 MCB, vol.10, no.2, pp.107-135, 2013

Challenge of Biomechanics

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Abstract: The application of mechanics to biology – biomechanics – bears great challenges due to the intricacy of living things. Their dynamism, along with the complexity of their mechanical response (which in itself involves complex chemical, electrical, and thermal phenomena) makes it very difficult to correlate empirical data with theoretical models. This difficulty elevates the importance of useful biomechanical theories compared to other fields of engineering. Despite inherent imperfections of all theories, a well formulated theory is crucial in any field of science because it is the basis for interpreting observations. This is all-the-more vital, for instance, when diagnosing symptoms, or planning treatment to a disease. The notion of interpreting empirical data without theory is unscientific and unsound. This paper attempts to fortify the importance of biomechanics and invigorate research efforts for those engineers and mechanicians who are not yet involved in the field. It is not aimed here, however, to give an overview of biomechanics. Instead, three unsolved problems are formulated to challenge the readers. At the micro-scale, the problem of the structural organization and integrity of the living cell is presented. At the meso-scale, the enigma of fingerprint formation is discussed. At the macro-scale, the problem of predicting aneurysm ruptures is reviewed. It is aimed here to attract the attention of engineers and mechanicians to problems in biomechanics which, in the author's opinion, will dominate the development of engineering and mechanics in forthcoming years.

Keywords: Biomechanics; cell; fingerprints; aneurysm

1 Why biomechanics

Engineering was born in wars. The word 'engineer' dates back to 1325 when it originally referred to "a constructor of military engines" (Simpson and Weiner, 1989). In this context an "engine" referred to a military machine – a mechanical

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device used in war.

Later, non-military 'civil' engineering emerged as a more peaceful alternative to the traditional use of the term. Encyclopedia Britannica notes: "Although the engineering profession can be traced back into earliest times, the records of history do not appear to contain any mention of the formal education of engineers until 1747, when the French engineer Jean Rudolphe Perronet was given the task of instructing "designers in the sciences and practices needful to fulfilling with competency the different occupations relating to... bridges and highways." The Corps des Ponts et Chaussees, which he headed, had been established in 1716 and the school established in 1747 for the workers in the organization became the Ecole Nationale des Ponts et Chaussees, the first engineering school. It has been said that the French were the leaders in engineering in the 17^{th} and the 18^{th} centuries; they were not only the leaders but also the pioneers in engineering education. In 1778 there was founded the school that later became the Ecole Nationale Superierure des Mines; in 1974 the Ecole des Travaux Publics, which became the Ecole Polytechnique; and in 1788 the Ecole d'Arts et Metiers. The Ecole Centrale des Arts et Manufactures was established in 1829." Most engineering schools in the world have adopted the French model as a prototype.

Since then, newer branches of engineering have separated from Civil Engineering, namely Mining, Mechanical, Aerospace, Chemical, Electrical etc. Though formally the new branches emerged from non-military Civil Engineering they were largely encouraged and supported financially by the military which flourished in the 20^{th} century – a century of two world (and numerous local) wars. At the beginning of the 21^{st} century, human military activity is at a steep decline. Weapons of mass destruction have rendered the hitherto mundane business of war dangerous and thereby scarce. Globalized entertainment, led by sportsmen and actors, is now the main constituent of day-to-day life. Will the occupation of engineering continue to fade as military activity declines? Hopefully, it will not. It will seek new venues, health care being eminent.

Prospects of applying engineering methods in medicine were nascent at the end of the 20^{th} century, when Biomedical Engineering (BME) departments were organized in leading research universities. These new entities appeared mainly as interdisciplinary groups, gathering faculty from various departments involved in biomedical applications. Today BME departments are well established, though the term is still somewhat unsettled. Mechanicians were well presented at BME departments from the get-go because of the overwhelming success of mechanics as a theoretical basis for the traditional engineering disciplines. Somewhat exaggerated expectations of the biomechanical approach were not fulfilled, building up a skeptic view of the field, and dissipating much of the enthusiasm directed at incorporating

mechanicians into BME departments. This turn of events, however, triggered a shift of biomechanical research toward more traditional engineering departments, whose faculty was very well qualified for the new challenging problems. Nowadays biomechanics is progressively integrating into traditional engineering curricula. It is taught in contexts of Civil, Mechanical, Aerospace, and Chemical Engineering to list a few.

Last but not least, it is noteworthy that biological applications refresh interest in fundamental mechanics, which was largely lost in past years when members of once popular departments of Theoretical and Applied Mechanics were thinly spread over other engineering departments. Biomechanics will give a boost to the old discipline of mechanics.

2 Challenge of biomechanics

The subject of biomechanics is the mechanical behavior of living materials. It was a structural engineer, Yuan-Chen Fung – Fig. 1 – who shaped the discipline by publishing a three-volume set of very readable texts on foundations of biomechanics: Fung (1990; 1993; 1996) – see also Kassab (2004).

Figure 1: Yuan-Chen Fung

The fact that materials (in biomechanics) are living imposes a great challenge mainly comprised of three ingredients.

The **first** ingredient is coupled behavior, where mechanics should be united with

electricity and/or bio-chemistry and/or thermodynamics. Moreover, the coupled systems evolve in time enigmatically and genetics plays an important role in this enigma. In fact, the relationship between genetics and environment during tissue evolution (epigenetics) is unknown. Mechanisms of these multi-attribute interactions remain to be uncovered. For example, *mechanotransduction* is a phenomenon of the conversion of the cell mechanical stimulus into the chemical activity like in the cases of touch, balance, and hearing. Various mechanisms of the phenomenon exist or are claimed, but full understanding has yet to be attained. Another example of coupling is the electro-mechanical interaction that underlies the work of heart. One more example of coupling is the crucial role of thermal effects on our bodies, observable every minute of every day, four seasons a year. Thus, the electro-thermo-bio-chemo-mechanical coupling is characteristic of the mechanical behavior of living tissues. Needless to say, the coupling does not make the life of a theorist easier, but rather more interesting.

