Structure-Based Mechanics of Tissues and Organs

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Autobiographical Postscript

My research career follows closely the development of Biomedical Engineering (BME) in Israel, a goal to which I devoted a significant portion of my time and efforts. This turn of events was not planned ahead. Growing up during the first years of the State of Israel, like many youngsters at that time I was a member of a youth movement whose goal was to prepare us for life in the Kibbutz, with the mission to settle and build the country. These personal plans had to be changed due to a sport accident. I decided to go for higher education related to agriculture, so that my education could be of use to my future Kibbutz. Since my inclination was towards exact sciences, I chose agricultural engineering at the Technion in Haifa, the only engineering school in Israel at that time. In the third year of study, I added civil engineering to my curriculum. It was during these Technion years that I realized I had a great deal of curiosity, often asking myself "why" or "what is the underlying mechanistic reason"? It was then that I first entertained the thought of a possible research career.

Upon graduation in 1962, I joined a Kibbutz in the dry southern part of Israel—the Negev. It soon became clear that the small Kibbutz at that time could not benefit from my engineering skills, so I took a job as a water system engineer in the nearby town of Beer Sheba. My responsibility was to design and oversee construction of water supply networks to the new farms in the dry southern Negev area which occupies nearly half of the area of Israel and extends from Beer Sheva down south to the Red Sea, and to the Dead Sea in the east. Although the job provided me with a great deal of practical engineering experience, it required little of advanced engineering skills.

In 1964 I accepted an offer to work in Benin City, Nigeria, on a large-scale project aimed to supply treated fresh water to each village and town in the mid-eastern region of that country. In addition to satisfying my professional curiosity, the work was an opportunity to get to know Nigeria, its people and culture. I was attracted by the importance of the job which sought to reduce the rate of infectious diseases, especially the rate of infant mortality, estimated at that time to be above 80 %. This was caused primarily by consumption of untreated water from nearby rivers. The project was completed a couple of years after I left Nigeria. I was proud to learn

that it achieved its goal: infant mortality dropped down to 10–15 %, still too high, but nonetheless a significant improvement.

After 1 year in Nigeria I was recruited by my Kibbutz to take the position of R&D engineer in the newly established drip irrigation factory—Netafim. Drip irrigation was conceived by an Israeli water expert and proved to be well suited for dry areas due to the substantial saving in water and the significant increase in yields compared to other methods such as sprinkle irrigation. It faced, however, a number of technological problems which I had to attend to. Today, drip irrigation is well established. Netafim is a highly successful multinational consortium, well known in countries using irrigation. The work was interesting and involved some research work. It became however clear that serious research can be done only in a well-equipped facility of an academic institution. Hence, after 2 years in the job I returned to the Technion in 1968 and took a job in the Hydraulics Laboratory as an R&D engineer. The renewed interaction with an academic environment was highly fulfilling, and just a few weeks into the job, I decided to pursue an academic career.

M.Sc. training at the Technion required a full research thesis. While searching for a suitable topic, I was informed of a new research field, Biomedical Engineering (BME). New, interdisciplinary, and with endless perspective, it seemed like an attractive field. In the late 1960s, one of the hottest topics in BME research was the pulsatile blood flow in arteries. Research in that topic flourished after the breakthrough work of John Womersley, who showed that for an oscillatory flow of a Newtonian fluid in an elastic tube, the flow is characterized by a parameter, which today bears his name (the Womersley number). In looking for a specific thesis topic, I browsed the literature and discussed various possibilities with Uri Dinnar and Hillel Rubin. The question came up on how the flow would be affected if one considered the blood vessels' viscoelasticity and the non-Newtonian nature of blood. It seemed an interesting extension of the Womersley theory and one that could be experimentally tested in the laboratory. While developing the theory, it turned out that Womersley analysis can be generalized to Maxwellian fluids (Holzinger and Rubin 1970) and to general linear viscoelastic fluids in elastic-viscous tubes (Lanir and Rubin 1971, 1972), by replacing the Newtonian Womersley number with a complex viscoelastic one, and the tube elastic parameters with its complex, elastico-viscous counterpart. In the experimental investigation, I used viscoelastic CMC polymer solutions of various concentrations. The theory and experiments were in good agreement and showed an unexpected result: unlike in Newtonian fluids in which the wave velocity increases monotonically with frequency, in viscoelastic fluids, it attains a maximum level at a low frequency and decreases thereafter.

I submitted my M.Sc. thesis in the summer of 1970. Two weeks later I was surprisingly notified that since my work was of a level and scope of a Ph.D. research, the Technion decided to grant me a Ph.D. degree. Although satisfying and exciting, this rather unusual and unexpected development presented a problem: I was just accepted for Ph.D. training at the University of California at San Diego (UCSD) under the supervision of Prof. Y.C. Fung. Determined to work with Dr. Fung, I decided to take my chance. My wife Suzi and I landed in San Diego shortly after

my Ph.D. defense, with the intention to embark on postdoctoral training. Dr. Fung, after reading my Ph.D. papers, was satisfied with my credentials. However, due to severe recent cuts in his NASA research funding, he could not support me. In the face of this news, I decided to wait for 1 month before looking for another job. Luckily, a small leftover of a US Air Force research budget was found. I embarked on a work on fiber composite materials.

