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Y.C. "Bert" Fung: The Father of Modern Biomechanics

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It is a great fortune to have Professor Y.C. Fung as the Honorary Editor for the journal "Mechanics and Chemistry of Biosystems". It is also my great fortune that Professor Satya Atluri (Editor-in-Chief) has asked me to write a tribute to Dr. Fung and his contributions to mechanics of biosystems or biomechanics. In casting off the first volume of the journal, this dedication is most appropriate since it is the intent of the Editors to publish articles that follow in the strong tradition of biomechanics set forth by Dr. Fung. Dr. Fung's contributions span the fields of bio-fluid and bio-solid mechanics and have touched upon nearly every mechanical organ system in physiology. He has authored nearly 300 publications and 3 books, and is the editor of 6 additional books on biomechanics (see References). It is, of course, impossible to describe all of Dr. Fung's contributions to the field of biomechanics in the allotted space. In this tribute, I will briefly describe some of the highlights of the past four golden decades.

In the mid sixties, Fung left an illustrious 20-year career in aeroelasticity and aeronautical engineering at Caltech and joined UCSD to focus on biomechanics. Within one decade of the move, he delved into many areas of mechanics of microcirculation. Fung's objective was to develop the principles of continuum mechanics for the microcirculation, and to determine its structure and constitutive properties, so that biophysical problems can be analyzed with mathematical precision. His first paper in biomechanics was published in 1966 entitled "Elastic environment of the capillary bed". He observed that the capillary blood vessel was much more rigid than expected. He carried out a detailed analysis to show that the rigidity of the capillary vessel stems largely from its surrounding tissue and hence came the birth of the "tunnel-in-gel" concept.

Fung's early work on the flow in the microcirculation led to a number of important conclusions. In the capillary vessels, he predicted that the entry length is short (about 1.3 times the radius of the capillary tube) while the entry length increases in larger vessel (with increase in Reynolds number). Furthermore, based on theoretical arguments, he pointed out that at a branching point of a capillary the branch with a faster stream gets most of the red blood cells, thus explaining the extreme nonuniformity in hematocrit distribution in the capillaries. Fung shed light on a number of other fluid mechanics problems in the microcirculation including entry effects, plug effect of the red cells, bolus flow, vessel peristalsis, wall permeation, valved vessels and vessels with local constrictions. For bolus flow, it was found that the gap between cells and endothelium is of great significance and that at higher hematocrit, the resistance does not increase very much with increase in hematocrit.

In the microcirculation, the structural and mechanical properties of the individual red blood cell (RBC) are very important. Fung proposed a theoretical analysis of the sphering of RBC as a means to evaluate the mechanical properties of the cell membrane. A number of important results surfaced. Flexibility of RBC was consistent with the assumption that the interior of the red cells is in a liquid state and that the cell membrane is elastic. The biconcave geometric shape of the red blood cells enables them to deform into a wide variety of shapes without inducing any stress in the cell membrane; i.e., the strength of RBC comes from its flexibility. Furthermore, Fung considered the mechanical interaction between RBC and capillary blood vessel and determined the shear forces and pressure drop. He also addressed questions such as: what is the largest cell diameter in N cells? The extreme values were found to satisfy Gumbel limiting distribution. This analysis of microcirculation demonstrated that many treasures can be uncovered through the continuum mechanics approach.

Early on, Fung stressed the importance of the stress-strain-history law for progress in biomechanics. Hence, the early stage of his biomechanics research was concerned with the determination of the constitutive equa-

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tions. A rigorous program on arteries, skin and other soft tissue was initiated. Fung proposed an exponential stress-strain law which was found to describe the highly non-linear elastic properties of these tissues under uniaxial conditions. In an effort to theoretically unify creep, relaxation and hysteresis (viscoelastic features), he proposed a quasi-linear viscoelastic law. The analysis was extended to more complex soft tissues such as ureter and heart muscle. For the heart muscle, it was postulated that the passive properties have a significant influence on cardiac dynamics. For the active heart muscle, Fung modified Hill's famous equation for skeletal muscle. He proposed the basic formalism for a mathematical model of the heart muscle and the whole heart that considers the dynamics of quick release and quick stretch and mechanics of fibers.

