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Epilogue

Biomechanics is often defined as "mechanics applied to biology" (Fung, 1993). Although this is certainly true, it is hoped that the reader now appreciates that biomechanics can and must be much more. Because of the complexity of tissue structure and behavior, there is a need for new, sophisticated theoretical frameworks; because of the continuing lack of data, there is a need for new, clever experiments; because of the geometric complexity of cells, tissues, and organs, there is a need for robust computational methods; and because of the significant morbidity and mortality that results from disease and injury, there is a need for improved modalities for diagnosis and treatment. Clearly then, we must continue to expand the scope of biomechanics, to seek new concepts, postulates, technologies, and techniques upon which a rigorous understanding can be based. Biomechanics is thus better defined as the development, extension, and application of mechanics to answer problems of importance in biology and medicine. Biomechanics is a vibrant field—one with great promise.

This book was designed to be but an introduction to biosolid and biofluid mechanics. There are, of course, many other areas of introductory biomechanics (e.g., studies of whole-body motions, such as gait analysis and athletic performance) that were not covered. Reflecting on what was presented in Chaps. 1–11, however, one of the most important things to realize is that *mechanics offers a consistent and rigorous method of approach to study the wide variety of initial and boundary value problems that arise in biology and medicine.* Another important thing to realize is that biomechanics requires advanced study; hence, this book is a beginning, not an end. Finally, it is important to know that there are many ways that a young biomechanicist can contribute to basic science and health care delivery.

12.1 Future Needs in Biomechanics

The first author (JDH) was asked a number of years ago to review some of the past achievements of the *Continuum Mechanics of Soft Biological Tissues* and to suggest areas that are in need of further study (Humphrey, 2003a). Among the many needs and promises, it was suggested that fundamental research is needed in eight particular areas:

Molecular and Cell Biomechanics
Developmental Biomechanics
Biomechanics of Growth and Remodeling
Injury Biomechanics and Rehabilitation
Functional Tissue Engineering
Muscle Mechanics
Fluid-Solid Interactions
Biothermomechanics

Much progress has been made in these areas, yet much remains to be accomplished. Moreover, many new areas of need have arisen, including understanding the roles of mechanics in inflammation/infection and cancer. The interested student is thus encouraged to review the current literature for additional "future needs". Nevertheless, note that:

Cells are the fundamental units of life; understanding their biomechanical behavior will thus reveal may new insights into the biology and mechanics of health, disease, injury, and clinical treatment. Cell mechanics is essential, for example, for explaining basic processes such as cell adhesion, contraction, division, migration, spreading, and even phagocytosis (i.e., the engulfing and digestion of extracellular material). Likewise, it appears that cellular apoptosis (i.e., programmed cell death), the synthesis and degradation of the matrix, and the production of growth regulatory molecules, cytokines, and cell surface receptors are also influenced greatly by mechanics. Cells consist of a multitude of different types of molecules, however; thus, to understand the cell, we must ultimately understand the mechanics of the associated proteins, phospholipids, and even nucleotides. Of primary interest, at present, is how the three primary cytoskeletal proteins (actin, the intermediate filaments, and microtubules) change their organization in response to mechanical loads. Inasmuch as the function of these three proteins is controlled in large part by a host of accessory proteins (e.g., α-actinin, myosin, and talin), there is a similar need to understand the contribution of the accessory proteins to the mechanics. Cells interact mechanically, chemically, and electrically with other cells, and they likewise interact with the extracellular matrix. There is a pressing need to understand the mechanics of the molecules, particularly the adhesion molecules, that govern these interactions. For example, extracellular matrix–integrin–cytoskeletal interactions are clearly important to the mechanobiology, but much remains

unknown. Finally, we must realize the importance of understanding better how the mechanics directly affects the chemistry. It is generally believed that deformations of the cells can change the conformations of the molecules, which, in turn, can change binding energies. This, too, must be understood better.