In the presence of field coupling, the importance of experiment rises. Here the **second** ingredient of the biomechanical challenge comes to play: desirable experiments are difficult or even impossible to carry out. There are two main approaches to experimentation with living materials: *in vivo* and *in vitro* (*ex vivo*). *In vitro* experiments are performed on the components of living tissues or organisms that are isolated (usually cut) from their natural biological surroundings. The isolation allows simplifying the object, letting analysis of the individual tissue components. Unfortunately, this simplification is not always beneficial and can, in fact, be very misleading since living things are interconnected and are *not* equivalent to a superposition of their components. The latter is in stark contrast to traditional engineering disciplines, in which experiments carried out with very small samples of material often suffice for determining properties of large scale systems. In a sense, the traditional scientific approach based on partition and analysis does not always work. To grasp the behavior of a *system in vivo,* experiments are needed which do not violate its integrity. This type of experiment, usually performed on animals, faces natural difficulties (as the reader can imagine). Even disregarding ethical issues involving such experiments, interpreting their results is far from trivial. Indeed, it is very difficult to pinpoint the role of various components of a system based on its overall response. Also, results from animals might not be directly applicable to human beings. It may appear paradoxical, but the very difficulty of experimentation with living materials and organisms signifies the role of theoretical models. It is pure illusion that empirical data can be understood and interpreted without theories. Those who claim the opposite also use theories, albeit very poor ones.

Theoretical sophistication and experimental difficulties naturally lead to the **third**

ingredient of the challenge of biomechanics – the interdisciplinary collaboration. While it is possible to assume that outstanding Renaissance-type individuals exist who feel equally comfortable in math, physics, biology etc. the vast majority of scholars build expertise in one field (if not a sub-sub-problem of a sub-problem of a problem). To this end collaboration is necessary. Necessary and may not be simple – it may be demanding. I shall share my own experience with the reader. On one occasion I approached quite a well-known biologist offering my help on problems in mechanics that arose in his biological studies. He welcomed me under an imposition – in order to speak to him I must first study the language of biology from the list of books he prepared. Interestingly enough, he did not ask for a list of books on mechanics to understand the language of mechanics. Eventually, the collaboration ended before it had even started. The root of the problem was the attempt to make a mechanician a biologist (and, probably, vice versa). Suppose this excellent plan worked. In that case, no collaboration would have been needed at all. The point here is that collaboration is a mutually complementing effort. Without it, theoretical models of mechanicians may lose contact with reality on the one hand, while on the other hand, 'home-made' mechanics of biologists is naïve at best. Further speaking out of personal experience I have to add that the collaboration between engineers and medical doctors can be fruitful despite the mathematical tastes of the former and the very busy schedules of the latter. I learned that in 2004-2005 during my sabbatical stay at the Musculoskeletal Biomechanics Lab of Johns Hopkins University led by Ed Chao – Fig. 2 – who also set a similar (and huge) Biomechanics Lab in the Mayo Clinics before moving to Baltimore. Professor Chao proved *in vivo* that the interaction between medical doctors and engineers can be joyful and successful.

Finalizing this discussion, it is difficult to resist quoting the famous biologist Albert K. Harris, who understood the need for collaboration and its benefits as no one else had: "Systems of interacting forces and stimuli do not have to be very complicated before the unaided human intuition can no longer predict accurately what the net result should be. At this point computer simulations, or other mathematical models, become necessary. Without the aid of mechanicians, and other skilled in simulation and modeling, developmental biology will remain a prisoner of our inadequate and conflicting physical intuitions and metaphors."

In what follows I will demonstrate the challenge of biomechanics by presenting to the reader three sample unsolved problems at varying length scales.

3 Micro-scale: what is the cell structure?

The living cell is a major object of study in modern science. Infinitely many papers were written and prizes awarded on the topic. There is, however, a simple question

Figure 2: Edmund Chao

that has not been answered yet: what is the cell structure? This question should not be confused with the question of the cell composition: what are the components of the cell? The latter issue is quite well-understood – see Fig. 3.

While the components comprising the cell are identified and even their role in the cell's bio-chemistry is reasonably understood (Alberts et al, 2008), the architectural organization of the cell as a structure that bears mechanical loads remains uncomprehended. Recently, a significant effort was undertaken to clarify the cell structure from the standpoint of mechanics: Bray (2000); Howard (2001); Pollack (2001); Boal (2002); Mofrad and Kamm (2006). Despite progress, much work remains to be done.

In the trend of asking the simplest questions one comes to wonder whether the cell is fluid or solid[1]. For a long time, the dominant view of a cell was that of a fluid-like gel surrounded by a soft membrane: the model of the viscous fluid balloon. Putting aside viscosity one can even consider a rubber balloon filled with water as a large scale physical model of the cell. Placed upon a thin substrate, such a balloon would tend to spread over it freely – Fig. 4.

This thought experiment was actually carried out with living cells by Harris et al (1980) producing amazing results: unexpectedly, the thin rubber substrate folded under the spread cells – Fig. 5.

The observed folding is not in peace with the fluid balloon model. A rational explanation appears under the assumption that the cell comprises a substance which

[1] See Volokh (2011a) for more detailed discussions.

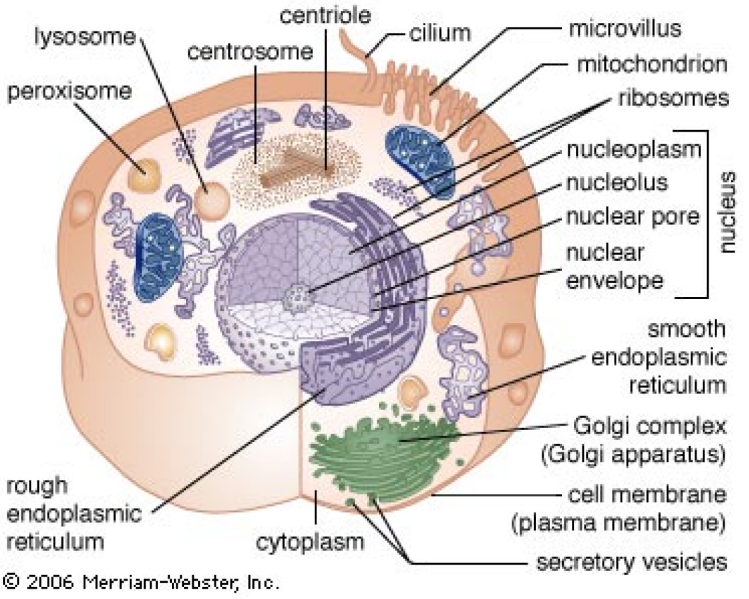

Figure 3: Cell composition (Brittanica.com)