Fiber composites were extensively studied under tension and shear loading. The question at hand was how they would respond to compression in the fiber direction, especially when the matrix Poisson's ratio exceeded that of the fibers, a situation which could lead to de-bonding and fiber buckling. My analysis showed that although fibers may indeed buckle in a mode which increases with compression, in the range of infinitesimal deformations, this has insignificant effect on the composite response (Lanir and Fung 1972). For a while, I believed that this research and its results would be of no special significance, only to discover much later that the work is of interest in nanotubes research (Lourie et al. 1998).

My next project was in tissue biomechanics. This research occupied me for the rest of my postdoctoral training and shaped much of my future research. In this I could not have wished for a better mentor than Dr. Fung—"the father of modern biomechanics" (Kassab 2004). I was asked by Dr. Fung to develop the first biaxial large deformation tissue tester and apply it to study the properties of flat tissues, specifically the skin. Three criteria directed the setup design. For reliable characterization, the stretched specimen should be under uniform deformation; the strain measurement should be a no-contact one so as not to affect the soft tissue response; in view of tissue viscoelasticity, the rate of loading should be adjustable and controlled. The developed setup fulfilled all three criteria (Lanir and Fung 1974a). The test protocols included biaxial stress relaxation tests, constant rate of stretch tests at different rates, and tests of temperature effects (Lanir and Fung 1974b). The data clearly demonstrated the skin's anisotropy, nonlinearity, time dependence, and preconditioning adaptation. The effects of temperature were found to depend on the imposed rate of temperature change and on the tissue stretch: at low stretch levels the skin has a negative thermoelastic response (it contracts with increasing temperature, as rubber-like materials), while at high stretch levels it is positive (expanding with temperature, as in crystallized materials such as metals). Later, I learned that this is due to the transition from the amorphic, elastin-dominated low stretch range to the high stretch one dominated mainly by the structured collagen.

In 1972, I joined the Technion as the first full-time BME faculty (also first in Israel). The BME unit was an interdisciplinary program which offered solely graduate courses but no research facilities. Courses were conducted by secondary affiliated faculty members who lectured on their field of expertise. Yet the curriculum lacked a clear plan or structure. I was asked to head this unit with the mission to develop the research activity and introduce coherence and clear tracking to the graduate program. This was a challenging task for a newly appointed faculty member. After 1 year in the job I realized that although I was able to move the department in the right direction and recruited new faculty members, the job was

too time consuming and thus unsuitable for a new, young faculty and could risk my academic progress towards tenure. After 1 year as department head, I resigned to resume my research work.

In Fung's laboratory at UCSD, I enjoyed experimental research in a well-equipped and properly staffed setting. These conditions were unavailable in the Technion BME laboratory at that time. I opted to invest my efforts in theoretical research. My first project was aimed at characterizing the skin mechanical properties based on the data collected at UCSD. Tissue characterization was up to that time exclusively phenomenological, culminating in Fung's exponential law (Fung 1967, 1972) and in the material laws of polymers such as the Mooney–Rivlin one. It turned out, however, that none of these hyper-elastic phenomenological laws adequately fit the skin's biaxial response. In looking for a better representation, I wondered if something can be learned from looking at the internal processes which give rise to the global tissue response. In searching for the relevant information, I was fortunate to come across a few histological studies which were published around that time on the response of tissue microstructure to uniaxial and biaxial stretch (Gibson et al. 1965; Viidik 1969, 1972; Millington and Brown 1970; Chu et al. 1972; Brown 1973). Three distinct processes could be identified from the published images: First, in the uniaxially stretched tendon, there is a gradual straightening (recruitment) of collagen fibers with stretch (Viidik 1972, 1978) and this is accompanied by an increase in the tissue rigidity. Second, in addition to collagen, flat tissues such as the skin and the mesentery consist also of elastin fibers which become straight at lower stretch levels than the collagen (Gibson et al. 1965; Chu et al. 1972; Evans et al. 1980). Third, in addition to straightening, in flat tissues there is a process of fiber rotation towards the direction of highest stretch (Brown 1973; Evans et al. 1980). The challenge was to find a way by which these processes could be incorporated into a general hyper-elastic constitutive formulation. After testing a number of possibilities, the most promising one proved to be the stochastic approach—to assign distribution functions to the fibers' straightening strains and orientations, for both the collagen and elastin fibers, and sum up all the fibers' contributions. The formulation is based on four assumptions: (a) affine deformation field, i.e., each embedded fiber responds kinematically as if it were an element in the tissue continuum; (b) the tissue's total strain energy equals the algebraic sum of its fibers' strain energies; (c) the strain energy of a slender fiber is solely due to its axial stretch and vanishes under compression due to buckling; and (d) the fluid-like ground substance matrix renders the tissue incompressible and contributes hydrostatic pressure to the global tissue response. The natural outcomes of these ideas were that the observed nonlinear and anisotropic properties of tissues result from the fibers' gradual recruitment (straightening) and their nonuniform orientation distributions.