In the same first decade, Fung initiated a program of blood circulation in the lung. Prior to that, the problem of blood flow in the lung had a long history and huge literature. The fuzziest area in the field was the blood flow in the capillaries. Direct observations show that the capillary blood vessels in the pulmonary alveoli are relatively short and closely knit unlike the usual notion of a blood vessel as a long cylinder. Therefore, a new term – sheet flow – was introduced by Fung and Sobin to describe blood flow through the pulmonary capillary vessels. Explicit results concerning blood flow, alveolar blood volume, regional differences, and transit time distribution were derived from the sheetflow theory and were found to agree with experimental evidence available in the literature.

Fung's sheet flow theory exhibits in a simple form the effects on flow of the arterial, alveolar, and venous pressures, the alveolar area, the mean path length between arterioles and venules, and the elastic and surface tension in the alveolar membrane; thus the theory provides a quantitative understanding of a large number of variables. The theory was used to make numerous hemodynamic predictions such as pressure-flow relationship, transit time distribution, blood volume distribution in the lung as a function of pulmonary arterial and venous pressure, impedance analysis, water volume in extravascular space, and regional distribution of flow. A number of pulmonary issues were examined including the Starling mechanism of filtration and the issue of recruitment versus distensibility of capillaries. A program to elucidate the ultra-structure of the pulmonary alveoli was also advanced. Many new features of distribution of collagen fibers and structure of posts were documented. In addition, a basic theory of elasticity of lung parenchyma based on the ultra-structure was proposed. The theory was used to understand regional interdependence, expiratory flow limitation, emphysema, etc.

Fung's studies marked the beginning of the development of a rational mechanics of the microcirculation of the lung. He showed that the tools of mechanics can put the microcirculation on firmer grounds and allow us to understand a complex system quantitatively and rigorously. Within the first decade, Fung received the 1975 Eugene M. Landis Award for his contributions to microcirculation where he delivered a memorable lecture on the "Microcirculation as Seen by a Red Cell".

In the second decade, Fung continued to develop the principles of continuum mechanics for the lung. The lung tissue was tested under bi-axial loading and triaxial data on stress and strain were determined. This work was one of the first systematic studies of the mechanical behavior of lung tissue. Prior to this work, physiologists were content with pressure-volume curves of the lung as a measure of their elastic behavior. These one-degree-of-freedom measurements contain very little information to predict the mechanical behavior of the lung under many conditions such as its distortion by gravity, the stresses that develop when the parenchyma is distorted by disease, and the pressures which occur around blood vessels and bronchii during lung inflation. For these reasons and also for the more fundamental reason that knowledge of this kind is essential to a further understanding of pulmonary statics and dynamics, the measurements proposed by Fung represented a breakthrough.

The next task was to reduce the experimental data on the elasticity of lung parenchyma to a single mathematical expression. This needed a theoretical basis. A general theory based on the spatial structure of the lung parenchyma was given by Fung. With the constitutive equations of the lung parenchyma verified by experimental results, the fundamental equations describing stress and strain distributions were derived. Solutions which are relevant to the problem of atelectasis (alveoli collapse) were examined. Additional problems of stability of the alveolar structure were considered. Previous to Fung's work, many authors regarded the human lung as a collection of 300 million bubbles independently connected to cylindrical tubes. Under surface tension such a model is inherently unstable in the sense that the small alveoli would empty into the large ones so that the lung would consist only of collapsed and hyper-inflated alveoli. Fung showed that this basic model is wrong and that both sides of each interalveolar septum are exposed to ventilated air. Each interalveolar septum was found to be a minimal surface and there is no problem of inherent instability.

For a complete continuum mechanics analysis of the lung and the airway, it is necessary to know the constitutive equations of all the tissues including lung parenchyma, arteries and veins and their morphometric properties. Hence a vigorous program was pursued to measure the elasticity and morphometery of the pulmonary arteries and veins in collaboration with MRT Yen. At the microvascular level, one fundamental question is the spatial topological structure of the arterioles and venules relative to the capillaries. It was found that each alveolus is not a unit of microcirculation; i.e., it is not supplied by one arteriole and drained by one venule. Instead, the concept of islands of arterioles in an ocean of venules emerged. This led to a morphological definition of average length of capillary blood vessels as a constant multiple of the sum of the radius of the arterial islands and the half width of venous channels.