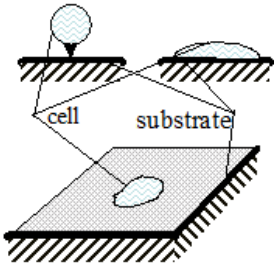

Figure 4: Expected behavior of the fluid cell-balloon on a substrate

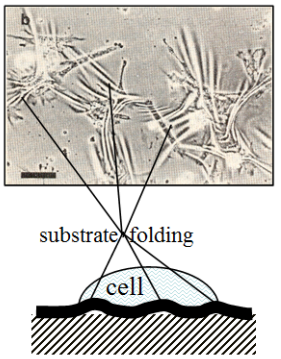

Figure 5: Substrate folding in Harris et al (1980) experiments

contracts in reaction to a spreading of the cell. In turn, contraction exerts force on the substrate via the cell's attachment sites. This 'substance' can only be made of microfilaments, intermediate filaments, and microtubules constituting cytoskeleton. This implies cytoskeleton has load-bearing capacity, thereby playing a significant role in the mechanical response of the cell. The latter idea is of fundamental importance and should be examined in independent experiments. For instance, it is natural to monitor the nucleus of a cell while pulling at its receptors. Maniotis et al (1997) did this by disturbing cell receptors with micropipettes and observed immediate changes in nucleus position – Fig. 6.

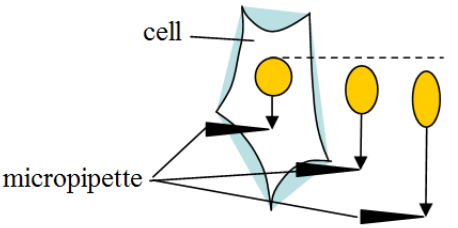

Figure 6: Immediate rearrangements inside the cell after pulling surface receptors by Maniotis et al (1997)

The aforementioned experiments are a testament to the capacity of the cell interior to sustain tension. Cytoskeleton is the network that provides cell stiffness. Donald Ingber (1993; 1997; 1998) suggested this network has so-called *tensegrity* (= tension + integrity) architecture in which the tension of microfilaments is induced through compression of microtubules. A simple spatial tensegrity structure

is shown in Fig. 7.

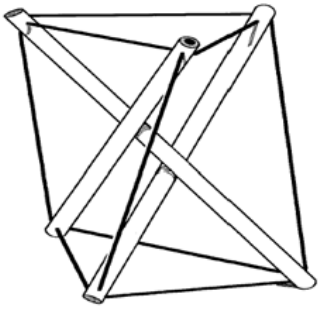

Figure 7: Simple tensegrity cell

It is noteworthy that only one strut enters a node while the number of cables-tendons entering the node is not restricted. This notion of tensegrity structures is formalized by considering an assembly of pin-jointed struts in some reference state.

The energy stored by the assembly can be written in the form

$$\psi = \sum_{n=1}^{N} \psi_n, \tag{1}$$

where ψ_n is the stored energy of the nth element and N is the number of elements.

The assembly is in equilibrium when the first perturbation of the total energy, including the stored energy and the energy of the external forces, with respect to the nodal displacements, $\delta\mathbf{u}$, equals zero. This condition is used for formulating equilibrium equations and finding the element forces and displacements. However, not every formal solution of the equilibrium equations can be observed in reality. Only stable solutions have physical meaning. The structural stability criterion takes the following form

$$\delta^2\psi = \delta\mathbf{u}^T\mathbf{K}\delta\mathbf{u} > 0, \tag{2}$$

where the *tangent stiffness matrix* can be presented in the form

$$\mathbf{K} = \mathbf{B}^T\mathbf{C}\mathbf{B} + \mathbf{D}. \tag{3}$$

Here the matrix of direction cosines, $\mathbf{B}$, is N by M where M is the number of the nodal degrees of freedom. The entries of the matrix can be calculated as follows:

$B_{nm} = (X_m - X_k)/L_n$, where X_m designates nodal coordinates; L_n designates the referential chord length of the nth element; m and k are proper indices of the element coordinates. The uncoupled stiffness matrix, $\mathbf{C}$, is N by N diagonal with entries: $C_{nn} = S_n/L_n$, where S_n is the axial stiffness of the nth element. The geometric stiffness matrix, $\mathbf{D}$, is M by M symmetric with entries: $D_{mm} = \sum_{n=1}^{j} P_n/L_n$; $D_{mt} = -P_n/L_n$, where P_n is a pre-stress force in the nth element. The sum is over all j elements joined at the node with the m^{th} degree of freedom. Index t is the properly chosen degree of freedom at the second edge of the nth element.

Since displacement perturbations are arbitrary, condition (2) implies that tangent stiffness matrix $\mathbf{K}$ must be *positive definite* to provide stability of the assembly. At this point two different possibilities appear to provide stability of the structural assembly. The first possibility is that matrix $\mathbf{B}^T\mathbf{CB}$ is positive definite. In this case since the element axial stiffness is usually much greater than the possible pre-stress, $S_n >> P_n$, the second term on the right hand side of (3) can be ignored as compared to the first one and we have

$$\mathbf{K} \cong \mathbf{B}^T\mathbf{CB}. \tag{4}$$

Such an approximation is characteristic of the classical structures whose stability is due to the material elastic properties. The infamous structure of this type is shown in Fig. 8 (left).

