, where $J = \det \boldsymbol{F} > 1$. Whereas Fung and colleagues considered various functional forms for Q, including linear, quadratic and cubic in terms of the components of $\boldsymbol{E}$, based on fits to data and the ease of parameter estimation, they settled primarily on a quadratic form,

$$Q = \tfrac{1}{2} c_{ABCD} E_{AB} E_{CD}, \tag{3.2}$$

where c_{ABCD} are material parameters and repeated indices imply summation per the usual Einstein convention. Indeed, Fung showed further that the number of independent parameters in the material parameter matrix could be specified for various

material symmetries using arguments similar to those in the theory of linearized elasticity. That is, of the 81 possible values of c_{ABCD}, 9 are needed for orthotropy, 5 for transverse isotropy and 2 for isotropy. In many respects, it is remarkable that equations (3.1) and (3.2), with so few material parameters, have been shown to describe reasonably well the diverse nonlinear behaviours exhibited by many different soft tissues (Fung 1990, 1993). Note, too, that many tissues exhibit a nearly incompressible behaviour under physiologic loading, which is thought to arise from the high volume fraction of water in most soft tissues provided that the conditions of interest do not allow the water to diffuse into or out of the tissue during the period of interest. Equation (3.2) applies to this incompressible case as well, given the modification that

$$\boldsymbol{S} = \frac{\partial \tilde{W}}{\partial \boldsymbol{E}} - p\boldsymbol{C}^{-1} = c\mathrm{e}^{Q}\frac{\partial Q}{\partial \boldsymbol{E}} - p\boldsymbol{C}^{-1}, \tag{3.3}$$

where p is a Lagrange multiplier enforcing the constraint of incompressibility ($\det \boldsymbol{F} = 1$) and $\boldsymbol{C}$ is the right Cauchy–Green tensor: $\boldsymbol{C} = \boldsymbol{F}^{\mathrm{T}} \cdot \boldsymbol{F}$. The utility of the compressible and incompressible exponential relations has been demonstrated over the years based on data from compressible lung parenchyma as well as heart tissue, skin, arteries and the bladder to name a few (see Fung 1990, 1993; Humphrey 2002*a*). A material whose behaviour under particular conditions can be described by equations (3.1) or (3.3) is often called *Fung-elastic*.

Of course, many other forms of strain-energy functions have been proposed to describe the behaviour of the various soft tissues (Maurel *et al*. 1998). Among others, Holzapfel *et al*. (2000) provide a nice comparison between various relations for arteries; they also emphasize the need to calculate best-fit values of the material parameters so as to respect convexity requirements, an important but seldom addressed issue. Not unexpectedly, based on the specific results in Green & Adkins (1970), which were motivated predominantly by the desire to describe incompressible rubber-like behaviour, many of the early forms of W proposed for soft tissue embodied an assumption of isotropy: $W = W(\mathrm{I}_C, \mathrm{II}_C)$, where $\mathrm{I}_C = \mathrm{tr}\,\boldsymbol{C}$ and $2\mathrm{II}_C = (\mathrm{tr}\,\boldsymbol{C})^2 - \mathrm{tr}\,\boldsymbol{C}^2$ are coordinate invariant measures of the deformation. This assumption was 'justified' in many cases based on fits of the constitutive relation to single sets of uniaxial data, which are not sufficient to evaluate the anisotropy. Rather, multiaxial tests, which reveal that most soft tissues exhibit an anisotropic behaviour, are needed to formulate robust constitutive relations. This reminds us that borrowing ideas from other fields often brings new advances, but one must be discriminatory in what is borrowed and careful how it is evaluated.

Because of the utility of multiaxial testing in the quantification of anisotropic behaviour, another important advance was that of Vito (1980), who reported the first closed-loop, computer control of multiaxial tests on planar and cylindrical samples of soft tissues. Using such computer-aided experimentation, for example, Humphrey *et al*. (1990) were able to borrow and extend an idea from the seminal paper of Rivlin & Saunders (1951), whereby one seeks solutions to tractable boundary-value problems (i.e. experimental set-ups) that allow response functions (i.e. derivatives of the strain energy with respect to coordinate invariant measures of deformation) to be determined directly from data. Whereas Rivlin & Saunders were interested in isotropic behaviours, Humphrey *et al*. studied a sub-class of transversely isotropic behaviours defined by a $W = W(\mathrm{I}_C, \mathrm{IV}_C)$, where $\mathrm{I}_C = \mathrm{tr}\,\boldsymbol{C}$ and $\mathrm{IV}_C = \boldsymbol{M} \cdot \boldsymbol{C} \cdot \boldsymbol{M}$, with $\boldsymbol{M}$ defining a preferred direction in a reference configuration. Myocardium, for

example, may be locally transversely isotropic, at least within each myolaminae, with the preferred direction defined by the predominant muscle fibre direction. Humphrey *et al.* showed that the requisite response functions could be determined directly from a biaxial stretching test on a thin planar sample (state of plane stress) via

$$\frac{\partial W}{\partial \mathrm{I}_C} = \frac{f_2/(\ell_1 h)}{2(\lambda_2^2 - \lambda_3^2)}, \qquad \frac{\partial W}{\partial \mathrm{IV}_C} = \frac{(\lambda_2^2 - \lambda_3^2) f_1/(\ell_2 h) - (\lambda_1^2 - \lambda_3^2) f_2/(\ell_1 h)}{2\lambda_1^2(\lambda_2^2 - \lambda_3^2)}, \tag{3.4}$$

where f_1 and f_2 are the applied biaxial loads, ℓ_1 and ℓ_2 are specimen dimensions in the deformed configuration, h is the deformed thickness and $\boldsymbol{M} = (1, 0, 0)$ with $\boldsymbol{F} = \mathrm{diag}[\lambda_1, \lambda_2, \lambda_3]$ and $\lambda_3 = \lambda_1^{-1}\lambda_2^{-1}$ by incompressibility. Humphrey *et al.* (1992) similarly showed that such response functions could be determined from a tension–torsion test on a solid cylindrical specimen like the papillary muscle within the heart, namely

$$\left.\begin{aligned} \left.\frac{\partial W}{\partial \mathrm{I}_C}\right|_{r=a} &= \frac{(2 - a^2\gamma^2)(\gamma^2 M_\gamma + 3\gamma M) - (a^2\gamma^2)(2\gamma L_\gamma + 4L)}{8\pi\beta^2\gamma^2 a^4}, \\ \left.\frac{\partial W}{\partial \mathrm{IV}_C}\right|_{r=a} &= \frac{(a^2\gamma^2)(2\gamma L_\gamma + 4L) - (2 - 2(\beta/\gamma)^2 - a^2\gamma^2)(\gamma^2 M_\gamma + 3\gamma M)}{8\pi\beta^2\gamma^2 a^4}, \end{aligned}\right\} \tag{3.5}$$

where γ is a twist per unit length, λ an axial extension (with $\beta = 1/\sqrt{\lambda}$), M a twisting moment, L an applied axial load and a the outer radius of the cylinder in the deformed configuration; $M\gamma$ and $L\gamma$ are derivatives of the applied loads with respect to the twist. The key observation here is that the right-hand sides of equations (3.4) and (3.5) are experimentally measurable—applied loads, dimensions and deformations—and that it is theory that defines which experiment should be performed and how to interpret the results (Truesdell & Noll 1965). That is, whereas most would simply plot stress versus strain to infer the constitutive relationship, these equations show that the response functions can be found directly from data, in principle, by plotting appropriate combinations of experimentally measured quantities versus the invariants for various constant invariant tests. Given that

$$\begin{aligned} \boldsymbol{t} &= -p\boldsymbol{I} + 2\boldsymbol{F} \cdot \frac{\partial W}{\partial \boldsymbol{C}} \cdot \boldsymbol{F}^{\mathrm{T}} \\ \rightarrow \boldsymbol{t} &= -p\boldsymbol{I} + 2\frac{\partial W}{\partial \mathrm{I}_C}\boldsymbol{B} + 2\frac{\partial W}{\partial \mathrm{IV}_C}\boldsymbol{F} \cdot \boldsymbol{M} \otimes \boldsymbol{M} \cdot \boldsymbol{F}^{\mathrm{T}}, \end{aligned} \tag{3.6}$$

where $\boldsymbol{t}$ is the Cauchy stress tensor and $\boldsymbol{B}$ $(= \boldsymbol{F} \cdot \boldsymbol{F}^{\mathrm{T}})$ the left Cauchy–Green tensor, this process would thereby determine the specific functional form of the desired stress–strain relation (i.e. step 3 in the aforementioned acrostic *DEICE*, which is often the most difficult step in a constitutive formulation). See Humphrey (2002*a*) for more details, including generalizations for cases wherein the biaxial stretching is not principal or when the solid cylinder is surrounded by a thin membrane that introduces a gross heterogeneity. It should also be noted that, based on biaxial tests on non-contracting myocardium, it appears that under certain conditions this material exhibits a polynomial-type response, not a Fung-exponential response, thus there is a need to explore objectively and individually the form of the constitutive relation for each tissue under each condition of interest. Moreover, it also appears that the form of the relation determined from biaxial stretching may not describe behaviour under

shear, thus the need for caution when one desires to employ relations determined under restricted experimental conditions. That is, given the acrostic *DEICE*, there is always a need to evaluate predictive capability for conditions different from those in the revealing experiments.

Finally, it should also be noted that Ogden advanced the idea that forms of W for isotropic behaviour can be determined as functions of the principal stretches rather than the classical invariants of $\boldsymbol{C}$ (see Ogden 1997). Such forms have proved very useful in rubber elasticity and thermoelasticity, and the Ogden model (like the neo-Hookean and Mooney–Rivlin models) is found in many commercially available nonlinear finite-element codes. Although Ogden models have been inappropriately applied (probably because it is tempting to use, rather than extend, commercially available codes) to describe the behaviour of various soft tissues that exhibit anisotropy, this reminds us that we must not restrict our attention to limited classes of relations, whether Fung-elastic or invariant-based. Indeed, Criscione *et al*. (2000) recently showed further utility in constitutive formulations for isotropic behaviour that base W on measures of the natural strain $\ln \boldsymbol{V}$, where $\boldsymbol{V}$ is the left stretch tensor. In particular, this constitutive approach separates distortional and dilatational responses in a way that yields orthogonal response terms, which can be determined more robustly in appropriately designed experiments than those associated with the classical invariants of $\boldsymbol{C}$. This general approach has been extended to describe laminar materials with one family of fibres, such as myocardium, and thus presents new opportunities to formulate more robust constitutive relations for use in biomechanics (Criscione *et al*. 2002). There is clearly a need to explore carefully such alternative descriptors, again emphasizing that biomechanics is not just the application of mechanics, it must also include the development or extension of mechanics to the study of living things.

(*b*) *Membrane theory*

Membranes are defined differently in biology and mechanics. In biology, a membrane is defined as a thin layer of tissue that covers a surface, lines a cavity or divides a space. In mechanics, the word membrane also implies a thin structure, but more specifically, one that offers negligible resistance to bending. That is, the effects of bending moments and transverse shears are neglected in comparison with the in-plane load carrying capacity. As it turns out, most biological membranes can be modelled mechanically via a continuum theory of membranes under many conditions (Humphrey 1998).