It is purported that Aristotle (384–322 B.C.) stated 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 A.K. Harris (1994), however, "without the aid of mechanicians, and others skilled in simulation and modeling, developmental biology will remain a prisoner of our inadequate and conflicting physical intuitions and metaphors."

For obvious reasons—in particular the smallness of tissues and organs in the embryo and fetus—biological development has attracted less attention in biomechanics than many other areas. Fortunately, however, the desire to understand molecular- and cellular-level phenomena has led to technological advancements (e.g., atomic force microscope) that can also be useful in the study of development. An interesting example of how understanding development may increase our understanding in many other areas, not the least of which is tissue engineering, is a comparison of aortic development versus changes induced in maturity due to hypertension. During development, the blood pressure increases from ~0 before the heart beats to ~120/80 mmHg in maturity. This increase in pressure is followed by a concomitant increase in wall thickness, which appears to maintain the wall stress at a "preferred" value. In development, this thickening is accomplished by adding more and more layers of elastin–collagen–smooth muscle, each of equal thickness. Conversely, in hypertension in maturity, the wall also thickens in response to an increasing pressure so as to return the wall stress toward its preferred value, but this thickening occurs via the addition of material to extant layers, not by adding new layers. Why? We do not yet know the answer to this simple question, but this example should illustrate that understanding development will likely provide important clues for those who seek to understand many issues in biomechanics.

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. 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, many investigators have used the concept of optimization to understand and predict various aspects of biological growth and remodeling. One such case was discussed in Chap. 10. The key question, however, is optimization of what? In 1952, Turing showed that we must also consider the production and removal of morphogens as well as

their possible diffusion. In 1981, Skalak showed that we must also consider the pointwise kinematics of growth, and, soon thereafter, Fung showed that we must address stress-mediated changes in mass. Biological growth and remodeling is clearly complex, involving changes in morphology, reaction–diffusion chemistry, kinematics, stress, and mass production. We are only beginning to scratch the surface of this important area.

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 damage is balloon angioplasty, the 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. Angioplasty works, in part, by weakening (i.e., damaging) the wall, fracturing the atherosclerotic plaque, and sometimes by creating small dissections between the plaque and wall. Although referred to as a "controlled injury," the actual level of control is poor because we do not understand the details of the injury/damage process. Perhaps a greater understanding could help reduce the 20–30% failure (i.e., restenosis) rate, hence the increased use of stents. Understanding damage mechanics likewise holds promise in the area of robotic-assisted surgery. Whereas a robot can perform certain operations much more repeatedly and precisely than a human surgeon, it lacks the tactile feedback and control that is second nature to the skilled surgeon. To prevent robot-induced damage, we must understand the associated strength of the tissues involved.

Related to the general topic of injury biomechanics is the process of healing. For example, whereas it may seem natural to immobilize, and thereby protect or reduce pain in an injured limb, findings over the last 35 years suggest that this may be naive. It appears that immobilized collagenous tissues undergo histological changes that include a loss of material and, thus, strength. Indeed, it appears that the production of new tissue (e.g., wound healing) is hastened by certain levels of mechanical loading. To understand some aspects of healing, therefore, we need to understand better the associated biomechanics and mechanobiology.

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." Toward this end, the U.S. National Committee on Biomechanics suggested the following needs (Butler et al., 2000): (1) In vivo stress and/or in vivo strain histories need to be measured in normal tissues for a variety of activities; (2) the mechanical properties of the native tissues must be established for subfailure and failure conditions; (3) a subset of these mechanical properties must be selected and prioritized (i.e., 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); (4) standards must be set when evaluating the

repairs or replacements after surgery so as to determine "how good is good enough?;" (5) we must determine what physical regulation cells experience in vivo as they interact with an extracellular matrix; and (6) 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.

In 1983, Fung 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; indeed, we cannot even understand activities of the cell such as migration. Clearly, the mechanics of muscle and motor proteins is fundamental to understanding key activities of life at the organism, organ, tissue, and cellular level. Fortunately, we have learned much about muscle since the 1950s and the early work by Huxley and others. Yet, the early idea that muscle contraction is one dimensional still pervades the literature even though it is now clear that the force generation due to muscle contraction can be multiaxial. A better constitutive equation for muscle is thus imperative.