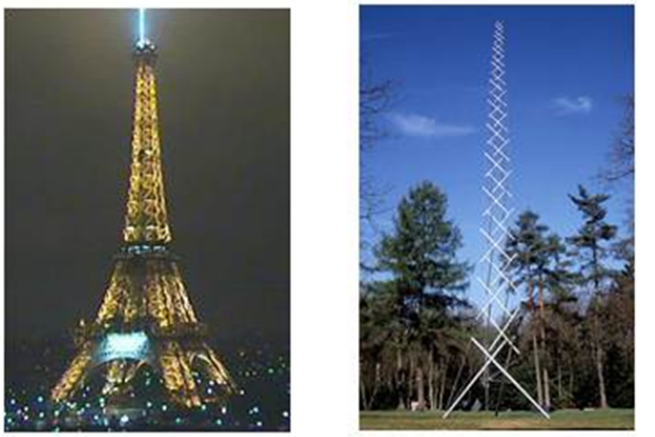

Figure 8: Eiffel tower – regular structure (left); Snelson tower – underconstrained tensegrity structure (right)

It can occur, however, that $\mathbf{B}^T\mathbf{C}\mathbf{B}$ is singular

$$\det(\mathbf{B}^T\mathbf{C}\mathbf{B}) = 0, \tag{5}$$

and the account of the second term on the right hand side of (3) becomes crucial. Of course, in this case the pre-stress should exist and stabilize the structure providing positive definiteness of $\mathbf{K}$.

Condition (5) appears in a very special class of structures that lack constraints. The latter suggests referring to this class of structures as *underconstrained* – Fig. 8 (right). Tensegrity structures fall within this class – obeying condition (5). It is crucial to realize that despite pre-stress possibly being able to regularize the tangent stiffness matrix, $\det\mathbf{K} \neq 0$, it may not be enough to stabilize the assembly providing positive definiteness of $\mathbf{K}$. It can be shown for *all pre-tensioned* elements that the assembly is always stable because $\mathbf{K}$ is positive-definite. If, however, the assembly comprises both tensioned and compressed members – as in the case of tensegrity structures – its stability cannot be taken for granted.

In summary, tensegrity structures are singular structures, and their stability is due to pre-stress rather than elastic properties of elements. Pre-stress is achieved with the help of stiff struts that can withstand compression. These compressed struts sustain tension in cables which in turn stabilize the whole assembly.

Tensegrity is by no means the only hypothesis concerning the structure of the cell. Historically, continuum models of the cell appeared first. They were triggered by the intuitively appealing vision of the cell as a liquid drop surrounded by a membrane. The liquid includes all the interior cell components dominated by cytoplasm. First models considered Newtonian liquid (Evans and Kukan, 1984). They were subsequently complicated by introducing non-Newtonian liquids (Tsai et al, 1993), solids (Mijailovich et al, 2002; Dao et al 2003), and solid-fluid mixtures with various rheological properties (Ateshian et al, 2006). Though the continuum theories are phenomenological, somewhat subtle microstructural considerations can guide their development as in the case of the soft glassy material models by Fabry et al (2001). Needless to say, the use of the continuum theory is a gross approximation. With the inclusion of the nucleus, the inner space of eukaryotic cells is heterogeneous. Nonetheless, continuum models are simple; a pleasure to deal with. They are useful when the whole-cell response is of interest. For example, the Suresh group (Suresh et al, 2005) used continuum models to detect the disease state of malaria infected red blood cells. They modeled and observed that the infected red blood cells underwent significant structural changes and their bulk stiffness increased. The stiffness increase affected the motility of infected cells during their advance inside the pipette allowing them to be easily identified. Various aspects of continuum models in cell mechanics were recently reviewed by Lim et al (2006).

Based on the works in this direction it is reasonable to assume that choice of a continuum model should depend on the intended application. In this way even a rough model that is open for criticism can be usefully and successfully employed under appropriate circumstances.

While continuum models are based on the idea of homogenization of cell constituents, structural models emphasize the different roles of different constituents in the design of the cell. Among the structural models, we mention the open-cell foams that consider networks of interconnected struts (Budiansky and Kimmel, 1987; Warren and Kraynik, 1997; Satcher and Dewey, 1996; Satcher et al, 1997) and tensegrity systems considering cytoskeleton as an assembly of the pre-stressed microtubules and microfilaments (Coughlin and Stamenovic, 1997; Wendling et al, 1999; Volokh et al, 2000). Tensegrity models were considered above. Although structural models can yield interesting qualitative insights on the mechanical behavior of the cell, they are computationally intensive and therefore limited by a small number of elements.

Finally, we should separately mention polymer-based cell models that link different length scales analogously to the statistical theories of rubber-like materials: MacKintosh et al (1995); Gardel et al (2004); Storm et al (2005).

Though various models were proposed to explain the mechanical behavior of living cells none of them is preferable. This demonstrates the failure at grasping cell mechanics via one simple theory. Probably no simple cell model can be created at all, and the choice of model should depend on the specific circumstances under consideration. **The problem remains open**. Moreover, understanding of the cell structure alone is not enough without an understanding of the multi-field coupling, e. g. mechanotransduction – see Chen et al (1997), for example.

4 Meso-scale: why are fingerprints different?

Figure 9: Friction ridges of a human fingerl

Fingerprints are impressions left by the friction ridges of a human finger – Fig. 9. Fingerprints are important in traditional forensic applications as well as the expanding field of biometric recognition techniques. It is believed that fingerprints are unique and invariable for each individual. Intuitively, the reader can expect that information about fingerprints is stored in DNA. Thus, the process of the skin and ridge formation, i.e. the skin morphogenesis, is essentially genetic. There is an argument, however, which questions this purely genetic scenario of skin formation: identical twins with the same genetic makeup and virtually indistinguishable DNA have different fingerprints! Thus, the role of the environment may be crucial in the formation of the ridges, and the process of skin morphogenesis is most likely epigenetic. If so, there is room for mechanics in studying the process of skin evolution.

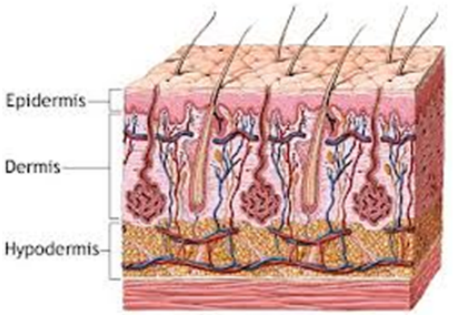

Figure 10: Skin composition

The skin (Fig. 10) develops ridges starting from the 10th week of pregnancy – see Babler (1991); Hale (1951); Hirsch (1973); Okajima and Newell-Morris (1988); Penrose and O'Hara (1973). They appear at the basal layer of epidermis and gradually create the fingerprint patterns on the skin surface. Three major hypotheses were proposed to explain the ridge formation: the folding hypothesis; the nerve hypothesis; and the fibroblast hypothesis – see Kucken' review (2007). According to the folding hypothesis the fingerprint topography emerges as a result of a mechanical process that skin undergoes during morphogenesis. This qualitative idea gave rise to the work by Kucken and Newell (2004; 2005) in which a mathematical model was used to explain the appearance of ridges. The authors assumed that ridge patterns were created by buckled basal layer of epidermis. They used the von Karman theory of flexible shells to describe the basal layer and placed it on an elastic foundation composed of nonlinear springs. – Fig. 11. Kucken and Newell (2004; 2005) used sophisticated numerical procedures to analyze buckling

of a flexible shell on elastic foundation and obtained nice patterns resembling real fingerprints.