There are many different membranes within the human body, including cell membranes, saccular aneurysms which form within the vasculature, the mesentery which connects the small intestine to the dorsal wall of the abdomen, the pericardium which surrounds the heart, the epicardium which invests the heart, the pleura which invests the lungs, the meninges that envelop the brain and spinal column, the sheaths that surround tendons, the epimysium that envelops muscles, the urinary bladder, the lens capsule which encloses the ocular lens and even the skin which covers our bodies. Hence, understanding the mechanics of biomembranes is important to almost every medical specialty.

The theory of elastic deformations of membranes is largely a special case of the general theory of plates and shells; hence one might be inclined to consult primarily

the classical texts on plates and shells (e.g. Green & Zerna 1960; Kraus 1967). Yet, the particular appropriateness of membrane theory for studying finite deformation problems of thin rubber-like structures and biological membranes has resulted in specialized ideas and approaches, and thus a separate literature (see Green & Adkins 1970; Libai & Simmonds 1988). For example, one may use a 2D strain-energy function $w(\boldsymbol{C}_{2\mathrm{D}})$, defined per reference surface area, rather than the usual 3D function $W(\boldsymbol{C}_{3\mathrm{D}})$ defined per reference volume. These functions can be related simply via $w = WH$, where H is the undeformed thickness and $h = \lambda_3 H$, with h the deformed thickness and λ_3 the out-of-plane stretch ratio. For isotropy, Pipkin (1968) showed that the principal stress resultants T_α ($\alpha = 1, 2$) are related to the principal stretches λ_α via

$$T_1 = \frac{1}{\lambda_2}\frac{\partial w}{\partial \lambda_1}, \qquad T_2 = \frac{1}{\lambda_1}\frac{\partial w}{\partial \lambda_2}. \tag{3.7}$$

Perhaps the best-known constitutive descriptor for biological membranes, however, is the form suggested by Skalak *et al.* (1973), now known as the SZTC relation. It is

$$T_1 = 2\left(\frac{\lambda_1}{\lambda_2}\right)\left(\frac{\partial \tilde{w}}{\partial \mathrm{I}_E} + \lambda_2^2 \frac{\partial \tilde{w}}{\partial \mathrm{II}_E}\right), \qquad T_2 = 2\left(\frac{\lambda_2}{\lambda_1}\right)\left(\frac{\partial \tilde{w}}{\partial \mathrm{I}_E} + \lambda_1^2 \frac{\partial \tilde{w}}{\partial \mathrm{II}_E}\right), \tag{3.8}$$

where $\mathrm{I}_E = \operatorname{tr} \boldsymbol{E}_{2\mathrm{D}}$ and $\mathrm{II}_E = 2 \operatorname{tr} \boldsymbol{E}_{2\mathrm{D}} + 4 \det \boldsymbol{E}_{2\mathrm{D}}$ and

$$\tilde{w} = \tfrac{1}{8} c(\mathrm{I}_E^2 + 2\mathrm{I}_E - 2\mathrm{II}_E + \Gamma \mathrm{II}_E^2), \tag{3.9}$$

where c and Γ are material parameters. This relation was proposed for describing the behaviour of red blood cell membranes, which was thought to be dominated by an isotropic membrane-like character. In some cases, this membrane also appeared to deform in such a way that its surface area was conserved. This kinematic constraint (similar to incompressibility in three dimensions) introduces a Lagrange multiplier into the constitutive relation for the stress resultants (see Humphrey 1998).

Not surprisingly, because of the utility of the Fung-exponential in describing the behaviour of many soft tissues in three dimensions, many have used a 2D version: $w = c(\mathrm{e}^Q - 1)$, where c has units of force per length, rather than units of stress as in equations (3.1)–(3.3) and Q is quadratic in $\boldsymbol{E}_{2\mathrm{D}}$. Just as in the 3D version, caution must be exercised in the calculation of the best-fit values of the material parameters to ensure that convexity requirements are respected. It can be shown (Humphrey 2002*a*) that such a relation does not admit a load-induced change in the degree of anisotropy that is expected in soft tissues consisting of planar networks of elastin and collagen, but the relation appears to be a reasonable descriptor of some data under limited circumstances nonetheless.

Although the membrane theory affords considerable simplification in comparison with the 3D theory of finite elasticity, geometric and material nonlinearities still render the associated initial–boundary-value problems very challenging. For this reason, most theoretical, experimental and computational applications have focused on axisymmetric problems, and in particular membranes subject to a uniform distension pressure P (e.g. saccular aneurysms, urinary bladder and spherical red blood cells). In this case, the governing equations of equilibrium reduce to

$$\frac{\mathrm{d}}{\mathrm{d}r}(rT_1) = T_2, \qquad \kappa_1 T_1 + \kappa_2 T_2 = P, \tag{3.10}$$

which, with the aid of the Gauss–Codazzi relation from differential geometry,

$$\frac{\mathrm{d}(r\kappa_2)}{\mathrm{d}r} = \kappa_1,$$

where κ_1 and κ_2 are the principal curvatures, admits a closed-form solution for the stress resultants, namely

$$T_1 = \frac{P}{2\kappa_2}, \qquad T_2 = \frac{P}{\kappa_2}\left(1 - \frac{\kappa_1}{2\kappa_2}\right), \tag{3.11}$$

for all r, including $r = 0$. Hsu *et al.* (1994) showed that such solutions can be used to suggest relations for the response functions following the method of Rivlin & Saunders (1951),

$$\frac{\partial w}{\partial E_{11}} = \frac{\lambda_2}{\lambda_1}\frac{P}{2\kappa_2}, \qquad \frac{\partial w}{\partial E_{22}} = \frac{\lambda_1}{\lambda_2}\frac{P}{\kappa_2}\left(1 - \frac{\kappa_1}{2\kappa_2}\right), \tag{3.12}$$

which in turn can be used to design and interpret experiments. Hsu *et al.* (1995) reported a computer-aided, tri-plane video-based experimental system for performing such tests on inflated biomembranes, but this general approach remains largely untested due to the lack of suitable human tissue for testing. Nevertheless, these two papers illustrate well how theory should dictate the design and interpretation of experiments rather than letting available technology dictate laboratory activity.

Axisymmetric membrane solutions have been used, for example, to explore potential structural instabilities in quasi-statically (e.g. limit-point bifurcations) and dynamically (e.g. resonance-related) loaded membranes (Humphrey 2002*a*). Such analyses explain the aforementioned experimental observations of Osborne (1909), who compared the inflation response of a rubber balloon with that of a urinary bladder. Likewise, such analyses have been used in the design of elastomeric balloon-tipped catheters used in clinical interventions such as neuroangioplasty (a procedure wherein balloons are inflated within brain arteries to counteract the insidious effects of haemorrhage-induced vasospasm). For example, physicians initially reported difficulty in controlling the diameter of these balloons. Such difficulty was due, in part, to a limit point instability, which can be shown to exist in all neo-Hookean spherical balloons at a critical stretch $\lambda_{\mathrm{cr}} = 7^{1/6}$. Finally, it should be noted that much of our recent insight into mechanosensitive responses by cells has come from tests wherein a monolayer of cells is cultured on an elastomeric or biologic membrane that is stretched, often via a distension pressure. Production of various molecules as well as changes in gene expression by the cell are thereby correlated to the mechanical stretch by knowing the mechanics of the stretched membrane. There are, therefore, many different applications of membrane mechanics in soft-tissue biomechanics. See Humphrey (1998) for additional specific examples and references.

(*c*) *Viscoelasticity*

The body and its constituent parts (cells, tissues and organs) consists largely of water by wet-weight; thus it is not surprising that biological soft tissues exhibit both solid-like and fluid-like behaviours depending on the conditions of interest. That is, they often exhibit characteristic behaviours of viscoelasticity: they creep under

a constant load, they stress relax under a constant displacement, and they exhibit hysteresis under cyclic loading.

Theories of viscoelasticity developed along two separate lines: those of differential-type (e.g. Maxwell, Voigt and Kelvin models) and those of integral-type (e.g. Boltzmann models). Yet, because of the inherent nonlinear behaviour exhibited by most soft tissues, often over finite strains, standard models of linear viscoelasticity are not applicable in general. Fung, in 1972, was among the first to address this deficiency, which led him to propose a so-called *quasi-linear viscoelasticity* (QLV) theory. In one dimension, Fung suggested the following relationship for the first Piola–Kirchhoff stress P_{11} and stretch λ (Fung 1990)

$$P_{11}(t) = \int_{-\infty}^{t} G(t-\tau)\frac{\partial P_{11}^{\mathrm{e}}}{\partial \lambda}\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\,\mathrm{d}\tau, \tag{3.13}$$

where G is a reduced relaxation function, with $G(0) = 1$, $P_{11}^{\mathrm{e}}(\lambda)$ is the nonlinearly elastic response function and λ is an axial stretch ratio. Fung also noted that it is common to express the relaxation function in terms of a finite sum of exponential decay functions. Noting problems common to such approaches, including finding $G(\infty)$, Fung further noted that the observed relative insensitivity of the hysteresis during cyclic loading suggests the need for a continuous relaxation spectrum. The literature reveals many subsequent applications of Fung's QLV theory.

Recently, however, numerous investigators have suggested that QLV is not sufficiently general to describe many of the complicated behaviours exhibited by soft tissues, including a strain-dependent relaxation and fundamentally different short-term and long-term viscous responses. Building upon the many advances in viscoelasticity since World War II (by Green, Rivlin, Pipkin and Bernstein among others (see Ferry 1980)), various approaches have been proposed. These include the single integral finite strain model of Johnson *et al.* (1996), the combined differential-integral model of Pioletti & Rakotomanana (2000), the generalized elastic-Maxwell model of Holzapfel & Gasser (2001) and Holzapfel *et al.* (2002*a*), and the modified superposition model of Provenzano *et al.* (2002) to name but a few. These, in addition to mixture models that account for viscoelastic effects through momentum exchanges between solid and fluid constituents, reveal the considerable diversity of approaches. Yet, much more research is needed. Again, we should remember that diverse approaches may be needed to address the diverse conditions found in health, disease, injury and clinical intervention.

(*d*) *Mixture theory*

As noted above, cells, tissues and organs can be classified as mixture-composites, for they consist of multiple solid constituents plus ample bound and unbound water. It is very natural, therefore, to employ the concept of mixtures to describe certain behaviours of soft tissues, particularly those due to significant exchanges of mass, momentum or energy between constituents. The origins of the continuum theory of mixtures can be traced to A. Fick and W. Darcy in the 1850s, but the modern theory owes much to a 1957 paper of Truesdell (see Truesdell & Noll 1965, § 130). Briefly, Truesdell put forth two 'guiding principles' for the construction of a *continuum theory of mixtures*:

(1) every property of the mean motion [of the mixture] is a mathematical consequence of the properties of the motion of the constituents;

(2) if all effects of diffusion [constituent interaction] are taken into account properly, the equations for the mean motion are the same as those governing the motion of a simple medium.