As noted briefly in Chap. 11, the division of continuum mechanics into disciplines such as "solid mechanics" and "fluid mechanics" is artificial and simply a natural consequence of historical developments. In the body, however, solidlike and fluidlike behavior go hand in hand. Whether it be the removal of wastes by the renal system, the transport of blood by the cardiovascular system, the functioning of an articulating joint, or even the response of an individual cell to an abrupt change in load, fluid-solid interactions are critical. In the future, therefore, there will continue to be a pressing need for research and teaching to address directly such couplings.

Advances in laser, microwave, radio-frequency, and similar technologies continue to encourage the use of thermal energy (heat) to treat disease and injury. Most clinical applications have been motivated primarily by the availability of the technology, however, not a detailed understanding of the associated biothermomechanics. There is a need, therefore, to understand better the effects of heat on cells and tissues and, in particular, to determine optimal dosing protocols in terms of clinically measurable and controllable parameters such as the temperature level, state of stress during heating, and the duration of heating. For example, until recently it was not commonly appreciated that mechanical load can play just as important of a role in the thermal denaturation of proteins as the temperature level; that is, whereas the effect of temperature appears to affect the denaturation through the activation energy via an Arrhenius-type process (Sect. 11.6), the effect of mechanical load appears to affect the process through the activation entropy. Because tissue elasticity is due more to changes in the configurations of the underlying proteins (i.e., changes in

configurational entropy) rather than to changes in bond energies (i.e., energetic elasticity), understanding better the biothermomechanics may yield new insights into tissue mechanics as well as thermal treatments.

12.2 Need for Lifelong Learning

Much has been learned in and through biomechanics, particularly over the last 35 years, and there is now an extensive literature. We must build upon prior understanding and achievements; 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 new observations. The challenges, and likewise the promises, of biomechanics have never been greater.

An introductory course is clearly the beginning, not the end of one's learning. The interested student is thus encouraged to pursue intermediate and advanced courses in biology, mathematics, and mechanics as well as specialized courses in biomechanics. Yet, formal course work, even through the doctoral degree, is not the end of one's learning. Advances are being realized every day; one must continually consult the archival literature to stay abreast of the latest developments. In biomechanics, this means that we should be especially aware of that which is reported in the leading journals: the *Journal of Biomechanics*, which was founded in 1968, the ASME *Journal of Biomechanical Engineering*, founded in 1977, *Computer Methods in Biomechanics and Biomedical Engineering*, founded in 1998, and, most recently, *Biomechanics and Modeling in Mechanobiology*, founded in 2002. These journals and others such as the *Annals of Biomedical Engineering*, the *IEEE Transactions for Biomedical Engineering*, and the *Journal of the Royal Society Interface* continue to promote the growth of biomechanics. Note, too, that new ideas are presented at national and international meetings such as the World Congress of Biomechanics, which began in 1990 via a meeting at San Diego and has been followed by meetings in 1994 at Amsterdam, in 1998 at Sapporo, in 2002 at Calgary, in 2006 at Munich, in 2010 at Sinapore, and in 2014 at Boston (which included over 4000 presentations from investigators from over 50 countries). These focused meetings, as well as symposia at many different technical meetings, promote the exchange of ideas and thus contribute to the rapid growth of continuum biomechanics. Students should try to attend such meetings whenever possible.

We must also remember 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. These sources must be consulted as well, and we must seek to work in multidisciplinary teams consisting of experts from the many allied areas of study.

12.3 Conclusion

Biomechanics is intellectually stimulating and challenging. More importantly, however, it is vitally important. Whereas physicians see human pain and suffering on a daily basis, few engineers do. Nonetheless, we must continually remind ourselves that the ultimate goal of biomechanics is to contribute to the improvement of health care delivery, a goal that deserves our very best effort.