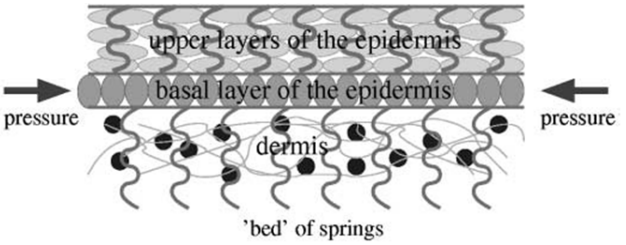

Figure 11: Buckling model of thin basal epidermis layer laying on the soft dermis foundation presented by nonlinear springs (from Kucken and Newell, 2004)

Appreciating the pioneering works by Kucken and Newell (2004; 2005) on fingerprints and similar works by Green (1999) and Steele (2000) on morphogenesis, the reader should not overlook points inviting further elaboration. Indeed, the shell-on-elastic-foundation model tacitly assumes the stiffness of the basal layer (of the epidermis) is much greater than the stiffness of the upper epidermis and the dermis layer. Experiments are needed to validate this hypothesis. Besides, from the engineering standpoint, skin development can be thought of as a process of deformation due to mass alteration. Mass evolution, however, is not directly involved in the Kucken–Newell model.

Alternatively to the shell-on-elastic-foundation theory, a different buckling mechanism can be considered in which ridges form due to growth induced surface instability of the skin – Fig. 12.

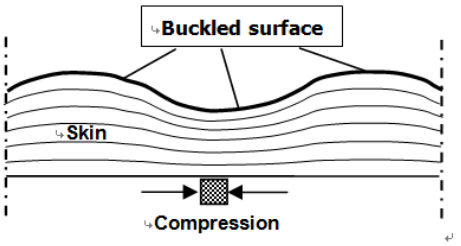

Figure 12: Surface buckling

For instance, Volokh (2006a) uses a simple continuum mechanics theory of tissue growth that includes equations of momentum and mass balance, aided by constitu-

tive equations. The coupling of material deformation and mass transport is based on the idea that skin swells during mass supply – analogously to metal expansion under heating – the thermo-elastic analogy. Such an analogy immediately grants a qualitative insight on the growth process: if a uniform growth is free then it produces no stresses – just as uniform heating does not stress a steel pipe expanding volumetrically. If, however, growth is constrained then, it is accompanied by stressing. Among the constraints are geometrical: the attachment of the dermis to subcutaneous fat; and physical: inhomogeneity and anisotropy. The latter is again analogous to thermo-elasticity – a steel pipe is stressed under uniform heating if it is anisotropic. Skin is constrained both physically and geometrically. Eventually, stresses are accumulated during growth. Such stresses, called residual stresses, have been discovered experimentally in soft biological tissues in the 1970s (Fung, 1990). It is important that residual stresses are predominantly compressive. The latter leads, for instance, to a delay of the onset of rupture in arteries (Volokh, 2008) – just as man-induced compressive stresses delay crack expansion in prestressed concrete. It should be noted that residual compression in soft tissues may cause instability – buckling. The phenomenon of buckling is typical of thin-walled structures whose lateral stiffness is significantly lower than the longitudinal one. Buckling instability, however, is not necessarily related to the thinness of a structure – it can occur in thick structures too in the form of surface buckling – Fig. 12.

The surface buckling scenario of tissue morphogenesis has been examined in Volokh (2006a) based on the assumption that in-plane stiffness of the growing layer is significantly higher than its out-of-plane stiffness. Such an assumption is reasonable in the case of skin, because the load-bearing collagen fibers are arranged in the plane of the dermis layer (Fung, 1993). Surface buckling analysis indicates the appearance of wavy patterns on the surface. These patterns fade away from the surface. It is of fundamental importance that the critical magnitude of the mass supply parameter – which corresponds to surface buckling – is independent of pattern wavelength, so generally, various patterns can be generated during growth. The patterns generated in each finger depend on small (infinitesimal) geometric perturbations, mechanical properties, and mass sources (cells) of the specific skin. The latter, perhaps, explains why no similar fingerprints have been found – their probability tends to zero.

The crucial issue in modeling ridge formation is a description of tissue growth and morphogenesis. Biological or biochemical mechanisms of growth are not well understood though plenty of scenarios exist in biological literature. There is no shortage of continuum mechanics models of soft tissue growth either: Hsu (1968); Skalak et al (1982); Rodriguez et al (1994); Taber (1995); Drozdov 1998; Epstein

and Maugin (2000); Rachev (2000); Kuhn and Hauger (2000); Kuhl and Steinman (2003); Garikipati et al (2004); Menzel (2005); Klisch and Hoger (2003). Unfortunately, the mathematical apparatus of existing approaches is rather complicated and includes variables that are difficult to interpret in simple terms and assess in measurements. For example, the multiplicative decomposition of the deformation gradient $\mathbf{F} = \mathbf{F}^e\mathbf{F}^g$ in which the deformation gradient is decomposed into pure growth $\mathbf{F}^g$ and elastic deformation $\mathbf{F}^e$ tensors is the most popular tool to describe growth. Unluckily, the multiplicative decomposition is difficult to interpret physically or biologically because the abstract intermediate configurations are generally neither observable nor unique. Thus, partial deformation gradients $\mathbf{F}^g$ and $\mathbf{F}^e$ are internal variables. The same difficulties are characteristic of the origins of growth-deformation decomposition – elastic-plastic decomposition: $\mathbf{F} = \mathbf{F}^e\mathbf{F}^p$ – a standard concept in finite plasticity theories. In principle, it is possible to formulate a finite plasticity theory, and analogously a growth theory, without multiplicative decomposition (e.g. Volokh, 2013a). However, there is no need to follow this analogy because the processes of growth and plastic flow are different. Indeed, in the case of plasticity, introduction of internal variables to present inelastic deformations is, in a sense, unavoidable. On the other hand, in the case of growth there is a natural additional variable – mass density – which can replace internal variables. Needless to say, superfluous variables should be avoided whenever possible. Such eliminations of redundant quantities are routinely made in science via Occam's razor, yet this traditional concept seems to be ignored by theorists tackling tissue growth.