That is, whereas the mixture as a whole is required to respect the classical balance equations for mass, linear momentum and energy, which in a spatial formulation can be written as

$$\frac{\mathrm{d}\rho}{\mathrm{d}t} + \rho\nabla\cdot\boldsymbol{v} = 0, \qquad \nabla\cdot\boldsymbol{t} + \rho\boldsymbol{b} = \rho\boldsymbol{a}, \qquad \rho\frac{\mathrm{d}\epsilon}{\mathrm{d}t} = \boldsymbol{t} : \boldsymbol{D} - \nabla\cdot\boldsymbol{q} + \rho g, \tag{3.14}$$

where ρ is the mass density of the mixture, $\boldsymbol{v}$ its velocity, $\boldsymbol{b}$ the body force, $\boldsymbol{a}$ the acceleration, ϵ the internal energy density, $\boldsymbol{D}$ the symmetric part of the velocity gradient tensor, $\boldsymbol{q}$ the spatial heat flux and g the heat supply density, the individual constituents $\alpha = 1, 2, \ldots, N$ are postulated to obey

$$\left.\begin{aligned} \frac{\mathrm{d}^{(\alpha)}\rho^{(\alpha)}}{\mathrm{d}t} + \rho^{(\alpha)}\nabla\cdot\boldsymbol{v}^{(\alpha)} = m^{(\alpha)}, \qquad \nabla\cdot\boldsymbol{t}^{(\alpha)} + \rho^{(\alpha)}\boldsymbol{b}^{(\alpha)} - \rho^{(\alpha)}\boldsymbol{a}^{(\alpha)} = \boldsymbol{p}^{(\alpha)}, \\ \rho^{(\alpha)}\frac{\mathrm{d}^{(\alpha)}\epsilon^{(\alpha)}}{\mathrm{d}t} - \boldsymbol{t}^{(\alpha)} : \boldsymbol{D}^{(\alpha)} + \nabla\cdot\boldsymbol{q}^{(\alpha)} - \rho^{(\alpha)}g^{(\alpha)} = E^{(\alpha)}, \end{aligned}\right\} \tag{3.15}$$

where $m^{(\alpha)}$, $\boldsymbol{p}^{(\alpha)}$ and $E^{(\alpha)}$ are mass, momentum and energy exchanges between constituents, quantities that require appropriate constitutive relations. The notation $\mathrm{d}^{(\alpha)}\cdot/\mathrm{d}t$ emphasizes that the material derivative is taken with respect to time as measured by an observer moving with constituent α. Truesdell offered three theorems that provide restrictions on these exchanges, as, for example, that $\sum m^{(\alpha)} = 0$ based on principle (2) and the assumption that the increase in mass of one constituent must occur at the expense of the decrease in mass of another constituent in a closed thermodynamic system.

Based on this seminal paper, there was tremendous activity devoted to developing and extending this basic theory of mixtures, particularly during the period 1964–1976 as revealed by two excellent reviews: Atkin & Craine (1976) and Bowen (1976). More recent developments are noted in Rajagopal & Tao (1995). Whereas the associated details cannot be documented here, it must be noted that there was (and remains) significant controversy over issues of proper second law restrictions, assigning boundary conditions for partial (constituent) quantities and proposing specific constitutive relations, particularly for the constituent exchanges. Indeed, most important here is the realization that a theory of mixtures, with additional balance relations, necessitates the formulation of additional constitutive equations for quantities that are generally not directly accessible to the experimentalist. Therein lies the greatest challenge, particularly in biomechanics wherein (a) tissues consist of various cell types embedded in an extracellular matrix that may include elastin, various collagens, muscle fibres, diverse proteoglycans, accessory proteins such as fibronectin, laminin or osteopontin and abundant mobile water, and (b) cells consist of various organelles embedded in a cytoskeleton consisting of intermediate filaments, actin, microtubules, hundreds of accessory proteins such as α-actinin or myosin-II and abundant cytosolic water. Given this complexity, it is not surprising that there

has yet to be a complete, widely accepted theory of mixtures for soft tissues or cells in general.

V. C. Mow and colleagues were the first to apply and develop continuum mixture theories for biological tissues, specifically articular cartilage (Mow *et al*. 1980). Their so-called *linear biphasic theory* treated cartilage as a solid (i.e. the composite response due to type II collagen, proteoglycans, etc.), which exhibited a linearly elastic isotropic response, plus a viscous fluid. For example, they considered constitutive relations for the solid and fluid stresses of the form

$$\left.\begin{aligned} \boldsymbol{t}^{(\mathrm{s})} &= -\phi^{(\mathrm{s})} p\boldsymbol{I} + \lambda_{\mathrm{s}} \operatorname{tr}(\boldsymbol{\varepsilon})\boldsymbol{I} + 2\mu_{\mathrm{s}}\boldsymbol{\varepsilon}, \\ \boldsymbol{t}^{(\mathrm{f})} &= -\phi^{(\mathrm{f})} p\boldsymbol{I} - \tfrac{2}{3}\mu_{\mathrm{f}} \operatorname{div} \boldsymbol{v}^{f}\boldsymbol{I} + 2\mu_{\mathrm{f}}\boldsymbol{D}, \end{aligned}\right\} \tag{3.16 a}$$

and, for the momentum exchanges,

$$-\boldsymbol{p}^{(\mathrm{f})} = \boldsymbol{p}^{(\mathrm{s})} = p\nabla\phi^{(\mathrm{f})} + K(\boldsymbol{v}^{(\mathrm{f})} - \boldsymbol{v}^{(\mathrm{s})}), \tag{3.16 b}$$

where the superscripts and subscripts 's' and 'f' denote solid and fluid constituents, hence $\boldsymbol{v}^{(\mathrm{s})}$ and $\boldsymbol{v}^{(\mathrm{f})}$ are solid and fluid velocities, respectively. Finally, the $\phi^{(\alpha)}$ are constituent fractions, μ_{s} and λ_{s} are the classical Lamé constants for the solid, μ_{f} is the fluid viscosity and $\boldsymbol{\varepsilon}$ is the linearized strain in the solid. The fluid viscosity could be neglected, thus allowing tissue viscoelasticity to be accounted for solely via the momentum exchange between the solid and diffusing fluid, where K is related to the permeability coefficient. Mow and colleagues have developed this theory over the years to account for additional factors, including the presence of diffusing ions (see, for example, Lai *et al*. 1993). Because of the complexity of the mixture theories, as well as the inherent geometric complexities associated with most real boundary-value problems, finite-element methods will continue to prove essential. See, for example, Spilker *et al*. (1990) for such formulations. In summary, one can now find many different applications of mixtures in the literature on soft tissues, and, indeed, the past success and future promise of this approach mandate intensified research in this area, research that must not be simply application, but rather should include development and extension of past theories.

(*e*) *Growth and remodelling*

It was long thought that the most important general characteristics of soft tissues are the often nonlinear, inelastic, anisotropic, nearly incompressible behaviours that they exhibit over a wide range of physiologic and pathophysiologic conditions. Recently, however, we have come to appreciate a more important characteristic: the ability of tissues to grow and remodel in response to disease, injury and even subtle changes in their mechanical environment. Although the idea that mechanical factors (e.g. stress) correlate well with the structure and function of biological tissues was put forth in the late 19th century with regard to bone (so-called Wolff's law), surprisingly little attention was given to comparable issues in soft tissue until the early 1980s. Skalak (1981) suggested that a key goal was to '... form a framework within which growth and deformation may be discussed in regard to the kinematics involved', that is, to develop a theory of *kinematic growth*. It is noteworthy that Skalak's ideas suggested the possibility of a locally incompatible growth that could give rise to residual stresses. Based on prior observations of radially cut arteries,

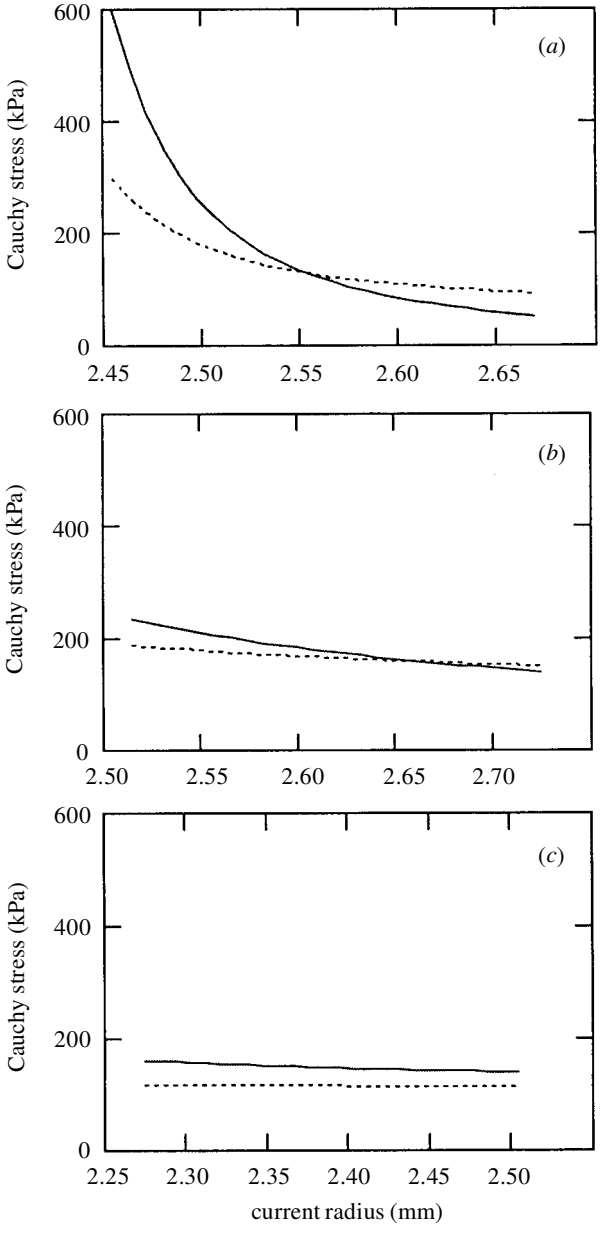

Figure 5. Computed stresses in the wall of an artery (the solid line is the circumferential stress and the dashed line is the axial stress). Note the tremendous reduction in the predicted transmural gradient when residual stress is accounted for: (*a*) shows passive results ignoring residual stress and (*b*) shows passive results with residual stress included according to Fung and colleagues. Finally, (*c*) shows values when residual stress and smooth muscle activation are accounted for, leading to a nearly homogeneous and equibiaxial stress field. Complexities such as wall heterogeneity remain to be quantified well.

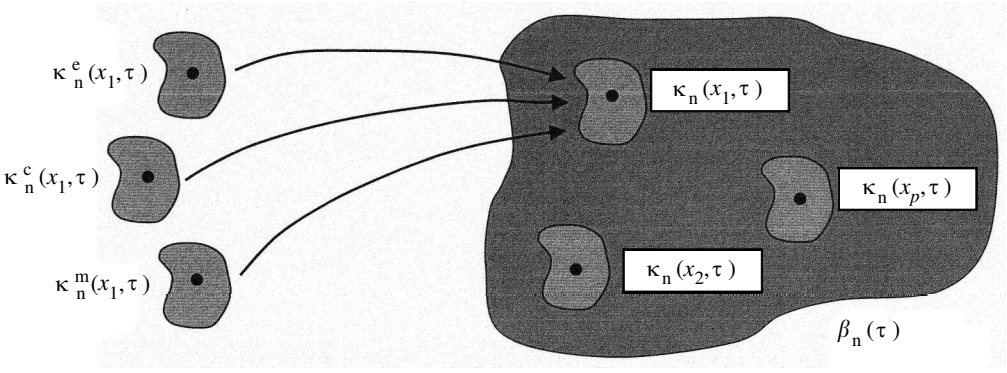

Figure 6. Schema emphasizing that observed local natural configurations κ_n (a local concept) are actually the integrated result of the separate natural configurations of each of the constituents in the neighbourhood of interest (here the superscripts 'e', 'c' and 'm' denote elastin, collagen and smooth muscle as in an artery). In the context of growth and remodeling, therefore, mixture theories that account for different properties of the different constituents are appropriate and promising.