The morphometric measurements were extended to the collagen and elastin fibers in pulmonary alveolar septa and alveolar mouths. To synthesize the measurements, Fung proposed a geometric theory of the alveolar ducts and their connection to pulmonary capillaries, arterioles and venules. He then studied the blood flow, the transport of water in lung tissue, the formation of edema, and the flow of gas in the airways, alveolar ducts and alveoli. This led the way to the studies of edema caused by impact loads, the shock and mach waves in the lung due to impact on the chest, impact trauma, etc. The shock and trauma of the lung were studied both theoretically and experimentally, leading to a hypothesis of lung trauma which explained why the lung is particularly susceptible to injury. All these were parts of a plan to offer a rational analysis of pulmonary circulation.

Gas flow in the airways is another important aspect of biomechanics of the lung. As problems of aerodynamics, this is a difficult subject. Fung focused on flow separations and forced perturbation of respiratory system and found that flow separation and re-attachment occur several times along the airway, both in inflation and in deflation. Furthermore, calculation of the pressure drop and flow relationship can be very wrong if this flow separation is not taken into account.

Towards the end of Fung's second decade in biomechanics, he made an observation that changed a universally accepted assumption in vessel mechanics. The discovery came about because Fung was dissatisfied with a theoretical result concerning the stress distribution in the blood vessel and left ventricle walls. Previously, every paper pointed to the existence of a stress concentration at the inner wall of the blood vessel and the ventricle, to the extent that the circumferential tension at the inner wall is much higher than that at the outer wall. The stress concentration implied high local energy consumption by the vessel or ventricle; a high oxygen demand at the inner wall. Fung questioned the starting assumption that the unloaded ventricle or blood vessel is at the zero-stress state and indeed found it to be wrong. This brought about the discovery of the zero-stress state of the blood vessel and ventricle which was found to be an open sector. The open sector was quantified by the opening angle. This fact resolved the stress concentration problem at the homeostatic *in vivo* condition and simplified the stress-strain relation.

The biological implications of residual strains and stresses occupied the third decade of Fung's efforts. A systematic search for the variation of the opening angle and residual strains was carried out to identify the rules of the phenomena. It was found that the opening angle is larger when the vessel is curved and thicker. A general rule for regional variation of opening angle was also uncovered. There were many additional explorations for the zero-stress state in various arteries and veins, esophagus, small intestines and trachea of various species. In 1991, Fung received the ALZA Award from the Biomedical Engineering Society in New Orleans where he summarized his discovery and its implications in an elegant lecture entitled "What are the residual stresses doing in our blood vessels?".

The attention was then shifted to the remodeling of pulmonary blood vessels because of the realization that the zero-stress state is the best state in which to study tissue remodeling. In the zero-stress state, any change in structure is exhibited without the effect of deformation. It was found that rapid remodeling of tissues occurs within hours and that the change of opening angle is caused by non-uniform remodeling of the vessel wall. Vascular remodeling of aorta, pulmonary vessels and micro-vessels due to hypertension were also quantified. The effects of cigarette smoking and diabetes on the opening angle were also significant. For example, it was found that diabetes affects the pulmonary arteries to about the same degrees as it affects the aorta. Unfortunately, the diabetic research community did not consider diabetes as a pulmonary disease and the study called attention to this oversight. The remodeling of the zero-stress state in response to physical and chemical stimuli was undertaken by many researchers in the US and abroad. As in the past, Fung's research opened up new paths that others have followed.