Regarding mathematical descriptions of growth, a subtle point should be addressed concerning the 'number' of material points. Sharp distinction between real physical material, i.e. material particles comprising continuum, and the mathematical concept of material point should be kept in mind (Volokh, 2006b). This distinction is illustrated in Fig. 13, in which material deformation-growth is considered on different length scales.

On the macroscopic scale, a material body can be divided into an infinite set of material points. It is assumed that position $\mathbf{x}$ in physical space can be ascribed to every material point before growth-deformation. These material points form the material continuum. It is further assumed that during growth-deformation every point moves to a new position $\mathbf{y}(\mathbf{x})$ preserving the continuity of the body. This mapping is smooth to the necessary degree. Moreover, it is assumed that the mapping is one-to-one, i.e. the 'infinite number' of material points does not change during growth-deformation. Of course, the concept of the material point is purely mathematical. Material points do not exist; they are mathematical abstractions. Material always occupies some volume. 'Material point' merely refers to very small volume. Such small volumes are considered on the mesoscale of the growth-

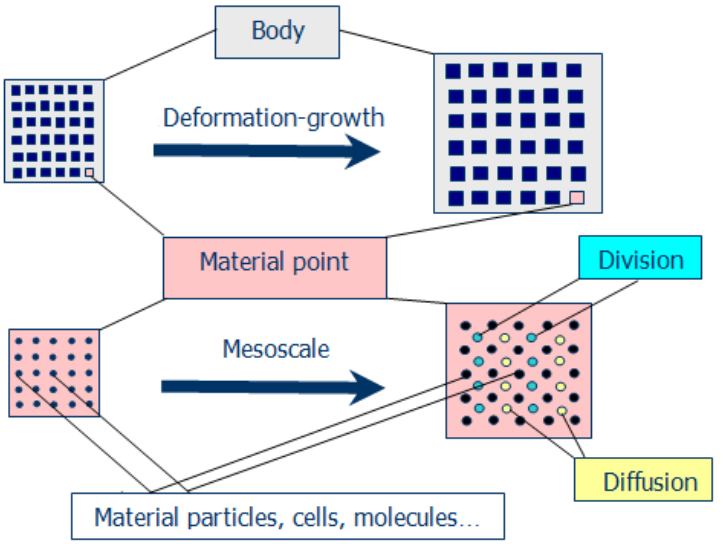

Figure 13: Multiscale mechanics of growth

deformation process as shown in Fig. 13. Under 'higher resolution' it can be seen that the material point is a very small physical volume, which in the case of living tissues includes cells, molecules, pores, and various tissue particles. It is crucial to emphasize that the number of material particles does change within a 'material point' due to division and diffusion. Therefore, if the reader could track behavior of a referential material point he would discover a variable mass density within it. The latter means that referential mass density changes during deformation-growth: $\rho \neq$ constant, and mass is not conserved. This violation of mass conservation is inherent to all open systems exchanging material with their environment.

Summarizing the discussion of fingerprint formation and tissue morphogenesis in a wider perspective I conclude that **both problems remain open**. They await reader intervention.

5 Macro-scale: can aneurysm rupture be predicted?

From the engineering standpoint, the cardiovascular system is a system of pipes – veins and arteries – through which blood pumped by the heart travels. Normal arterial wall – Fig. 14 – consists of three layers: intima, media, and adventitia. Intima

is the innermost monolayer of endothelial cells attached to a basement membrane composed of type IV collagen and laminin. Media is the middle layer comprising smooth muscle cells embedded in extracellular matrix composed of elastin, various collagen fibers, and proteoglycans. Adventitia is the outermost layer comprising fibroblasts embedded in collagen and elastin (Humphrey, 2002).

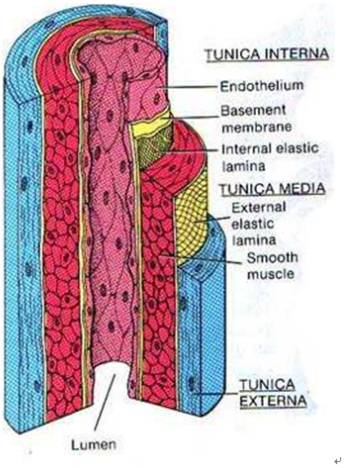

Figure 14: Arterial wall

During human lifetime the arterial wall alters and a local dilation of the wall – *aneurysm* - may develop. The bio-chemical cause of the aneurysm is unknown, yet various assumptions have been made concerning the risk factors including obesity, hypertension, smoking, alcoholism, high cholesterol, copper deficiency, and increasing age. The two most frequent types of aneurysms are abdominal aortic aneurysm (AAA) and intracranial saccular aneurysm (ISA) shown in Fig. 15.

Unfortunately, aneurysms can enlarge and rupture. For instance, AAA is found in $\sim$2% of the elderly population, with new cases diagnosed each year and increasing occurrence. In many cases AAA gradually expands until rupture, causing a mortality rate of 90%. The AAA rupture is considered the 13^{th} most common case of death in US (Patel et al, 1995). Since AAA treatment is expensive and bears considerable morbidity and mortality risks it is vital to predict when the risk of rupture justifies repair attempts.

Medical doctors tend to operate AAA when its maximum diameter exceeds 5.5 cm or/and the expansion rate is greater than 1 cm per year. These criteria are purely empirical and they are based on experience only. Regrettably, smaller aneurysms (less than 5 cm in diameter) may rupture while larger aneurysms may not.