Chuong & Fung (1986) soon thereafter showed the potential importance of residual stress in soft tissues, which is now a widely recognized essential aspect of the biomechanics (figure 5). Continuing his ideas on growth, Tozeren & Skalak (1988) suggested further that there is a need to relate the 'evolution of the stress-free configuration and the changes in the stiffness of the tissue to the evolution of its microstructure during growth and remodelling.' It was Rodriguez *et al.* (1994), however, who finally put forth a formal framework to describe such kinematic growth. Briefly, they suggested that kinematic growth can be modelled via a growth tensor $\boldsymbol{F}_{\mathrm{g}}$ that describes deformations between two fictitious stress-free configurations: the original body is cut into small stress-free pieces, each of which is allowed to grow separately via $\boldsymbol{F}_{\mathrm{g}}$. Because these growths need not be compatible, internal forces are often needed to assemble (via $\boldsymbol{F}_{\mathrm{a}}$) the pieces into a contiguous configuration, with the internal forces producing residual stress. Finally, elastic deformations are described from the residually stressed configuration via a usual deformation gradient tensor $\boldsymbol{F}_{\mathrm{e}}$, and initial–boundary-value problems solved via the classical balance relations. The key to this formulation, therefore, is the prescription of $\boldsymbol{F}_{\mathrm{g}}$ via evolution equations. Among others, Taber (1998) and Rachev *et al.* (1998) have employed the concept of kinematic growth to study problems in vascular mechanics.

Recently, however, Humphrey & Rajagopal (2002) suggested that the concept of kinematic growth merely accounts for certain *consequences* of growth, not the actual *processes* by which growth and remodelling occur. Biological growth and remodelling necessarily occur in stressed configurations via imbalances in the production and removal of the individual constituents that comprise the tissue (e.g. elastin, collagen, muscle fibres and cells). Because each constituent can have individual rates of production and removal, as well as individual material properties and natural configurations, it was suggested that a mixture theory is better suited to describe the mechanics. Yet, because of the difficulty in prescribing certain boundary conditions in mixture theory (e.g. partial stresses for solids), and based on assumed negligible momentum exchanges between solid constituents during growth and remodelling (see, for example, Roy *et al.* 1999), it was suggested that it would be advantageous to

invoke a constrained mixture homogenization for the stress responses rather than a full mixture approach. In this way, advantages of the full mixture theory (with regard to mass balance) can be exploited while advantages of homogenization (with regard to momentum balance) can simplify the formulation. Whereas full details on the constitutive formulation can be found in the original paper, a few points are noteworthy. First, this theory emphasizes that soft tissues are materially non-uniform regardless of their gross homogeneity. That is, via the usual volumetric averaging employed in continuum mechanics, the material properties at a point (i.e. averaged over a neighbourhood about that point) result from the integrated manifestations of the homogenized properties of multiple constituents, each of which may have individual (evolving) natural configurations (figure 6). Hence, even the stress-free configurations discussed by Skalak and Fung are not so simple: any stress-free configuration observed in the laboratory for tissue consisting of multiple constituents is actually an integrated manifestation of the individual, competing natural configurations of each constituent. This means that the requisite natural configurations are not available for observation, and thus there is a need for competing hypotheses related to the mechanisms by which the natural configurations occur and evolve. Second, there is a need to focus on the rates of production and removal of individual constituents, and in particular how these constituents are incorporated within the existing tissue. Although the biochemistry is very complex for the synthesis, secretion and cross-linking of extracellular proteins, first-order kinetics may be a reasonable first approximation (see Humphrey 2002*a*). What is needed, therefore, is information on how the associated rate parameters change with changes in the chemical milieu and mechanical environment. Moreover, it may be that cells seek to deposit extracellular matrix at an optimal tension. If so, these optimal conditions must be found. Such issues are discussed further in § 4 *c*. Clearly, there is much more to learn in this regard.

(*f*) *Thermomechanics*

The body regulates its temperature within a narrow range about 37 °C, for above and below this body temperature cells and proteins tend to lose their structure and hence function. For this reason, there has tended to be little motivation over the years to study thermomechanics of soft tissues. Two notable exceptions, however, are Lawton (1954) and Flory (1956), who showed that tissue elasticity is primarily entropic, similar to that of rubber, rather than energetic, like that of metals. That is, given the constitutive relation (from second law arguments) for the first Piola–Kirchhoff stress $\boldsymbol{P}$ as well as the definition of the Helmholtz potential $\psi = \epsilon - \eta T$, where ϵ is the internal energy, η the entropy and T the temperature, we have

$$\boldsymbol{P} = \rho_0 \frac{\partial \psi}{\partial \boldsymbol{F}^{\mathrm{T}}} = \rho_0 \left(\frac{\partial \epsilon}{\partial \boldsymbol{F}^{\mathrm{T}}} - \frac{\partial \eta}{\partial \boldsymbol{F}^{\mathrm{T}}} T \right), \tag{3.17}$$

which reveals the energetic and entropic contributions, respectively. Lawton's finding supports the contention by Treloar (1975) that early advances in tissue and rubber elasticity went hand in hand for the 'unusual' characteristic behaviours exhibited by both classes of materials result largely from changes in polymeric conformations. Indeed, recall that Roy (1880) had observed much earlier the similarities in the thermoelastic behaviour of soft tissue and elastomers. With the exception of elastin, however, which is the most thermally stable protein in the extracellular matrix, the

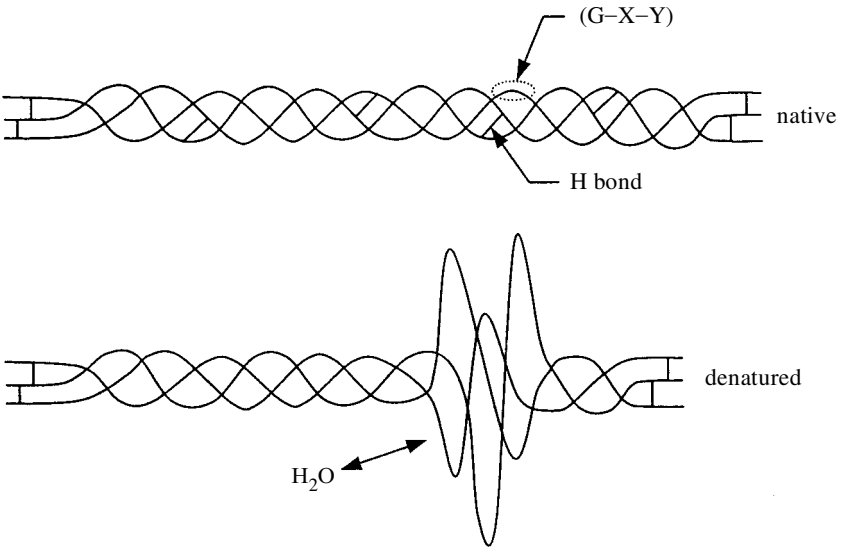

Figure 7. Schema of the hydrogen bond stabilized triple-helix structure of the collagen molecule, which is lost in part during thermal denaturation, the gross indication of which is often overall shrinkage of the tissue.

issue of thermal damage is actually more important at elevated temperatures than the nonlinear thermoelasticity.

Note, therefore, that advances in laser, microwave, radio-frequency and similar technologies have encouraged the widespread use of thermal energy to treat a host of diseases and injuries (Humphrey 2003). Examples can be found in most medical specialties and have included the treatment of arteriovenous malformations, asthma, atherosclerosis, benign prostatic hyperplasia, various cancers, cardiac arrhythmias, chronic pain, hyperopia, joint laxity, menorrhagia, port wine stains, Parkinson's disease, secondary cataract, and so on. Most of these applications have been motivated by two simple observations: supra-physiologic temperatures can kill cells (e.g. malignant cells) and they can denature proteins (e.g. collagen, which shrinks when heated). Here, let us briefly discuss the latter.

As noted above, collagen is the most abundant protein in the body. Collagen molecules are comprised of three α-helix polypeptide chains, each consisting of some 1300–1700 amino acid residues. Much of the length of these chains (*ca.* 1000 amino acid residues each) is co-organized into a central triple (super) helix configuration that is of the order of 285 nm long and 1.4 nm in diameter and that consists of a repeating triplet, $(G–X–Y)_n$, where G is glycine and X and Y are often proline or hydroxyproline (Ayad *et al.* 1994). The collagen molecule is organized by extensive intrachain and interchain hydrogen bonds, many associated with hydroxyproline, with water-bridges likely playing an essential role. The fibrillar types I and III collagen are the primary structural forms; they are found in skin, tendons, blood vessels and the cornea, amongst other tissues. Types I and III collagen exhibit a characteristic 67 nm periodicity that results from long assemblies of quarter-staggered molecules (four to five in a cross-section) into microfibrils. These structures are the building blocks for collagen fibres, which are organized further by intramolecular

and intermolecular cross-links (many involving lysine or hydroxylysine). The effects of heating collagen can be reversible or 'irreversible'. Moderate heating can result in a local unfolding within the protein that is reversed upon the restoration of normal temperatures (e.g. unfolding may be due to the breaking of a small number of consecutive hydrogen bonds). Severe heating results in a time-dependent irreversible transformation of the native triple-helix structure into a more random (coiled) structure (figure 7). It is thought that the latter transformation occurs primarily via the breaking of longer sequences of hydrogen bonds that stabilize the triple helix, but heating-induced breakage of reducible cross-links may also play an important role. According to Miles & Bailey (2001), type I collagen has a 65-residue-long domain within the triple helix (from residues 877 to 941) that is completely devoid of hydroxyproline (which readily forms hydrogen bonds that stabilize the molecule), thus rendering this domain particularly susceptible to thermal damage. Types II and III collagen have similarly susceptible domains (65 and 59 residues long, respectively), although there is a one hydroxyproline residue within this domain in type II collagen and two hydroxyproline residues within this domain in type III collagen. Miles & Bailey suggest that 'these hydroxyprolines serve to reduce the effective length of the thermally labile domain resulting in a smaller activation enthalpy determined by isothermal calorimetry'. Specifically, they report activation enthalpies (in solution) of 1255, 644 and 372 kJ mol^{-1} for types I, II and III collagen, respectively. Note, however, that collagen in solution has a much lower thermal stability than that in native tissue wherein molecules/fibrils are stabilized further by molecular interactions that include covalent cross-links (enzymatic and glycation), disulphide bonds (in type III) and interactions with proteoglycans. Indeed, Miles & Bailey suggest that 'the increased thermal stability of the intact fibre compared with the molecule in solution is brought about mainly by a reduction in the entropy of activation, but the precise mechanisms have not been worked out'.