This is how the microstructural approach to tissue constitutive modeling was born. If I have to identify a common trait to my research work since then, including studies unrelated to tissue mechanics, it is the strong inclination to look at the micro and to link the micro to the macro function. My experience has shown this to be a rewarding approach.

Today, the structural approach is widely used in tissue mechanics and applied in a variety of tissues (e.g., Belkoff and Haut 1991; Billiar and Sacks 2000; Chandran and Barocas 2006; Cortes et al. 2010; Crabb et al. 2006; Dahl et al. 2008; Driessen et al. 2005; Engelmayr and Sacks 2006; Federico et al. 2005; Gasser et al. 2006; Grytz and Meschke 2009; Hansen et al. 2002; Hollander et al. 2011a; Holzapfel et al. 2004; Horowitz et al. 1988a; Jhun et al. 2009; Lake et al. 2011; Lokshin and Lanir 2009a; Martufi and Gasser 2011; Nevo and Lanir 1989; Raz and Lanir 2009; Sacks et al. 2004; Sverdlik and Lanir 2002; Zulliger et al. 2004). Comparison with data of 1D (Raz and Lanir 2009; Sverdlik and Lanir 2002), 2D (Billiar and Sacks 2000; Lokshin and Lanir 2009a; Sacks et al. 2004) and 3D (Horowitz et al. 1988a; Hollander et al. 2011b) responses showed excellent agreement. The case of the arterial wall (Hollander et al. 2011a) is a recent example of the power of microstructural modeling. The arterial media is a 3D layered structure consisting of concentric lamellae, interlamellar thin elastin struts, and smooth muscle cells. The lamellae are composed of helical-oriented elastin and collagen fibers (Clark and Glagov 1985; Rhodin 1980; Wasano and Yamamoto 1983). Based on these structural features, together with David Durban and our student Yaniv Hollander and in collaboration with Ghassan Kassab we developed a microstructural constitutive model for the coronary media and validated it against 3D data of inflation/extension/twist tests carried out in Ghassan laboratory. By sensitivity analysis it was found that a reduced form of the model having only four parameters provided excellent fit to the entire 3D database (the model descriptive power). The model predictive power (fit to data not used in estimating the model constitutive parameters) was validated as well. In particular, characterization based on just inflation/extension data provides reliable estimates of the model parameters (thus saving the need to perform the more difficult twist test) and very good fit to the entire 3D data. Previous models of the media were either phenomenological or phenomenological–structural hybrids. Comparison of the structural with these models against the 3D data demonstrated the superior reliability of the structural approach in both its descriptive and predictive performances (Hollander et al. 2011b).

The theory of constitutive characterization imposes restrictions on material laws. One of these requires that the constitutive law must be convex under any deformation scheme. In essence, this restriction guarantees the existence and stability of the material response (Holzapfel et al. 2004; Truesdell and Noll 1965). I was able to prove that the structural constitutive formulation automatically satisfies the convexity conditions under any deformation (Lanir 1996). This distinct advantage stems from the convexity of the fibers' stress–strain relationships. Hence, in structural characterization there is no need to check the plausibility restrictions.

A daunting problem in tissue mechanics is the difficulty of finding a hyper-elastic law that is valid under any deformation scheme, i.e., while the response under a single protocol can be adequately represented by a variety of constitutive models, when attempting to fit data of multiple protocols with a single set of material parameters, no model proved to be adequate (Tong and Fung 1976). In studying this problem, I realized from the onset that since soft tissues are inelastic, it is unrealistic to expect that any hyper-elastic model can fit their inelastic

response. An inelastic constitutive formulation was needed. In looking for a suitable inelastic formulation, it turned out that the stochastic structural approach is well suited for such generalization. Since the inelastic properties of tissues derive from the inelastic properties of their fibers, generalization to inelastic cases (such as viscoelasticity and pre-conditioning) can be readily achieved by replacing the fibers' elastic stress–strain laws with their viscoelastic and viscoplastic counterparts. The resulting nonlinear inelastic structural constitutive models provided excellent fit to both 1D (tendon and skin (Raz and Lanir 2009; Sverdlik and Lanir 2002; Lokshin and Lanir 2009b)) and 2D (skin (Lokshin and Lanir 2009a)) data under multiple and different protocols. For example, with my student Einat Raz we found that in the structural formulation for the viscoelastic case, the predicted responses of the tendon under creep and stress relaxation tests are mutually compatible and interlinked by a relationship that depends on the protocol and constitutive law (Raz and Lanir 2009). Moreover, both the 1D and 2D investigations found that for reliable tissue representation, preconditioning must be included as an integral part of the constitutive formulation, in addition to viscoelasticity.