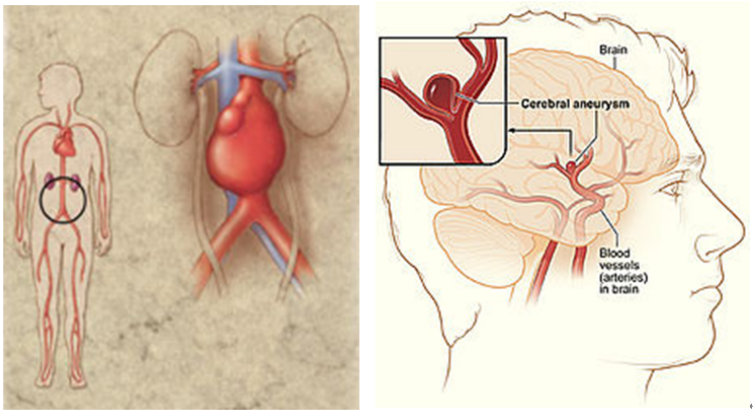

Figure 15: Abdominal Aortic Aneurysm (left) and Intracranial Saccular Aneurysm (right)

Since aneurysm growth and rupture are mechanical processes it is natural to try and predict aneurysm development via mechanics. Such predictions should be based on a mathematical model of growth and rupture of aneurysms. Recent reviews of aneurysm biomechanics can be found in Vorp (2007); Humphrey and Taylor (2008); and McGloughlin (2011) for example. Among original publications the following should be mentioned: Watton et al (2004); Baek et al (2006); Kroon and Holzapfel (2007); Volokh and Vorp (2008).

As in the case of tissue morphogenesis and ridge formation discussed in the previous section, a description of growth is crucial for modeling aneurism evolution. Humphrey and Rajagopal (2002) and Baek et al (2006) came up with the following formula for the internal energy of an aneurysm constituent

$$\psi(t) = \int_{-\infty}^{t} g(t,t_{dp})\dot{m}(t_{dp})f(t,t_{dp})dt_{dp}, \tag{6}$$

where $\dot{m}$ is the rate of constituent production; f is the strain energy of the deposited constituent; t_{dp} is the time of the constituent deposition; and the life cycle function $g(t,t_{dp})$ is defined by the constituent life time t_{lf} with the help of the Heaviside step functions H as follows $g(t,t_{dp}) = H(t-t_{dp}) - H(t-t_{dp}-t_{lf})$.

In the case of AAA elastin and smooth muscle are mostly lost during aneurysm development. Collagen turnover dominates the growth process. If so, the aneurismal wall can be thought off as a membrane composed from thin sheets of collagen fibers aligned in various directions. Then, for a given layer characterized by the

unit vector $\mathbf{M}$ in the fiber direction at $t = -\infty$, a new fiber is deposited in direction $\mathbf{M}_{dp}/\left|\mathbf{M}_{dp}\right|$ at time $t = t_{dp}$ following mapping

$$\mathbf{M}_{dp} = \mathbf{F}(t_{dp})\mathbf{M}, \tag{7}$$

where $\mathbf{F}(t_{dp})$ is the deformation gradient at the time of the collagen fiber deposition $t = t_{dp}$.

The deposited fiber undergoes deformation

$$\mathbf{m} = \left|\mathbf{M}_{dp}\right|^{-1}\mathbf{F}_{dp}\mathbf{M}_{dp} = \left|\mathbf{M}_{dp}\right|^{-1}\mathbf{F}_{dp}\mathbf{F}(t_{dp})\mathbf{M} = \left|\mathbf{M}_{dp}\right|^{-1}\mathbf{F}(t)\mathbf{M}, \tag{8}$$

where $\mathbf{F}_{dp} = \mathbf{F}(t)\mathbf{F}^{-1}(t_{dp})$ is the deformation gradient mapping the configuration at time $t = t_{dp}$ to the current configuration at time t.

Now, constitutive laws can be formulated. For example, a slightly modified version of the equations for fiber energy and mass balance used by Holzapfel et al (2000) and Watton et al (2004) can be written as follows

$$f = \eta\{\exp[k(\lambda_{pre}^2\left|\mathbf{m}\right|^2 - 1)^2] - 1\}, \tag{9}$$

$$\dot{m}_i = \beta\ \left|\mathbf{M}_{dp}\right|^{2\alpha}, \tag{10}$$

where η and k are fiber parameters; λ_{pre} is a pre-stretch of the deposited fiber; and β and α are growth constants.

Alternatively, Kroon and Holzapfel (2007) used a simpler version of the energy density function

$$f = \mu(\lambda_{pre}^2\left|\mathbf{m}\right|^2 - 1)^3, \tag{11}$$

where μ is a fiber stiffness parameter, and the rate of mass production is the same as in the previous case.

The mentioned theories and others (e.g. Kroon and Holzapfel (2008; 2009); Chatziprodromou et al (2007); Figueroa et al (2009); Watton et al (2009); Watton and Hill (2009); Schmid et al (2010); and Martufi and Gasser (2012); Wilson et al (2013)) were successfully used for modeling the inflation of aneurysms. That is not enough, however. Mechanical failure should be part of the theoretical description. The simplest way to introduce failure into the constitutive equations is to enforce a constant called *energy limiter* into the strain energy function. The limiter provides a saturation value for strain energy (Volokh, 2011b; 2013b). The new constant controls material failure and, can be interpreted as an average energy of molecular bonds from the microstructural standpoint. It is especially noteworthy that the approach of energy limiters allows for considering *strength* independently of *stiffness*. The

latter separation is vital for aneurysm modeling where *stiffening* is accompanied by the *loss of strength*[2].

The fiber strain energy incorporating failure can be written in the following general form

$$f = 0.1\,\Phi\{\Gamma[0.1,0] - \Gamma[0.1,(W/\Phi)^{10}]\}, \tag{12}$$

where $\Gamma[s,\ x] = \int_x^\infty t^{s-1}\exp(-t)\,dt$ is the upper incomplete gamma function; Φ is the energy limiter; and W is the strain energy of intact (without failure) material.

For example, Eq. (11) can be used as an intact energy function of a fiber

$$W = \mu(\lambda^2 - 1)^3, \tag{13}$$

where $|\mathbf{m}| = \lambda$ and $\lambda_{pre} = 1$ for the sake of illustration.