There is an extensive literature on the thermal denaturation of collagen (see Humphrey 2003), but just three general classes of tests. Differential scanning calorimetry (DSC) is widely used to evaluate the effects of pH, cross-linking, disease, age, Ca^{2+}, etc., on the thermal stability. DSC is motivated largely by work in the 1950s by P. J. Flory that suggested that the denaturation results from the melting of a crystalline structure. Indeed, hydrothermal isometric tension (HIT) testing is similarly motivated. In these tests, one maintains a sample at a fixed overall length and measures the force generated (as it tries to shrink) as the tissue is heated. It is now recognized, however, that denaturation is largely an irreversible rate process (Wright & Humphrey 2002), and there is a need to study the effects of various conditions on this rate. Note, therefore, that isotonic tests measure the shrinkage directly as a function of temperature. Weir (1949) showed, for example, that the rate of shrinkage (i.e. denaturation) varies with the isothermal temperature level, the applied mechanical load, the pH, the hydration level and the presence of cross-linking agents. Unaware of this work, Chen *et al.* (1998) confirmed and extended these early observations by showing that, under certain conditions (bovine chordae tendineae, a tissue consisting primarily of uniaxially oriented type I collagen, were subjected to temperatures from 65 to 90 °C from 3600 to 180 s over the range of first Piola–Kirchhoff stress from 0 to 650 kPa), applied loads delay the process whereas increasing temperatures hasten it. Specifically, a characteristic time τ_c for the sig-

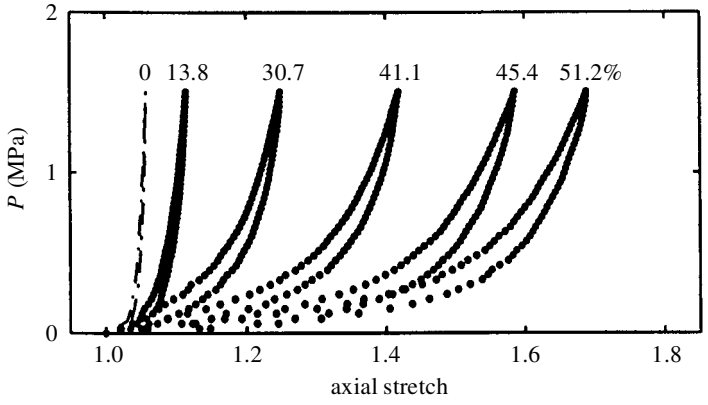

Figure 8. Stress–stretch data for chordae tendineae, a thin tissue with locally parallel collagen, before and after various degrees of prior thermal damage as denoted by the per-cent shrinkage (13.8–51.2%)

moidal shrinkage ξ process was found to be

$$\tau_{\mathrm{c}} = A \exp(\beta P_{11}) \exp(m/T), \tag{3.18}$$

where A, β and m are material parameters, P_{11} is the uniaxial first Piola–Kirchhoff stress and T is the temperature (conceptually, β can be thought to be related to the activation entropy and m to the activation energy). Scaling real time by this characteristic time allowed the data to be collapsed to a single master curve described by (with $\nu = \ln(\tau/\tau_{\mathrm{c}})$ a non-dimensional time)

$$\xi = (A_0 + A_1\nu)(1 - f(\nu)) + (a_0 + a_1\nu)f(\nu), \tag{3.19}$$

where

$$f(\nu) = \frac{\mathrm{e}^{a(\nu-\nu_{\mathrm{m}})}}{1 + \mathrm{e}^{a(\nu-\nu_{\mathrm{m}})}} \quad \forall \nu \in \left(\ln\left(\frac{\tau_a}{\tau_{\mathrm{c}}}\right), \ln\left(\frac{\tau_b}{\tau_{\mathrm{c}}}\right)\right)$$

and A_i, a_i and a are material parameters. The existence of such a master curve suggests a time–temperature–load equivalence, under some conditions, reminiscent of comparable findings in the viscoelasticity of polymers (Ferry 1980). That is, it appears that the denaturation process always occurs at the same rate relative to a material's 'internal clock', the speed of which may increase or decrease depending on the temperature and state of stress.

Although equation (3.19) for shrinkage ξ, a gross measure of thermal damage in one dimension, allows one to predict the extent of denaturation under isotonic conditions given the applied uniaxial load, temperature and duration of heating, there is a pressing need for extension to two and three dimensions and to formulate constitutive relations for the stress response as a function of evolving or prior thermal damage. Figure 8 shows, for example, the stress–stretch response of chordae tendineae before and after various levels of thermal damage. As it can be seen, the general character remains the same, although the degree of extensibility, hysteresis and compliance all increase with increasing denaturation. There is surprisingly little in the literature on such changes, however, particularly for multiaxial responses.

4. Open problems

Section 3 reveals that much has been accomplished, yet much remains to be done. Listed below are a few of the many areas in which biomechanics can and must provide a greater understanding of the foundations of soft-tissue structure and function and especially the associated mechanobiology. First, however, it is interesting to note some of the research needs that have been suggested over the past few decades.

In one of the seminal papers in biomechanics, Fung (1967) suggested that the 'high degree of nonlinearity in the stress–strain relationship of living tissues is known to most authors, but a theoretical framework in which experimental results can be imbedded is lacking'. About 15 years later, Fung (1983) suggested further that 'looking toward the future, I would say that the clarification of the constitutive equations of the muscles is the key to future development of biomechanics'. Hence, we see during this period a move from a perceived need for a basic framework to a specific biologically important application. Indeed, in a foreword for the new journal *Biomechanics and Modeling in Mechanobiology*, Fung suggests that biomechanics is the 'middle name' between biological structure and function. Hence, he suggests that biomechanics must also play a key role in the emerging areas of genomics and proteomics, applications of which are thought to hold tremendous industrial and clinical promise. Also see Lee (1987), who summarized accomplishments during the first *ca.* 20 years in biomechanics as well as future needs based on a report by the US National Committee on Biomechanics (USNCB); the 20th anniversary issue of the ASME *Journal of Biomechanical Engineering* (**115**, 451–622 (1993)) that celebrated biomechanical research within the American Society of Mechanical Engineering by reflecting on past achievements and suggesting needs at that time; and Prendergast & McCormack (2002), who list high-priority areas of research and development that were identified at the 12th Conference of the European Society of Biomechanics at Dublin in 2000. Finally, note that the US National Institutes of Health recently formed both a Bioengineering Consortium (BECON) and a new institute (National Institute of Biomedical Imaging and Bioengineering). Among other findings by the associated working groups (www.nih.gov/becon), it was suggested that biomechanics focus on three primary areas: tissue adaptation to stress, including repair, fatigue and failure; *in vivo* biomechanics, including a better understanding of the native environment into which prosthetic devices and tissue engineered constructs are placed; and molecular biomechanics, with particular attention to how forces and deformations at the cellular level result in altered gene expression. Indeed, these research needs are consistent with educational needs identified at recent Whitaker Foundation summits on biomedical engineering education. With these brief remarks as background, let us now consider more specifics on current open problems.

(*a*) *Molecular and cell biomechanics*

As noted above, the idea that mechanical factors play a key role in governing biological structure and function goes back at least to Galileo and Descartes, and resurfaced in earnest in the late 19th century due to the study of bone by Wolff and others. Nevertheless, it has only been since the mid 1970s (see Leung *et al.* 1976) that we have learned the underlying reason for this obvious influence of the mechanics: many cells change their gene expression in direct response to changes in their mechanical environment. That cells appear to sense and respond to even subtle

changes in mechanical stimuli has led many to ask whether it is stress, strain, strain energy, strain rate or a similar quantity that the cell actually senses (see Taber 1995; van der Meulen & Huiskes 2002), and there is now considerable debate in the literature. Such continuum metrics are but mathematical concepts, however, not physical entities or experimental measurables—they cannot be sensed by a cell (Humphrey 2001). Rather, cells probably sense conformational changes at the molecular level, or perhaps changes in interatomic or intermolecular forces. Regardless of the specific molecular *mechanisms*, which we must continue to search for and then model, continuum quantities such as stress and strain will continue to be useful metrics by which mechanosensitive responses can be *correlated* with changes in the mechanical environment. Quantification of both mechanisms and correlations are thus very important open problems, and continuum biomechanics thereby has a fundamental role to play in the field of mechanobiology.

For obvious reasons (e.g. ease of isolation), blood cells were among the first cells to attract detailed biomechanical analysis (by E. Evans, Y. C. Fung, R. Hochmuth and R. Skalak, among others). Dating back to the late 1960s and early 1970s, it was suggested that erythrocytes (and later leukocytes) may be modelled, under many conditions, as highly deformable solid shells surrounding a viscous interior. Depending on the range of deformation, the behaviour of the shell (i.e. cell membrane and supporting cortical actin-spectrin layer) was thought to be dominated by either its bending stiffness or its membrane-like character. Such modelling gave rise to the so-called 'cortical membrane models' for cells, the STZC strain-energy function, equations (3.8) and (3.9), being a good example thereof for describing an isotropic membrane-like behaviour. Although some investigative groups have recently advocated the use of cortical membrane models for additional classes of cells, this issue remains highly controversial (see, for example, Ingber *et al.* 2000). Indeed, many other approaches to modelling have been proposed: one finds tensegrity models, which emphasize the importance of pre-stress within a cell and the possibility of mechanical stresses acting at a distance; percolation theories that emphasize dynamic changes in cytoskeletal inter-connectiveness; soft glassy rheological models that suggest that the cytoskeleton is metastable, able to transform instantaneously from more solid-like to more fluid-like behaviours; and continuum models, based on cells as inclusions in a matrix that allow study of cell–matrix interactions (see Mow *et al.* 1994; Stamenovic & Ingber 2002; Humphrey 2002*b*, and references therein). No single model enjoys wide acceptance, however, even for a particular class of mechanocytes; thus there remains a pressing need for much more research on cell mechanics. Given the diversity of cell types and the various environments in which they function, we should probably expect that multiple approaches will be equally useful in modelling the many different aspects of cell mechanics.

Cell mechanics is essential, for example, for explaining basic processes such as cell adhesion, contraction, division, migration, spreading and even phagocytosis (the engulfing and digestion of extracellular material). Likewise, it appears that cellular apoptosis (i.e. programmed cell death), the synthesis and degradation of matrix and the production of growth regulatory molecules, cytokines and cell surface receptors are also influenced greatly by the mechanics. Each of these activities manifests itself at the tissue and organ level, of course, and they are linked to development, tissue maintenance, wound healing, growth and remodelling and pathogenesis.

Hence, whether one seeks to understand normal physiology, disease, injury, interactions between medical devices and tissues, or even the engineering of tissue or organ replacements, there is a need to understand the mechanics of cells. The interested reader is referred to the collection of papers in Mow *et al.* (1994) and a special issue of the *Journal of Biomechanics* (**28**, 1411–1572 (1995)) for a discussion of some of these issues.