During my sabbatical leave at Michigan in 1979 I met a young undergraduate student who showed a keen interest in Biomechanics. We had a couple of discussions on the experimental and theoretical aspects of tissue characterization. Our discussions may have impressed him enough to embark on a career in Tissue Biomechanics. He is Michael Sacks, a prominent researcher in the field and former editor of the ASME Journal of Biomechanical Engineering. Mike "blames" me for recruiting him to Biomechanics, a charge which I do not deny.

In the early 1980s I initiated the recruitment of Alice Maroudas to our BME department at the Technion. Alice's well-known experimental work on the articular cartilage and on intervertebral disc showed that in these tissues, due to the high concentration of their interstitial negatively charged proteoglycans, a major support against compressive loading is due to the osmotic-induced hydrostatic pressure of the ground substance (Maroudas and Bannon 1981). My own interest in this topic developed following a meeting with Richard Skalak of Columbia University who encountered a theoretical dilemma relating to the number of equations needed to solve a boundary value problem in biphasic materials. Two modeling approaches were known at that time: poroelasticity (McCutchen 1982) and biphasic theory (Armstrong et al. 1984; Kwan et al. 1984). Both considered elastic and viscous forces due to fluid filtration relative to the solid phase, but ignored the osmotic effects. Hence, both theories predicted that under equilibrium with external compression, it is the collagen fibers which bear the compressive load, while the fluid pressure vanishes, predictions which are in obvious contradiction to Alice and coworkers' experimental results. There was a need for a new constitutive approach. The challenge in developing a constitutive swelling theory for these tissues was to incorporate osmotic effects into a mechanical model. The solution which emerged following a discussion with Alex Silberberg of the Weizmann Institute was to integrate mixture theory (Truesdell 1962) with nonequilibrium thermodynamics (Silberberg 1982). The developed bi-component theory (Lanir 1987) extended the previous biphasic theories by introducing concentration (osmotic) forces into

the chemical potentials of the solid and fluid components, subject to the Gibbs–Duhem condition. Three important new results emerged: First, a self-consistent bi-component constitutive theory was developed for swelling tissues. Second, the new theory was in agreement with experimental observations as to both the role of hydrostatic pressure in bearing compressive loadings and the stiffening effect of osmotic forces on the tissue response. Third, the driving force for fluid filtration was identified as the "swelling stress" (the difference between the solid stress and osmotic pressure).

Although proteoglycan concentrations in soft tissues such as skin, blood vessels, and muscle are lower than in cartilage and disc, osmotic swelling still has significant functional and biological importance in these tissues as well. Since osmotic swelling is counterbalanced by tension in the tissue fibers, it follows that the unloaded tissue is not stress free, but is internally loaded by residual stress. In an earlier study by Skalak and coworkers (1996), it was proposed that residual stress stems from incompatible growth of tissue elements which is balanced by incompatible elastic strain, to produce a combined compatible deformation. It is that elastic strain which produces residual stress. It turns out, however, that growth is not the only mechanism of residual stress. Based on our combined experimental and theoretical studies involving controlled manipulation of the tissue osmotic pressure, my coworkers and I were able to show that in the left ventricle (Lanir et al. 1996b) and in the aorta (Guo et al. 2007), osmotic loading may have a dramatic effect on the residual stress. A parallel microstructural stress analysis in the left ventricle (Lanir et al. 1996b) supported this notion, indicating that a significant portion of the tissue's residual stress stems from its osmotic swelling. In two recent publications, this link between osmotic swelling and residual stress was explored in detail and shown to be valid in the cartilage and the disc as well (Lanir 2009, 2012).

The cardiovascular system (CVS) was of special interest to me since my Ph.D. training. It presents unique and interesting challenges: it is subjected to periodic loading by the beating heart; its function is primarily mechanical (to pump the blood, transport it to the periphery, and collect it); it is constructed of hollow organs; its tissues have 3D microstructure; and most CVS tissues contain muscle cells which render them active properties. In addition, CVS research is of important clinical value due to the major impact of vascular diseases (in particular, coronary arterial diseases) on health in the western world. The coronary circulation functions within the myocardium and is substantially affected by the cyclic contraction of the heart, resulting in a unique dynamic flow features. Progress in this field of research is impeded by the difficulties in measurements within the moving heart. Thus, modeling simulation is an attractive research alternative and is widely applied. Simulation of the coronary flow requires knowledge of the input loading conditions imposed by the myocardium on the coronary vessels.