Substituting (13) in (12) and differentiating the latter with respect to stretch it is possible to find the Cauchy stress: $\sigma = \lambda\,\partial f/\partial\lambda$. The stress-stretch curve is presented graphically in Fig. 16 for $\Phi/\mu = 0.05$. The limit point appears on the graph as a result of the bounded strain energy defined by the limiter, Φ. The limit point corresponds to the onset of failure. It is assumed that the fiber rupture is quite abrupt and the post-peak curve goes down steeply. Without the energy limiter the fiber would never break. This is obviously absurd, and physically meaningless.

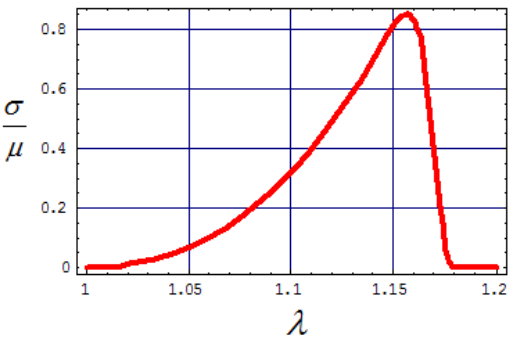

Figure 16: Sample stress-strain curve for a collagen fiber

An interesting illustration of the application of energy limiters can be found in Volokh (2010) in which the AAA strain energy was used in the form

$$f = \Phi\{1 - \exp[-W/\Phi]\}, \tag{14}$$

[2] Remarkably, continuum damage-mechanics theories usually describe failure through the decrease of stiffness while the aneurysms failure is accompanied by the increase of stiffness

$$W = \alpha_1(\lambda_1^2+\lambda_2^2+\lambda_3^2-3)+\alpha_2(\lambda_1^2+\lambda_2^2+\lambda_3^2-3)^2, \quad J=\lambda_1\lambda_2\lambda_3=1 \qquad (15)$$

where λ_is are the principal stretches and material constants $\alpha_1 = 10.3N/cm^2$; $\alpha_2 = 18.0N/cm^2$; $\Phi = 40.2N/cm^2$ were calibrated in the uniaxial tension test – Fig. 17.

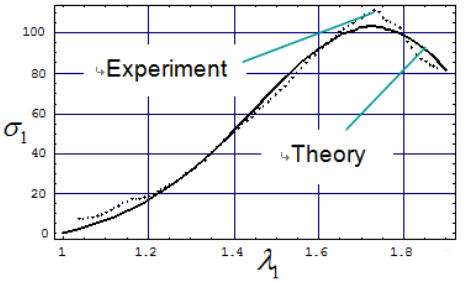

Figure 17: Cauchy stress [N/cm^2] versus stretch in the uniaxial tension of AAA material (from Volokh and Vorp, 2008).

Based on the presented AAA model it was possible to calculate the critical rupture states of an AAA sheet, when $\partial^2\psi/\partial\lambda_1^2 \cdot \partial^2\psi/\partial\lambda_2^2 - (\partial^2\psi/\partial\lambda_1\partial\lambda_2)^2 = 0$, under the varying biaxiality parameter

$$n = \ln\lambda_2/\ln\lambda_1. \qquad (16)$$

Uniaxial Tension (UT) corresponds to $n = -0.5$; Pure Shear (PS) corresponds to $n = 0.0$; and the equal Biaxial Tension (BT) corresponds to $n = 1.0$. Fig. 18 presents the failure criteria for critical states of sheet instability calculated for the constitutive model (14)-(15).

Von Mises stress was calculated as follows: $\sigma = \sqrt{3(\sigma:\sigma-(\mathrm{tr}\sigma)^2/3)/2}$.

Fig. 18 clearly shows that only the energy criterion is almost constant for the critical failure states with varying biaxiality. It is especially crucial that critical parameters corresponding to uniaxial tension, which are usually fitted in experiments, decrease with the developing biaxiality. Thus, the rupture under equal biaxial tension occurs under smaller values of the critical parameters (except energy) than is observed in uniaxial tension. This notion is very important because soft biological tissues are often in biaxial or triaxial stress-strain states, in which the strength criteria based on uniaxial tension tests might not be applicable (see also Volokh (2011b)).

The reader could notice that theoretical developments concerning a description of aneurysm growth and rupture have reached a respectful level of sophistication. Unfortunately, experimental calibration of these proposed theories seems to be far away. The patient-specific prediction of aneurysm rupture based on computer simulations **remains a dream**.

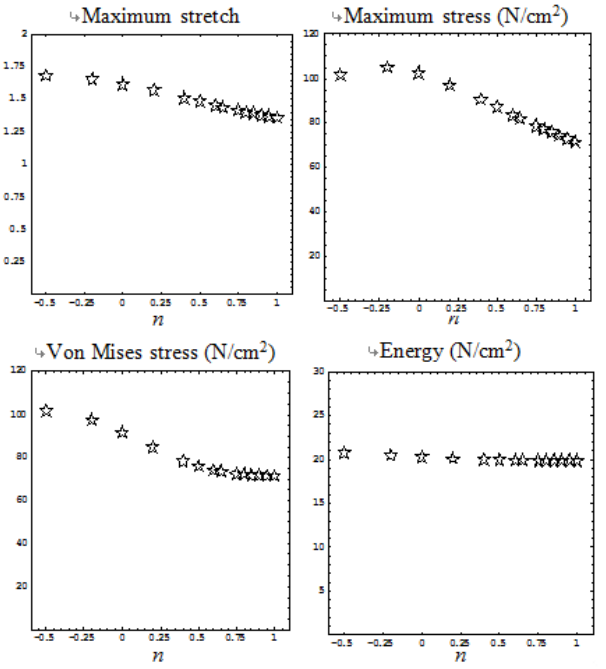

Figure 18: Critical failure criteria for Abdominal Aortic Aneurysm under varying biaxiality ratio

6 Concluding remarks

I tried to persuade the reader that tackling problems of biomechanics is very worthwhile. The problems of biomechanics involve natural challenges related to the multi-physics behavior of living materials, experimental difficulties, and necessity of collaboration with biologists and medical doctors. I assume it did not escape the reader's attention that the choice of sample problems was subjective and explained by my personal taste, or better said, limited experience. There are many other fascinating problems in biomechanics which deserve study. The solution of the mentioned problems and many others is difficult, but not hopeless. In any case we have no choice but solve them.

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