The excellent review by Zhu *et al.* (2000) correctly notes that 'Critical issues include how forces are applied to tissue cells that are adherent to the ECM, how these forces are transmitted into and distributed within cells and how they are transduced into biochemical signals that induce biological responses.' It has been suggested by many, for example, that transmembrane proteins called integrins (figure 1) play a key role in transducing mechanical stimuli to the interior of the cell (Ingber *et al.* 2000; Janmey 1998). There is a pressing need, therefore, to study the details of the so-called extracellular matrix–integrin–cytoskeletal axis. Complicating such studies, however, is the fact that there are literally hundreds to thousands of integrins decorating the surface of a typical cell, with clustered groups called focal contacts. Whether modelling should be attempted within a continuum framework or based on discrete molecular dynamics will thus be an important consideration, again depending on the particular conditions and questions of interest. Regardless, as noted further by Zhu *et al.* it cannot be overemphasized that 'it is necessary to elucidate the mechanisms by which forces and deformations regulate the structure-function relationships of biomolecules'. For example, it is thought that deformations of a tissue or cell influence the underlying molecular conformations (i.e. the 3D geometry of a molecule, which also depends on the particular polymeric sequence, the chemical milieu, electromagnetic field and temperature). Moreover, Zhu *et al.* noted that 'good conformational matches lead to strong and long-lasting bonds' between receptors and ligands, which in turn are essential for initiating many processes. There is, therefore, a pressing need to model the biomechanics of the individual molecules. There are two additional complications, however. First, the functions of the three primary cytoskeletal constituents (actin, intermediate filaments and microtubules) depend greatly on a host of accessory proteins (e.g. actinin, myosin, talin), interactions that are not well understood. Second, cytoskeletal constituents turnover continuously and consequently they continuously alter their intermolecular interactions, which is to say that the cytoskeletal architecture, properties and natural configurations typically change dramatically over short periods. Given that most technological advances that permit study of mechano-sensitive responses at the level of integrins (e.g. atomic force microscopy, magnetic bead cytometry, optical tweezers and even micropipettes) are likely to induce significant alterations in the stress/strain field within the neighbourhood of interrogation, we must be careful not to misinterpret measured responses and properties as necessarily native—they may simply reflect local dynamic changes in response to the local non-physiologic loads induced by the experimental probe (figure 9). Although this may not be as severe a concern as Heisenberg's uncertainty principle in particle physics, we are well advised to heed Heisenberg's general caution: 'The concepts initially formed by abstraction from particular situations or experimental complexes acquire a life of their own.' Clearly, there is considerable need for a better understanding of molecules and cellular mechanics as well as of cell–matrix interactions.

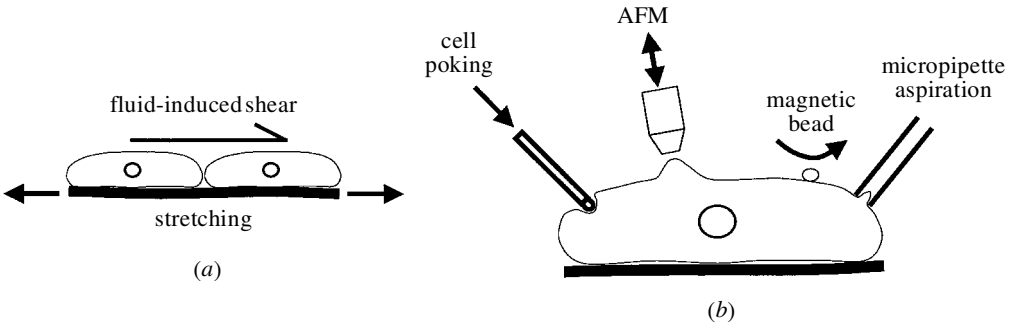

Figure 9. Schema of various types of tests performed on isolated cells for the purpose of interrogating cell behaviour. (*a*) Distributed and (*b*) localized loading. Because of the potentially large stress and ability of the cytoskeleton to adapt to changes in mechanical loading, this reminds us that there is a need for care in interpreting the meaning of such tests with respect to the desired native properties. Courtesy R. Gleason.

(*b*) *Biomechanics of development*

It appears that Thoma was the first, in 1893, to recognize that the arterial lumen adapts to local changes in blood flow as required to meet altered metabolic demands due to the production or removal of distal tissue (see Taber 1998). Briefly, Thoma observed in the developing chick embryo that arteries having greater flow increase in calibre, whereas those having lesser flow decrease in calibre. It was not until the 1980s, however, that it was realized that the increased wall shear stress associated with an increased blood flow correlates with an up-regulation of the production of nitric oxide, a potent vasodilator, which in turn allows constituents within the arterial wall to turnover in a dilated state and thereby increase the lumen during development (for details, see the discussion in Humphrey (2002*a*)). Similar mechanically stimulated developmental processes are operative in most other soft tissues. Not surprisingly, therefore, studying the biomechanics of development can provide tremendous insight into the developmental biology as well as into aspects of physiology and pathophysiology.

For obvious reasons, in particular the smallness of tissues and organs in the embryo and fetus as well as the rapidity of changes in their structure, function and properties, there has been much less attention to biomechanics during development compared with studies during maturity and ageing. Fortunately, however, technological advances aimed at molecular and cell mechanics promise to permit this important aspect of the mechanics to be studied experimentally in animals. The need for such is great. For example, in a provocative paper, Cowin (2000) asks the question, 'How is a tissue built?' The answer, of course, is found in development, an answer that Cowin correctly submits is essential to an increased understanding of many important aspects of normal morphogenesis, growth and ageing as well as wound healing, tissue engineering, etc. Cowin wrote further that 'A subject often advances by a critical experiment that distinguishes between two or more alternative hypotheses for a specific phenomenon. It is thought that there are not yet enough hypotheses for the influence of mechanical phenomena in developmental biology, consistent or inconsistent, to drive critical experimentation.'

It is interesting, for example, to compare the response of the aorta to an increased pressure during development to that during hypertension in maturity. During development, the pressure increases monotonically from near zero prior to the first heart beat to its near steady-state value in maturity (i.e. prior to subsequent gradual increases with ageing). In response to this monotonic increase, the aortic wall thickens during development—apparently so that the mean circumferential and perhaps axial stresses remain near homeostatic target values—via the addition of similar units, the so-called musculo-elastic fascicles. In contrast, in response to an increasing pressure (i.e. hypertension) during maturity, the wall thickens by adding material within extant fascicles, not by increasing their number. Understanding the reasons why these vessels respond to similar per-cent increases in pressure in very different ways at different times during the life of the organism promises to reveal significant new insight into the associated mechanobiology, particularly with regard to issues of optimization. As Cowin suggests, there is a need for testable hypotheses to guide new experimentation. Finally, note that although the two examples mentioned in this section relate to arteries, similar scenarios are found throughout the body.

Among others, L. A. Taber has truly embraced the need to study development within the context of nonlinear continuum mechanics, his attention being on the development of the embryonic chick heart which undergoes tremendous changes in geometry, microstructure and properties over short periods. For example, consider just the changes from stage 16 to stage 21 in the embryonic chick heart: between stages 16 and 18, the myocardium expands, the cardiac jelly (composed of glycosaminoglycans, glycoproteins and collagen fibrils) disappears, and circumferentially and radially oriented ridges of myocardium begin to form near the luminal surface of the outer curvature of the looped heart. These ridges of the stage 18 heart grow more prominent and interconnected, eventually forming the trabeculae found in the stage 21 embryo, which can be considered mechanically to be a nonlinear poroelastic solid filled with incompressible fluid. Hence, such changes are not subtle, they include dramatic changes in heterogeneity, material symmetry, volume fractions of constituents and the ability to contract. The interested reader is encouraged, therefore, to peruse the excellent reviews by Taber (1995, 2001). In conclusion, therefore, we emphasize that the importance of an idea need not correlate with its newness. It is purported that Aristotle (384–322 B.C.) suggested that 'Here and elsewhere we shall not obtain the best insights into things until we actually see them growing from the beginning.' Developmental biology clearly holds many keys to unlocking secrets of importance to clinical care. As noted by the biologist Harris (1994), however, 'without the aid of mechanicians, and others skilled in simulation and modelling, developmental biology will remain a prisoner of our inadequate and conflicting physical intuitions and metaphors.'

(*c*) *Biomechanics of growth and remodelling*

Murray (1926) suggested that biological 'organization and adaptation are observed facts, presumably conforming to definite laws because, statistically at least, there is some sort of uniformity or determinism in their appearances. And let us assume that the best quantitative statement embodying the concept of organization is a principle which states that the cost of operation of physiological systems tends to be a minimum...'. Over the years, a number of investigators have used this concept of the

minimization of a cost function to describe a variety of biomechanical observations. For example, the bifurcation patterns found in the vasculature appear to follow from Murray's law as does the aforementioned tendency of a blood vessel to regulate its calibre to maintain wall shear stress at a particular value that depends on the local normal pressure. See Humphrey *et al.* (2003) for more examples from the vasculature and Carter & Beaupré (2001) for examples from the musculoskeletal system. Nevertheless, there is a pressing need for more investigation into possible optimization criteria, that is, what tends to be optimized with respect to what in different stages of development, growth and remodelling and healing?

The forward-thinking A. M. Turing (of computing fame (see Ifrah 2001)) presented a seminal paper on biological morphogenesis, one that gave rise to a whole literature on modelling in mechanobiology. Briefly, Turing (1952) recognized the importance of mechanical and chemical stimuli in controlling morphogenesis (i.e. the development of form) and the associated complexity of such coupling. Yet he focused on the chemical aspects, and in particular on the reaction kinetics and diffusion of morphogens, substances such as growth factors that regulate the development of form. Turing postulated linear reaction–diffusion equations of the form,

$$\left.\begin{aligned}\frac{\partial X}{\partial t} &= a(X-h)+b(Y-k)+D_x\nabla^2 X,\\ \frac{\partial Y}{\partial t} &= c(X-h)+d(Y-k)+D_y\nabla^2 Y,\end{aligned}\right\} \tag{4.1}$$

where X and Y are morphogens, a, b, c and d are reaction rates, and D_x and D_y are diffusivities; h and k are equilibrium values of X and Y. Such reaction–diffusion models have since been generalized and used to study morphogenesis as well as problems of wound healing, tumour growth and tissue engineering (see, for example, Tranquillo & Murray 1992; Barocas & Tranquillo 1997; Gaffney *et al.* 1999; Jones *et al.* 2000). Some of these later papers extend the reaction–diffusion framework to incorporate issues of tissue mechanics, although often within the context of linearized elasticity or viscoelasticity. Clearly, such generalizations should be extended further to account for the ever-present finite deformations in soft tissues.

To the general classes of optimization and reaction–diffusion based models, we can add the aforementioned kinematic growth and constrained mixture approaches. Because the behaviour of each constituent is modelled separately in the latter, the elastic, viscoelastic and active-passive response functions will find some similarity with the so-called microstructural models for tissue (e.g. Lanir 1983). Briefly, Lanir and others advocated constitutive relations based on assumptions of the individual behaviours of the primary structural constituents (e.g. elastin, collagen, muscle) and their orientations. It should be recognized, however, that because of the lack of information on the interconnections between constituents, the requisite assumptions on constituent architecture render such approaches as structurally motivated, but phenomenological nonetheless. For example, little is known about the ability of a cell to detach and reattach to the extracellular matrix through the up- and down-regulation of integrins and how this affects the transfer of load from the matrix to the cell. Likewise, little is known about the roles of physical entanglements and secondary bonds in the preconditioning and physiologic responses of soft tissues. These unresolved issues alone are vital to a better understanding of mechanotransduction. There are, of course, many similar issues that remain unresolved and even

unidentified. There is a pressing need, therefore, for much more attention to the development of appropriate theoretical frameworks, and just as important, the collection of revealing data that address issues of spatial and temporal changes in the rates of production and removal of constituents, their cross-linking and their overall orientations, all under well-controlled stress and strain fields. These needs in growth and remodelling mechanics are among the most important in biomechanics today.