Since the coronary vessels are externally loaded by stress in the surrounding myocardium, a first step in the research is to establish the dynamic stress field within the contracting heart. Stress analysis in the heart is a special challenge due to its irregular shape, the complex passive and active properties of the myocardium, the effects of the dynamic volume changes due to blood sloshing in and out

of the embedded coronary vessels, and its loading by the papillary-mitral valve system during systole. The myocardium constitutive properties derive from its two major constituents, the collagen network and the myocytes. Following the success of the structural approach in other tissues, it was only natural to apply micromechanical analysis in the myocardium as well. My work was carried out in three stages. First, based on the histological data on the collagen network of the heart which became available at that time (Borg and Caulfield 1979, 1981; Borg et al. 1981; Caulfield and Borg 1979; Robinson et al. 1983; Streeter et al. 1969), a 3D structural constitutive equation for the passive myocardium was developed and validated against mechanical data (Horowitz et al. 1988a), and then implemented in constructing a 2D finite element for myocardial strips (Horowitz et al. 1988b) and a 3D one for the full thickness LV wall (Horowitz et al. 1988c). In the second stage, together with my student Erez Nevo we developed a 3D passive and active constitutive law for the myocardium and applied it in stress analysis of the cylindrically shaped equatorial region of the beating LV along the entire cardiac cycle, first without (Nevo and Lanir 1989) and then with (Nevo and Lanir 1994) the effect of residual stress. In the third stage, a full 3D structural passive and active myocardial finite element was developed and implemented in dynamic stress analysis in a truncated ellipsoid-shaped LV (Imanuel 1996).

A major determinant of the coronary flow is the network structure. The network consists of millions of vessel segments. The network flow and the myocardium loading on the vessels within it are inhomogeneous. Hence reliable flow analysis can only be carried out based on realistic model of the network structure. Up to the early 1990s, pertinent information was scarce and insufficient. As a result, most flow modeling studies were based on lumped concepts in which the whole network or large portions of it were represented as compartments. Unfortunately, such an approach does not consider the effect of the network structure on the flow, nor does it account for the local nature of the myocardium–vessel interaction (MVI) and for its variation across the heart wall. It was obvious that detailed structural information was in pressing need and that no significant progress can be achieved without it. Fortunately, this need was met in the early 1990s.

In 1990, Y.C. Fung initiated and chaired the First World Congress in Biomechanics held on the UCSD in La-Jolla, CA. The last presentation in the last day of the congress was by Fung's Ph.D. student Ghassan Kassab. The title related to the detailed morphometry of the coronary network. In his work, Ghassan was able to provide detailed statistics of the network morphometry. Our meeting marked the beginning of a long collaboration and friendship. Ghassan's data relate to the coronary arterial, venous, and capillary networks (Kassab and Fung 1994; Kassab et al. 1993, 1994, 1997). These data have served several investigators in reconstructing portions of the coronary arterial network based on some simplifications. Our collaboration, together with my student Benny Kaimovitz, resulted in reconstruction of the entire arterial system and embedding it within a prolate spheroid heart model (Kaimovitz et al. 2005). This was achieved by solving the network geometry as a large-scale multistep optimization problem. We then continued to the venous system, which was reconstructed as an optimization problem subject to a boundary

restriction that arterial and venous capillaries must be joined (Kaimovitz et al. 2010). The resulting network consists of close to ten million vessels. Its rendering (Wischgoll et al. 2007) highly resembles images of the native network.

Following the progress in the network reconstruction, it was possible to embark on realistic distributive coronary flow analysis. Three "mysteries" have perplexed the research community for many years, being subjects of confusion and debates. The first related to the question of the true nature of the dynamic myocardium–vessel interaction (MVI) in the beating heart (Westerhof et al. 2006). Together with my student Dotan Algranati and in collaboration with Ghassan Kassab, we developed an analytic/numeric platform which incorporated the coronary network structure and included a module for analyzing the in situ vessel nonlinear pressure–diameter relationship (PDR) and a module for network flow analysis based on our previously validated single vessel nonlinear flow model (Jacobs et al. 2008). With this platform, five MVI mechanisms were tested against published dynamic flow and diameter data of endocardial and epicardial microvessels. The results revealed (Algranati et al. 2010) that the only interaction mechanism which fits all the data consists of the combined effects of interstitial pressure (derived by the left ventricle pressure) and intramyocyte pressure (which develops as the myocytes contract). The second mystery related to the underlying reasons for the sub-endocardium higher vulnerability to hypo-perfusion ischemia, in spite of the fact that stenosis which induces ischemia occurs exclusively in epicardial vessels (Hoffman 1987). A detailed sensitivity analysis revealed (Algranati et al. 2011) that the basic reason for subendocardium vulnerability is the nonlinear nature of the vessels' PDR, coupled with the differences in the pressure work points between vessels in these two layers. From the clinical aspects, the analysis revealed that this vulnerability of subendocardial vessels can be moderated by lowering the heart rate and the left ventricle pressure. A third mystery was a clinical question relating to the reliability of indices used during catheterization in assessing functional stenosis severity, or its functional reciprocal—the predicted post treatment flow improvement (Spaan et al. 2006). Our analysis (Algranati 2010) focused on three commonly used indices, fractional flow reserve (FFR), percent stenosis area (%AS), and hyperemic stenosis resistance (HSR). In particular, the investigation related to the extent by which the predictive performance of these indices was affected by interpersonal variability in coronary hemodynamic and by mechanical factors. The results showed that while predictions of the true flow improvement of %AS and HSR are significantly affected by aortic blood pressure, hematocrit, and vessels' stiffness, FFR predictions are robust to changes in heart rate, hematocrit, and variability in aortic, venous, and left ventricle pressures. FFR predictions are, however, sensitive to changes in the vessels' stiffness, which may be affected by age and by pathological vessel remodeling due to smoking, diabetics, and hypertension.