When the materials and structure remodel under the influence of changing stress and strain, the elasticity of the tissue also changes. Fung and S.Q. Liu examined the constitutive equation of the arterial wall as it remodels under hypertension, diabetes, and cigarette smoking. On the choice of constitutive law, it is clear that Fung's pseudoelastic exponential strain energy function gives the most concise, general, and accurate representation of the constitutive equations of the blood vessel in the full range of strain from the zero-stress state to the *in vivo* state. The exponential form is widely accepted now; mainly, because it is the only form that is invertible; i.e., to derive analytically the tensorial strain-stress relationship from the stress-strain relationship. To increase the utility of the stress-strain relation, Fung addressed the issue of how nonlinear is the constitutive equation at the *in vivo* homeostatic condition? He introduced the notion of degree of nonlinearity of the *in vivo* state as the fraction of the nonlinear strain energy in the total strain energy.

In the third decade, Fung continued to emphasize that the greatest need lies in the determination of constitutive equations of cells and tissues. Despite the recognition of the significance of stress and strain in gene expression, cell biology, cell adhesion, and cell differentiation and proliferation, we are still unable to determine the internal stresses and strains because we do not know the constitutive equations for the different layers of the blood vessel wall. Most of the past determinations of the constitutive equation have treated the vessel wall as a homogeneous material. In the few studies that considered the layered structure, the wall was physically dissected which invites injury. Fung and his colleagues set out to determine the constitutive relations of the vessels *in vitro* and *in vivo*, without dissection into layers. Fung proposed the use of bending deformation of the wall, which introduces different strains in different layers. The results yielded the location of the neutral axis and the elastic constants of the intima-media and the adventitia layer in the neighborhood of the zero-stress state. The *in vitro* bending experiments were later combined with stretching to measure the various incremental elastic moduli of the two layers. The real challenge, however, remains in *in vivo* measurements. Fung rose to the challenge and formulated a multi-layered shell theory for the blood vessel, and on the theoretical basis proposed a new method of *in vivo* measurements. He showed that six types of *in vivo* experiments are necessary and sufficient to determine the various elastic constants of the two separate layers. The implementation of this theory along with the experiments will take biomechanics to new heights.

Fung's desire to know the internal stresses of a cell put the spotlight on the endothelium. Hundreds of previous studies had imposed shear stress on the endothelium and examined the morphological and biochemical responses of those cells. Fung considered the shear stress imposed by the flowing blood as the loading and examined the resulting tensile stresses in the membrane of the cell. The elegant analysis showed that stress in one cell depends on the stress in other cells and on the geometric shape of the cell junction. Hence, the tensile stress in one cell depends on the cooperative action of all endothelial cells. This led to the intriguing feature of stress transmission between neighboring cells and possible stress accumulation. This elementary analysis gave way to important conclusions about high stress concentration at the branching points of blood vessels which have high predilection to atherosclerosis. Furthermore, the theory recognized the ability of a turbulent flow to turn the mechanism of stress concentration off and on, which causes fluctuation of the cell membrane and cell nucleus. This offered a new way of thinking about the effect of turbulence and branching pattern on the stress distribution in the endothelium of the lung, and the associated phenomena of thrombus formation, inflammation, leukocytes activation, or cancer cell adhesion. Furthermore, the fact that high uniaxial tensile stress exists in the cell membrane in response to the shear load called attention to the stress-sensitive ion channels in the cell membrane. The study won the "Best Paper published in 1993 in an ASME Journal Award" and the Melville Medal in 1994. Once again, the biomechanics community reaped the fruits of Fung's approach.

The remodeling of biological tissue in response to changes in physical stress and strain is a very complex process. In order to understand such a complex process, Fung promoted the engineering approach: 1) vary one parameter at a time and 2) if possible, vary the input parameter as a step function. As always, Fung insists on the simplicity of experiments, varying one variable which is regarded as the *cause* (e.g., pressure or flow), and monitor others as the *effect* (e.g., geometry, mechanical properties, zero-stress state, gene expression, etc.). The blood vessel is considered as a black box and the transfer function of various parameters is sought through the determination of indicial functions; i.e., change of *effect* per change of *cause*. The significance of the indicial function is that when it is applicable (i.e., when *cause* and *effect* are linearly related) it greatly simplifies the interpretation of data and greatly enlarges the implications and applications of the data to physiology and medicine. It affords the power of prediction and forecast through a convolution process. This approach establishes a quantitative basis for vessel remodeling and forms a sound basis for *Tissue Engineering*; a term coined by Fung in 1987.