(*d*) *Injury biomechanics and rehabilitation*

Soft tissues are susceptible to a variety of injuries: abrasion, crushing, dissection, rupture and tearing to name a few. Whereas such injuries are typically thought to be due to accidental trauma, often in athletics, falls or vehicular crashes, others are purposefully induced clinically. An example of the latter is balloon angioplasty, a procedure wherein a balloon-tipped catheter is inflated within a diseased artery for the purpose of enlarging a lumen that is compromised by an obstructive atherosclerotic plaque. It was long thought (from 1964 to 1979, during which time over one million procedures were performed) that the mechanism by which angioplasty worked was a compression and reshaping of the atherosclerotic plaque. K. Amplatz and colleagues (see Castaneda-Zuniga *et al*. 1980) showed, however, that acute mechanisms include denudation of the endothelium, disruption of the plaque, with frequent dissections, and over-stretching of the media (mechanisms that remain as identified, but not understood fully). Thus, angioplasty is actually a controlled (at least it should be) injury wherein the wall-plaque structure is weakened so that the normal distending blood pressure can further expand the lumen. Computational biomechanics is now sophisticated enough to model procedures such as angioplasty (Holzapfel *et al*. 2002*b*), but there remains a need for better constitutive relations for processes such as smooth muscle damage, delamination between the arterial layers and fracture of the plaque. There are, of course, many other examples of controlled injuries that are a part of clinical care as well as many cases wherein one seeks to minimize injury. With regard to the latter, biomechanics has a tremendous role to play in the developing technology of robot-assisted surgery. In brain surgery, for example, there is tremendous need for knowledge of the mechanical properties of the tissues involved, including injury thresholds, which must be used as part of the feedback control of the computer-controlled surgical instrument (Kyriacou *et al*. 2002). As in the case of angioplasty, of course, we realize that understanding the biomechanics is not essential to *develop* a useful clinical procedure. That angioplasty continues to be successful in only 65–75% of all cases suggests, however, that knowledge of the associated biomechanics and mechanobiology may be needed to *optimize* many clinical procedures and the requisite medical devices. Toward this end, the greatest needs are improved constitutive relations and computational models. For sophisticated finite-element models on vascular injury that are setting a new standard for analysis, see Gasser *et al*. (2002) and Holzapfel *et al*. (2002*b*), who analyse the effects of vascular clamps and angioplasty. The need for such computational models is great.

Although considerable progress has been realized in the study of traditional engineering materials via the theory of continuum damage mechanics (see Lemaitre & Chaboche 1990), much less has been accomplished in describing damage and injury in biological soft tissues. The need for such is great, particularly under complex, time-dependent, multiaxial loading conditions rather than the more commonly used

quasi-static one-dimensional tests to failure. Injuries sustained during automobile accidents, for example, result from complex, high-strain-rate loading conditions. In the United States alone, such accidents account for over 40 000 deaths annually as well as tremendous financial burdens on families, companies and the state. Of particular concern is the high number of traumatic brain injuries and their associated high incidence of mortality and severe, lasting morbidity. Although there have been significant advances in computational modelling of brain injury due to impact loading (King 1993; Bandak *et al.* 1996), quantification of the complex, heterogeneous, solid–fluid properties exhibited by brain tissue remains incomplete. See, for example, Kyriacou *et al.* (2002) and references therein. Finally, as noted by Tong & Fung (2001), a better understanding of traumatic injuries requires much more attention to many other aspects of the biomechanics, including 'the complex phenomena of shock- and elastic-wave reflection, refraction, interference and, focusing [which] are made more complex in the human body by the fact that different organs have different damping characteristics and different sound speed[s].'

Related to general issues of injury biomechanics is the process of healing. Indeed, if we are to identify optimal conditions for rehabilitation, we must understand better the biomechanical aspects of healing. For example, whereas it may seem natural to immobilize and thereby protect or reduce the pain in an injured soft tissue such as a sprained ankle (i.e. over-stretched ligament), findings over the last 35 years suggest that this is naive thinking. It appears that W. H. Akeson and colleagues were the first, from 1961 to 1967, to demonstrate multiple detrimental effects of immobilizing injured tendons and ligaments. They showed, for example, that immobilized collagenous tissues undergo histological changes that include loss of glycosaminoglycans and associated water as well as alterations in matrix cross-linking. Since that time, others have shown that immobilization induces concomitant changes in biomechanical properties, including loss of stiffness, energy absorption and changes in extensibility. Fortunately, some of these detrimental effects are partly reversible upon the restoration of partial or normal loading. See, for example, the papers by Noyes *et al.* (1974), Woo *et al.* (1987), Woo & Buckwalter (1988) and Yamamoto *et al.* (1996), and references therein, for a historical perspective, specific findings and stated needs. In summary, there is a need to understand better the associated mechanobiology so that optimal rest and loading protocols can be identified as part of rehabilitation schedules following injury, surgery or other clinical intervention.

(*e*) *Functional tissue engineering*

According to Butler *et al.* (2000), 'The goal of "tissue engineering" is to repair or replace tissues and organs by delivering implanted cells, scaffolds, DNA, proteins, and/or protein fragments at surgery.' For more on the details of tissue engineering, see Patrick *et al.* (1998) and Lanza *et al.* (2000). Whereas much of the early attention was directed towards the design of bioreactors to keep dividing cells alive *ex vivo*, the engineering of biodegradable synthetic scaffolds on which these cells could adhere, migrate and grow, and the growing of tissue in desirable shapes, success in these areas has allowed some to turn more towards issues of 'functionality'. Toward this end, the US National Committee on Biomechanics formed a sub-committee in 1998 to identify primary objectives for engineering functional, not just viable, tissues. They suggest the following needs (Butler *et al.* 2000):

(i) *in vivo* stress and/or *in vivo* strain histories need to be measured in normal tissues for a variety of activities;

(ii) the mechanical properties of the native tissues must be established for sub-failure and failure conditions;

(iii) a subset of these mechanical properties must be selected and prioritized (that is, we cannot expect a tissue-engineered material to mimic exactly the native tissue, hence we must determine which properties are most important with regard to functionality);

(iv) standards must be set when evaluating the repairs/replacements after surgery so as to determine 'how good is good enough?';

(v) we must determine what physical regulation cells experience *in vivo* as they interact with an extracellular matrix; and

(vi) we must determine how physical factors influence cellular activity in bioreactors and how cell–matrix implants can be mechanically stimulated before surgery to produce a better outcome.

Clearly, continuum biomechanics has a key role to play in achieving most, if not all, of these objectives.

The paper by Butler & Awad (1999) on tissue engineering for purposes of the surgical repair of damaged tendons illustrates well many of the biomechanical issues regarding structural functionality. They report, for example, that mesenchymal-stem-cell-based tissue-engineered repairs of tendon defects exhibited load carrying capabilities from 16 to 63% of the maximum force experienced by the tendon during normal activity. The need for continued improvement in structural integrity is thus clear. Similarly, although the goal of early tissue engineering of arteries was primarily to achieve a viable, non-thrombogenic tubular segment of the correct diameter, success in this area has turned the attention to issues of burst strength and suture retention—that is, minimum structural functionality. In addition, however, a functional artery should be vasoactive, able to respond to altered hemodynamic demands and capable of growth and remodelling so as to function well under the inevitable changes in load. Much remains to be done in achieving true functionality.

At this juncture, it is important to emphasize that many of the current needs—molecular and cell biomechanics, biomechanics of development, growth and remodelling, the mechanics of wound healing, rehabilitation, tissue engineering, etc.—are all related. That is, we can and must learn from what are often portrayed as different sub-areas of investigation. Fung (1995) was exactly right when he wrote, 'one of the best ways to study tissue engineering is to investigate the changes that can occur in normal organs when the stress and strain fields are disturbed from the normal homeostatic condition.' Conversely, observations from tissue engineering promise to elucidate important aspects of normal physiology and perhaps pathophysiology. Hence, although we all recognize that we must learn from the cell, the effector of change, and from development, the blueprint to successful structure-function relations, we must also remember to learn from one another, which is to say to study allied literatures rather than focusing on but a single problem or issue.

(*f*) *Muscle mechanics*

The long-standing dogma in muscle mechanics comes from the classic works by A. F. Huxley, who proposed the cross-bridge model of muscle contraction, and A. V. Hill, who proposed a spring–dashpot type analogue model for muscle. That is, it has long been thought that the mechanics of muscle contraction is one dimensional, described by a tension T. For example, full constitutive relations have been suggested of the form,

$$\boldsymbol{t} = -p\boldsymbol{I} + \boldsymbol{t}^{\mathrm{p}} + T(\mathrm{Ca}^{2+}, \alpha)\boldsymbol{m} \otimes \boldsymbol{m}, \tag{4.2}$$

where $\boldsymbol{t}$ is the total Cauchy stress (active plus passive), p is a Lagrange multiplier enforcing incompressibility, $\boldsymbol{t}^{\mathrm{p}}$ is the passive contribution of the matrix to the stress (e.g. given by a Fung-elastic relation) and $T(\mathrm{Ca}^{2+}, \alpha)$ is an actively generated muscle tension in the direction $\boldsymbol{m}$, which is a unit vector in the direction of a muscle fibre in a deformed configuration; T is often assumed to depend on the intracellular calcium Ca^{2+} and the stretch α of the muscle fibre relative to a reference sarcomere length (with $\alpha\boldsymbol{m} = \boldsymbol{F} \cdot \boldsymbol{M}$, where $\boldsymbol{F}$ is the deformation gradient and $\boldsymbol{M}$ the original muscle fibre direction). Various forms of $T(\mathrm{Ca}^{2+}, \alpha)$ have been suggested in the literature as, for example,

$$T(\mathrm{Ca}^{2+}, \alpha) = A(\mathrm{Ca}^{2+})\alpha\left(1 - \left(\frac{\lambda_{\mathrm{m}} - \alpha}{\lambda_{\mathrm{m}} - \lambda_0}\right)^2\right), \tag{4.3}$$

which was proposed by Rachev & Hayashi (1999) for vascular smooth muscle. In this equation, A is a so-called activation function, λ_{m} is the stretch at which force generation is a maximum and λ_0 is the stretch at which activation ceases. This equation yields the familiar parabolic 'length–tension' curve for muscle; other relations emphasize the force–velocity behaviour. Although various forms of T are found in the literature, none enjoys widespread acceptance (see, for example, McCulloch 1995; Fung 1990, ch. 9–11).

Recent data suggest, however, that muscle is not one dimensional; it exhibits multiaxial effects upon contraction and relaxation (e.g. Strumpf *et al.* 1993). In hindsight, this multiaxiality is to be expected even from simple models of cross-bridge cycling—the generated force vector must have both axial and transverse components. There is a pressing need, therefore, to model this complex behaviour. Toward this end, Zahalak (1996) proposed a three-dimensional generalization of the classic Huxley cross-bridge theory—a new Huxley-type rate equation for the bond-distribution function includes effects of both axial stretch and lateral myofilament spacing, which changes with deformation. This equation was subsequently used in a finite-element model of the left ventricle, which revealed a significant effect of non-axial deformations on myocardial fibre stresses (Zahalak *et al.* 1999). There is clearly a need for much additional attention to the multiaxial mechanics of muscle. Indeed, Fung (1983) noted that without a theory of muscle mechanics we cannot understand human athletic performance or much of rehabilitation engineering; we cannot develop a theory of the heart or autoregulation of the vasculature; we cannot understand asthma or accommodation of the eye; and, indeed, we cannot even understand basic cell activities such as migration. The mechanics of muscle and motor proteins is thus fundamental to understanding life at the organ, tissue and cellular levels.