During the years since my first administrative experience as a young department head, I was assigned a number of administrative duties which were associated with developing of the BME academic activities in the Technion and outside of it. I declined, however, requests to accept major administrative responsibilities knowing that it would seriously distract from and impede my research. There was one

important exception: starting in 1995, I initiated and led the efforts to establish the BME undergraduate program, the first in Israel. In 1999 our department opened its gate to the first class of undergraduate BME students. Within a few years other universities and colleges followed suit.

My recent research focuses on two main topics. The first relates to soft tissues growth and remodeling (G&R). In contrast to inert materials, biological tissues have the unique ability to grow and remodel. Soft tissues adapt to altered mechanical environment by changing their size, structure, and mechanical properties. G&R occurs since in order to survive and proliferate, tissue cells strive for a homeostatic mechanical environment. They do so by adapting their extracellular matrix (ECM) via turnover (production and/or degradation) of ECM constituents. Modeling G&R can be of great value by unifying a collection of seemingly unrelated facts into a general scientific framework, thus providing insight into the processes involved. In practice, models serve for quantitative prediction and design (e.g., tissue engineering) where mechanical conditioning stimulates matrix production and plays a key role in the evolution of the constructs towards targeted microstructure and mechanical properties. Previous G&R models relate mostly to cardiovascular tissues. Earlier models focused mainly on the manifestation of G&R assuming that tissue dimension and structure adapt to the global stress or strain. For example, in blood vessels, the diameter and wall thickness remodel to maintain the luminal shear stress and wall hoop stress at their homeostatic range. However, since tissues G&R derives from loading-dependent local turnover events in the fiber level, a microstructural mechanistic G&R theory can mimic real adaptation events with high realism. To materialize this idea I developed the theory which incorporates the specific mechanical properties and turnover kinetics of each constituent, thereby establishing a general framework which can serve for integration of additional constituents and processes involved in G&R (Lanir 2015). The theory predictions show qualitative agreement with a number of well-known features of tissues including the fiber's nonuniform recruitment density distribution, the associated tissue convex nonlinear stress–stretch relationship, and the development of tissue pre-stretch and pre-stress states. In my ongoing research I attempt to extend the theory to multi-dimension tissues and to tissues with multiple fiber types, each characterized by its own turnover kinetics and mechanical response.

Another topic of my current research is the control of the coronary circulation. It is a natural extension of our previous coronary circulation research. In collaboration with Ghassan Kassab, we emphasize the combined modeling/experimental investigation of the detailed manner by which the coronaries regulate the flow to meet metabolic demand under a wide range of physical activity (the coronary reserve). Flow regulation is achieved through local control of the vessel's diameter (and associate resistance) by contraction/relaxation of smooth muscle cells in the vessel wall. Of particular interest are the yet unresolved questions on the effects of activation on the vessel/myocardium dynamic interaction, and of the mutual interactions between the three independent control mechanisms known to regulate the flow (pressure-induced myogenic control, shear control, and metabolic one). There are important clinical questions relating to the consequences of acute cardiac

changes (such as heart rate and perfusion pressure) on the spatial distribution of ischemic regions, and why and which conditions cause hypo-perfusion-associated failure of subendocardial tone regulation before subepicardial one, and the failure of profound ischemia to maximally dilate the vessels. In the first phase of the work, together with Jon Young and based on micromechanical modeling of the vessel interaction with its surrounding myocardium, we were able to show that effective flow regulation requires both an interstitial gap between vessel and tissue and slackness in their tethering, so that the vessel can easily contract requiring little energy. In parallel to the theoretical analysis, experimental work by Kassab group verified the existence of a gap and tethering slackness (Young et al. 2012).