In the fourth decade, Fung continues to focus on tissue remodeling. Since changes in blood pressure and consequently stress and strain are important stimuli for vascular remodeling, Fung sought a more precise way of characterizing the pressure wave. In collaboration with N. Huang, he used the intrinsic mode functions (IMF) method to characterize the blood pressure. The IMF method was shown to have many advantages in handling nonstationary, stochastic signals. This method is superior to Fourier and wavelet analysis which cannot always account for the nonlinear subharmonics and introduce artifacts because of the assumption of stationary random oscillations.

In recent years, Fung has embarked on studies to correlate a wide range of genes with blood vessel remodeling. Fung and W. Huang measured the gene activities of pulmonary arterial wall and determined the indicial functions of gene expression. The correlation coefficients between the indicial functions of various structural and mechanical parameters and gene expression were calculated to quantitatively assess the genes that are most relevant to physiology. This is a powerful method that connects gene expression to changes in cell, tissue and organ processes. This research will undoubtedly impact gene therapy, drug discovery and human health.

It is clear that Fung has established biomechanics as a discipline with its own approach and methodology. He has outlined the philosophy and methodology through numerous perspective articles and throughout his books. Fung's philosophy is that there are four basic prerequisites to the solution of any problem in biomechanics 1) the geometry of the system, 2) the materials of the system and their mechanical properties, 3) the basic laws governing the system, and 4) the boundary conditions. The first leads to anatomical, morphological and histological studies. The second leads to the study of chemistry and constitutive equations. The third is a philosophical issue that depends on the number of assumptions invoked. The ideal approach is to minimize the number of ad hoc assumptions and to allow only the most basic principles as axioms: Newton's law of motion, the principles of conservation of mass, momentum, and energy, and the second law of thermodynamics. The final requirement of boundary conditions depends on the specific problem at hand. It is easy to see the threads of this philosophy weaved throughout the four remarkable decades.

Fung's contributions to biomechanics have been recognized by his peers, community, nation and the world. He has received numerous awards and honors including the Theodore von Karman Medal (American Society of Civil Engineers), Lissner Award for Bioengineering (American Society of Mechanical Engineers), Poiseuille Medial (International Society of Biorheology), Timoshenko Medal (American Society of Mechanical Engineers), Borelli Award (American Society of Biomechanics), and many others. Most notably, he is a member of National Academy of Engineering, senior member of Institute of Medicine and Member of United States National Academy of Science. The elected membership to the three national academies is a distinction held by only a hand full of people in the world. Dr. Fung is also the recipient of the U.S. National Medal of Science, 2000. Fung's career is truly remarkable by any standard.

Although this dedication is intended to focus on Fung's scientific contributions to biomechanics, it is tempting to say a thing or two about the person. It is well known that Fung has profoundly influenced many lives in the biomechanics community. I am no exception. I am very fortunate to have been one of his last students who also collaborated with him for a decade thereafter. He shaped my thinking and humbled my soul. To those that don't know him, I would describe Fung as a genius with a warm heart and a wise soul. The remarks made by the late Professor Sidney Sobin (1914-2001), one of his dearest friends and longtime collaborator, on Fung's 65^{th} birthday in 1984 are most befitting:

How can one capture on a page the essence of an individual – the effervescence, vitality, laugh and spontaneity, that counterpoise with intellectuality, interspection, intuition, creativity, and so much more, yet cloaked with nobility, humanness, humility, generosity and integrity, that provides inspiration to so many, and even awe at the accomplishments. On a sideglance it is noted that while still an aerodynamicist, on a Guggenheim Fellowship and long before he knew living biologist as colleagues, he consumed a heavy tome on physiology. His unbound curiosity on the nature of things has a firm basis in the mathematical, physical and now biological disciplines. He has played a key role in the development of many careers. We can describe the man who has become a legend in his own time: ***Yuan-Cheng B. Fung***.

Dr. Sobin eloquently describes the man that is considered the "Father of Modern Biomechanics". Dr. Fung earned this distinction for his numerous seminal contributions to the field and for nurturing so many of us along the way.

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