(g) *Solid–fluid interactions*

The function of many organs depends upon solid–fluid interactions. Examples include the removal of waste products by the kidney, bladder and urinary tract; the pumping of blood by the heart and its conduction through the vasculature; the process of gas exchange within the lungs, and so on. Although such couplings are immediately obvious, much of biomechanics has nevertheless progressed along traditional lines—biosolid mechanics, biofluid mechanics and bioheat transfer, each studied separately. Conversely, future research and pedagogy must emphasize coupled problems within mechanics as well as those wherein mechanics is combined with related areas such as optics (e.g. stress-induced changes in birefringence), chemical reaction kinetics (e.g. stress-mediated thermal damage) and electromagnetism (e.g. electromechanics of the heart (see Hunter *et al.* 1997)). Given our vast knowledge base, it is unlikely that such research can be performed by single (renaissance) investigators; hence there is the well-recognized need for increased interdisciplinary and multidisciplinary teams.

Here, however, let us consider briefly a few specific examples of solid–fluid coupling. Perhaps the simplest (idealized) example is that of the elastodynamics of an intracranial saccular aneurysm that is distended by a pulsatile blood pressure while surrounded by cerebrospinal fluid (CSF). Considering a sub-class of aneurysms to be behave as a nonlinearly elastic, isotropic, spherical membrane and likewise that the domain of the CSF is spherical, Shah & Humphrey (1999) showed that the non-dimensional governing differential equation of motion is

$$\left(\frac{1}{x^2}+bx\right)\ddot{x}+\tfrac{3}{2}b\dot{x}^2+4m\frac{\dot{x}}{x}+2\frac{f(x)}{x}=F(\tau), \tag{4.4}$$

where x is the finite in-plane stretch ratio, b is a non-dimensional mass-geometry ratio ($=\rho_{\mathrm{f}}A/\rho H$, where ρ_{f} is the density of the CSF, A and H the undeformed radius and wall thickness of the aneurysm and ρ the mass density of the membrane), m is a non-dimensional viscosity of the CSF, f is a non-dimensional wall tension, F is a forcing function (Fourier series representation of blood pressure) and τ is a non-dimensional time. This equation recovers classical results for the elastostatics and elastodynamics of a thin-walled inflated spherical membrane (cf. early results by J. K. Knowles and C. C. Wang in finite elasticity) as well as the Rayleigh–Plesset equation for the oscillation of a bubble (with constant surface tension) within a fluid (which is an important problem in some areas of medical ultrasound). More importantly here, however, it is seen that effects of the exterior fluid on the response of the solid are captured in a single differential equation (this was made possible through a velocity matching condition at radius $a=xA$). Because of the nonlinearities, study of this equation requires methods from nonlinear dynamics (e.g. the geometric method of Poincaré). Rewriting this second-order equation as a system of two first-order equations allows a simple linearization about fixed points, however, which in turn allows a simple analysis of the associated dynamical stability. It can be shown, for example, that mechanical stability in the small requires that (Humphrey 2002*a*)

$$\frac{-4m}{\alpha^{-1}+b\alpha^2}<0 \quad \text{and} \quad \frac{1}{\alpha^{-1}+b\alpha^2}\left(F_0-2\frac{\mathrm{d}f}{\mathrm{d}y_0}(0,0)\right)>0 \quad \forall\alpha\geqslant 1, \tag{4.5}$$

where $x=\alpha$ is a fixed point, F_0 is the value of F at the fixed point and $y_0=x-\alpha$. Clearly, the first requirement is satisfied only for positive m, that is, a viscous CSF.

Hence, the viscosity of the cerebrospinal fluid plays an essential role in ensuring a stable dynamical behaviour of the elastic solid. That is, the solid–fluid coupling controls much of the dynamics, which illustrates in part the importance of solving such coupled problems. Inequality $(4.5)_2$ shows further that the constitutive behaviour of the solid (through the function f) plays an equally important role, thus emphasizing the need for robust constitutive relations (e.g. modelling the lesion as a rubber-like material suggests a dynamic instability, whereas models based on the Fung or Skalak equations for biomembranes suggest dynamic stability (see Humphrey 2002*a*)).

In contrast to this simple one-dimensional example, most coupled solid–fluid problems involve much more complex domains, and one must resort to sophisticated numerical methods such as finite elements (Holzapfel 2000). Although the solution of blood flow in a tapering, branching, curved rigid tube model of an artery is already computationally very challenging (e.g. Taylor *et al*. 1998), because of the sensitivity of vascular cells to even subtle changes in mechanical stimuli, there are many cases wherein we must solve the fully coupled problem (i.e. flow in a deforming vessel that exhibits a nonlinear behaviour). Because the equations and computational methods are generally well known for the separate solid and fluid problems, it is the computational challenge of enforcing the coupling that is most important. See, for example, Perktold & Rappitsch (1995) or Bathe & Kamm (1999). The need for continued research along these lines is critical.

The problem of blood flow within an artery is one of the most obvious solid–fluid interactions, but many other problems are equally important and challenging. For example, Wang & Tarbell (1995) showed the potential importance of the flow of interstitial fluid within the arterial wall on the mechanobiology of the smooth muscle cells; similar effects hold in other tissues, including cartilage and bone (Lai *et al*. 1993; van der Meulen & Huiskes 2002). Weinbaum & Chien (1993) similarly show a fundamental role of lipid transport into the arterial wall in atherogenesis. Yin and colleagues (Yin *et al*. 1996; Yin & Yamada 1997) show the important role of solid stresses in regulating blood flow within perfused tissues, a ubiquitous issue. Many other examples abound, including those within the context of the theory of mixtures in which momentum exchanges between solid and fluid constituents play potentially important roles within a cell or tissue. The need for research on coupled problems is thus great.

(*h*) *Thermal treatment*

It is interesting that it was the physician Julius von Mayer (1814–1878) who is often credited as being the first to postulate that energy is conserved, based in large part on his speculation that muscle force and body heat are derived from latent chemical energy in foodstuffs. Although thermodynamics thus had a biomechanical motivation and origin, the field of *biothermomechanics* has received little attention over the years. As noted above, this is due in large part to the ability of the body to regulate its temperature within such a narrow range. Recent technological advances have encouraged a host of clinical treatment strategies that rely on the thermal modification of cells and proteins, however, thus renewing the importance of biothermomechanics. There is, therefore, a pressing need to understand how stress/strain fields affect the kinetics of a thermal treatment and conversely how prior thermal exposure affects the subsequent mechanical and reparative properties. It is the mechanical properties, for

example, along with the geometry and loading conditions, that dictate the *in vivo* stress/strain fields, changes in which correlate with mechanotransduction. Hence, not only will thermal injury elicit a direct wound-healing response, it will also affect normal mechanosensitive activities that control the cell and matrix biology.

Among the many needs, Rajagopal & Tao (2002) showed that the now classical theory of continuum thermomechanics is formulated in such a way that the entropy inequality does not provide restrictions on the heat supply term (cf. equation $(3.14)_3$). For example, the Clausis–Duhem relation is often written as

$$-\rho\left(\frac{\mathrm{d}\psi}{\mathrm{d}t}+\eta\frac{\mathrm{d}T}{\mathrm{d}t}\right)+\boldsymbol{t}:\boldsymbol{D}-\frac{1}{T}\boldsymbol{q}\cdot\nabla T\geqslant 0, \tag{4.6}$$

which provides important restrictions on the Helmholtz potential ψ, entropy η and Cauchy stress $\boldsymbol{t}$, but which reveals that the heat supply term has been eliminated (by using results from energy, momentum and mass balances). In clinical applications, however, many of the heating modalities rely on portions of the electromagnetic spectrum (microwave, radio-frequency, laser, etc.); thus there is a critical need for more attention to the formulation of constitutive relations for the absorption of electromagnetic energy by tissues, and in particular how this absorption is affected by the hydration level, temperature, state of stress, etc. For a current review of such issues, see the excellent paper by Diller *et al.* (2000).

Note, too, that there appear to be significant changes in hydration due to thermal damage. The denaturation of collagen, for example, occurs in large part due to the breaking of hydrogen bonds that organize the triple-helix molecular structure. The denatured, more random coiled structure appears to imbibe significant water to form water bridges within. Because of the marked influence of hydration on biomechanical properties, such fluid shifts must be accounted for. Towards this end, Tao *et al.* (2001) suggested that a mixture theory can be used to describe a thermally treated soft tissue consisting of three primary constituents: mobile water, native solids and denatured solids. Whether additional detail—for example, modelling separately the contributions of the elastin, collagens and proteoglycans, which have very different thermal stabilities—will be needed is not yet clear, nor is it clear that a full mixture approach is needed in all cases as compared with a simpler homogenized constrained mixture approach as discussed above within the context of growth and remodelling. Much more research is needed.

5. Closure

In closing, it is obvious that this paper is meant to be but a brief survey; whole books can and should be written on each of the topics briefly mentioned as well as many that were not identified. The primary message, therefore, is simply that much has been learned, but much remains to be accomplished. Indeed, it is unfortunate that we must conclude that well-accepted constitutive relations remain lacking for the description of most behaviours of importance, including the multiaxial behaviour of muscle, biological development, growth and remodelling, damage and healing, cell mechanics, thermal denaturation, solid–fluid interactions, electromechanics, and so on. Less than a half a century old, continuum biomechanics is clearly still in its infancy and its promise remains great. Continued advances in technology are providing increased information via improved experimental (e.g. the atomic force

microscope, laser tweezers) and clinical (microcatheters, magnetic resonance imaging) capabilities; continued advances in computers and computational methods are increasing our ability to handle large amounts of data and to model complex initial–boundary-value problems; and continued improvements in diagnostics are allowing disease and injury to be treated earlier. Consequently, there is an ever-growing need to synthesize these expanding databases. As noted by the 1998 Bioengineering Consortium (BECON) Report of the US National Institutes of Health,

> The success of reductionist and molecular approaches in modern medical science has led to an explosion of information, but progress in integrating information has lagged... Mathematical models provide a rational approach for integrating this ocean of data, as well as providing deep insight into biological processes.

Biomechanics has a vital role to play in the development of the needed mathematical models and analyses. Because of the incredible complexity of the bio-chemo-physical aspects of soft tissues, however, biomechanics cannot develop in isolation. There is a need for increased interdisciplinary and multidisciplinary research efforts that bring biologists, biochemists, biophysicists, engineers, mathematicians and clinicians together in teams, both in research and education. Only in this way can we achieve our ultimate goal: to improve the human condition through a knowledge of continuum biomechanics.

I thank Professor R. W. Ogden for recommending that I write this review and Professor J. B. Pendry for inviting it. Just as it has helped organize my thoughts, I hope that it likewise serves to motivate some to undertake new research in continuum biomechanics. My ability to study part of this fascinating world of continuum biomechanics is made possible, in part, by grants from the National Science Foundation (BES-0084644), the National Institutes of Health (HL-58856 (M. Friedman, PI), HL-64372, HL-68118), and the Texas Advanced Research Program (000512-0097-2001), which are gratefully acknowledged.

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