In closing, I wish to reflect on possible future directions of research in tissue and organ biomechanics, with emphasis on the microstructural approach:

Experimental tissue-structure characterization: Tissue morphometry is the cornerstone of the structural approach. Previous structural characterization was for the most part indirect: general forms of orientation and waviness distributions were assigned based on qualitative histological observations, and parameters of these distributions were subsequently estimated to best fit given response data. Attempts to directly determine the distribution functions based on morphological observations have been impeded by computational difficulties in reliable extraction of the 3D complex structural features of tissues and by the inherent experimental inaccuracies due to the need to process the specimen, or by the use of differential digestions which likely distorts the tissue's microstructure. Recent developments in nonlinear optics (such as multiphoton microscopy and coherent anti-Stokes Raman scattering microscopy), when coupled with computer-interfaced sequential optical sectioning, hold great promise for 3D structural characterization. The advantage of these methodologies is that tissue samples are maintained in their native state (i.e., unstained and unprocessed). In addition, the application of two types of nonlinear laser/tissue interactions—two photon excited fluorescence (TPEF) and second-harmonic generation (SHG), allows retrieval of distinct structural data for the elastin and collagen type I fibers (Chen et al. 2011, 2013; Rezakhaniha et al. 2012; Zoumi et al. 2004), respectively.

Efficient microstructure representation: Implementation of the structural approach in finite element stress analysis presents a heavy computational load due to the need to integrate the contributions of fibers over all their 3D orientation distribution function. Although modern fast computing facilities render this task tractable (e.g., in the case of the left ventricle (Imanuel 1996)), attempts are being made to develop a computationally more efficient representation. Although promising first steps have been achieved, a methodology which is general enough for any tissue structure and fibers' material law is still in need. The quest for such representation is a challenging theoretical/numerical undertaking. One current approach relies on the application of the generalized structural tensor (Gasser et al. 2006; Freed et al. 2005) which represents the tissue's 3D structure. In application, this tensor is multiplied by a weighted average of the fibers strain. Comparison with the exact solution revealed, however, that this method is valid only when all the fibers are in tension and when the fiber distribution span is small (Cortes et al. 2010;

Federico and Herzog 2008). Moreover, I have recently shown that the structure tensor is a reliable descriptor of tissue structure only under very limited cases (Lanir and Namani 2015). A second class of methodologies attempts to represent the tissue properties by a discrete set of fiber bundles. There are three variants: One was developed for amorphous polymers and represents the tissue properties by an eight-chain 3D rectangle unit cell whose shape determines the tissue orthotropy (Bischoff et al. 2002). While this unit cell is a structure, it is unrelated to the real tissue structure. The two other variants represent the tissue's continuous 3D orientation distribution by a discrete set of fibers. In the first, the fibers in the set have fixed orientations, and weight is assigned to each of them to optimize the fit to the tissue response (Elata and Rubin 1994). This approach was shown, however, to introduce undesirable anisotropy to an isotropic material (Bazant 1986; Ehret et al. 2010). The other variant applies the spherical t-design (Delsarte et al. 1977; Hardin and Sloane 1996). The latter is a set of N points on a sphere (or their equivalent fiber orientations) such that the average value of any polynomial f of degree t or less on this set equals the integral of f over the sphere. Hence, integration over the 3D orientation distribution is replaced by a sum of discrete values of that function. The design degree t depends on the orientation distribution function and on the fiber material law (Federico and Gasser 2010). Hence, t must be established for each case (Martufi and Gasser 2011) and may change as parameter estimates evolve during iterative search for optimal parameters during the process of tissue material characterization. In summary, it is seen that this challenge of efficient representation is yet to be met.

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Dr. Lanir: A Personal Perspective

In 1979 as a very impressionable undergraduate in the Engineering Mechanics Program (now part of the Department of Mechanical Engineering) at Michigan State University, I was seeking some type of research experience and was very interested in the then new field of biomedical engineering that applied mechanics in some fashion. I was awarded a summer undergraduate research scholarship from the Program to work in the Department of Biomechanics located in East Fee Hall in the School of Osteopathic Medicine. There, I was exposed to all kinds of interesting and novel things: what living tissues are, how mechanics played a role in the understanding of their function, advanced computer-controlled equipment, and mathematical modeling. Heady stuff for a mere Junior. At that time the Department Chair, Dr. Robert Soutas-Little, would invite both domestic and international visitors to work for a time in the then new labs. One day Dr. Lanir showed up for what turned out to be a 2-year sabbatical. I recall his very friendly demeanor, and that he had a box of 3×5 cards for manuscript references that was very small when he arrived and that expanded to several large boxes before he left (there was no Google Scholar way back then). I often worked with Dr. Lanir, assisting in several projects and engaging in various discussions. Sometime later we were awarded an NSF summer undergraduate student research grant where, as part of a dedicated group of undergraduate students, we worked on the mechanics of skin grafts. Dr. Lanir was our faculty advisor and was very helpful in so many ways. He was never averse to meeting with us and was incredibly patient. The project was quite a success (at least to us), and we owed much to Dr. Lanir's detailed knowledge of skin biomechanics.

During his time at Michigan State University, I was introduced to Dr. Lanir's focus on tissue microstructure as a means to understand its function. I recall doing several things, including analyzing biomechanical data of spinal ligaments, measuring fiber crimp during carefully controlled uniaxial experiments on tendons. It should be noted that, at that time, there was an emphasis on developing phenomenological constitutive models of soft tissues based on related approaches to polymeric materials, which were the closest known material to soft tissues behavior. Most approaches were based on the pseudo-hyperelastic approach pioneered by Y.C. Fung. While very powerful in terms of relating the stress and strain behaviors,

these approaches were limited to the ranges in which their parameters were obtained. Moreover, there were major challenges in understanding how to interpret the complex, often highly coupled behaviors. One thing that I recall vividly was a growing appreciation for the incredible diversity of functions that soft tissues exhibit, even though they were built upon a comparatively limited set of materials (collagens, elastin, proteoglycans, glycosaminoglycans, etc.). Such diversity was built upon variations in the underlying structure rather than intrinsic changes in underlying materials. To me, this was the essence of Dr. Lanir's approach. After 2 years, Dr. Lanir headed back to the Department of Biomedical Engineering at the Technion and I went on to complete my degrees and pursued an academic career.

Yet, in the time since I realized that it was during my 2-year experience with Dr. Lanir that he had taught me so many things, both biomechanical and otherwise, that have stayed with me. I have retained a strong scientific interest in biosolid micromechanics and continue to be strongly influenced by his substantial oeuvre. For example, when Kristen Billiar and I were first observing the complex biaxial mechanical responses of the aortic heart valve, my first approach for constitutive model development was to develop a complex complimentary strain energy density function, since we were utilizing stress-controlled experiments. However, I then performed some basic inverse simulations based on a variation of Dr. Lanir's structural model, and we discovered how subtle changes in fiber alignment completely captured the observed responses with only three model parameters. Observations like this made us feel that we were on the right track. Above all, Dr. Lanir showed me what it meant to do sophisticated scientific research, with all its ups and downs, at a level that I had not seen before as an undergraduate and rarely since.

It is thus with great pleasure, on behalf of my co-Editor Dr. Ghassan Kassab and all the contributing authors, to present this book as an expression of our affections and gratitude for all of Dr. Lanir's contributions to our field.

Austin, TX Michael S. Sacks

Sari Lanir, Michael Sacks, and Yoram Lanir in younger days (circa. 1996)

Happy Birthday to Yoram: Professional and Personal Reflections

The first World Congress of Biomechanics in 1990 was Chaired by Dr. Y.C. Fung and held in San Diego. It was then and there that I first met Dr. Yoram Lanir. I had just completed my Ph.D. training with Dr. Fung and I was thrilled to meet Yoram who had previously been a postdoctoral fellow with Dr. Fung. I had read many of Yoram's publications on biomechanics of blood flow and solid mechanics of soft tissue with great interest. The depth of his focus and the mystery of biomechanics was obvious and his conclusions rigorous. His works were unhurried, systematic, and definitive. He had the talent to capture the heart of the subject and simplify the analysis without loss of realism. Yoram embodied the character of a great engineer who captured the essence of a problem. He was clearly a master modeler who believed in structure-based analysis.

The first meeting with Yoram in 1990 was very memorable both academically and personally. He was extremely approachable and very humble. Despite my junior status, Yoram treated me as a colleague and was very interested in my Ph.D. thesis work on morphometry of coronary vasculature. Given his interest in structure-based analysis, he recognized the utility of the morphometric data we had labored over for several years. He advocated the use of measured geometry (anatomy, microstructure, etc.), and mechanical properties as a foundation for realistic analysis of organ function based on laws of physics with as few ad hoc assumptions as possible. The imprints of the structural-based analysis approach can be found throughout his contributions to the mechanics literature on skin, lung, tendon, heart, and vessels. He is clearly a pioneer in microstructure-based biomechanical analysis. Yoram's early work on skin mechanics and its relation to microstructure (i.e., elastin and collagen) have set the stage for similar analysis on many other organs.

The early encouragement and support I received from Yoram were long lasting. He exemplifies a great citizen of science. He is open armed and encouraging of younger scientists. Yoram has a mentoring character and draws great affection and respect from all who work with him. Our groups have reaped the rewards of numerous collaborations and friendship over the years.

In the Fall of 2010, I had the pleasure of visiting Yoram in Haifa to serve in Dr. Benjamin Kaimovitz's (one of Yoram's Ph.D. students) thesis defense. I very

Left to right: Hanna Kaimovitz (Benjamin Kaimovitz's wife), Yoram, Sari Lanir (Yoram's wife), Jawhara Kassab (Ghassan's sister), and Ghassan.

much enjoyed Yoram's hospitality and tour of Jerusalem. He managed to show me Jerusalem in a day. I was not surprised by his depth of knowledge in history, religion, and cultures nor his high energy as a nonstop tour guide. This exemplifies his character as an energetic doer with both depth and breadth. Yoram does everything with passion and completeness. As seen in the picture, the intensity wore us out and we finally rested (only for a few minutes) under an olive tree.

On behalf of my coeditor, Dr. Michael Sacks, and all the contributing authors, I wish Dr. Yoram Lanir a wonderful 70th birthday. This book is composed of our affections and gratitude for all of Yoram's contribution to our field.

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