Warmest Congratulations to Dr. Yuan-Cheng Fung at His Centennial Celebration

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Abstract: Professor Y.C. Fung has made tremendous impacts on science, engineering and humanity through his research and its applications, by setting the highest standards, through educating many students and their students, and providing his exemplary leadership. He has applied his profound knowledge and elegant analytical methods to the study of biomedical problems with rigor and excellence. He established the foundations of biomechanics in living tissues and organs. Through his vision of the power of "making models" to explain and predict biological phenomena, Dr. Fung opened up new vista for bioengineering, from organs-systems to molecules-genes, and has provided the foundation of research activities in many institutions in the United States and the world. He has made outstanding contributions to education in bioengineering, service to professional organizations, and translation to industry and clinical medicine. He is widely recognized as the Father of Biomechanics and the leading Bioengineer in the world. His extraordinary achievements and commands in science, engineering and the arts make him a Renaissance Man for the world.

Keywords: Blood vessels; pulmonary circulation; remodeling; residual stress; tissue engineering

Dr. Fung is the Father of Biomechanics. He created the field by combining his outstanding expertise in engineering mechanics with his innovative work in biomedical sciences and their applications. His contributions are so immense that it is not possible to cover them in a short article. This article is based on the one that I wrote for the "International Symposium on Genomic Biomechanics: frontier of the 21st Century" in celebration of the 90th birthday of Professor Yuan-Cheng "Bert" Fung that was published in 2009 [1]. A similar paper will be published in another celebration of Dr. Fung's 100th birthday [2]. Most of Dr. Fung's publications have been collected in a two-volume treatise entitled "*Selected Works on Biomechanics and Aeroelasticity*" [3], which provides a wonderful reference resource for his superb scientific contributions.

Dr. Fung's Early Life in China

Dr. Fung was born on September 15, 1919, in Yuhong, Wutzin, Jiangsu, China. He received his college education at the Central University, which is a top university in China that had moved from the capitol in Nanjing to the temporary capitol of Chongqing following the beginning of the Sino-Japanese war in 1937. Dr. Fung received his B.S. (1941) and M.S. (1943) in Aeronautics there, graduating at the top of his classes. While he was studying for his M.S. degree, He also taught as an Instructor at the Ta-Kung Technical School in Shapingpa, Chongqing. Dr. Fung worked as a Research Fellow at the Bureau of Aeronautical Research in Chengdu from 1943 to 1945, when he came to the United States to pursue his graduate study at California Institute of Technology (CalTech). Although Dr. Fung has been in the United

States for over seventy years and is a most patriotic American, he always feels a strong tie to his motherland and has devoted tremendous amounts of time and energy to advance research and education in China. He played a major role in the birth of biomechanics and biomedical engineering in China. He trained the Chinese scientists to become leaders in the field, as well as giving lectures and organizing meetings (such as the China-Japan-US Conference on Biomechanics that he initiated) in China.

Dr. Fung at CalTech

Dr. Fung won a highly competitive scholarship in 1945 and came to Pasadena to pursue his Ph.D. study in CalTech following a long boat trip via India. Because of miscommunications during the wartime (World War II), he learned upon his arrival at CalTech in January 1946 that the scholarship he had earned was no longer available. However, he was able to get support from his advisor, Dr. Ernst Sechler. In less than three years, Dr. Fung completed his Ph.D. study (Summa Cum Laude) in Aeronautics and Mathematics in 1948. After graduation, he stayed in the Department of Aeronautics at CalTech as a Research Fellow, advanced through the ranks of Assistant and Associate Professors, and became a Full Professor in 1959. Dr. Fung's research in Aeronautics at CalTech focused on the dynamics of airplanes in turbulent weather, and on safety, performance and design of aircraft and spaceship. He wrote a definitive textbook on *Aeroelasticity* [4]. Because of his outstanding accomplishments, he was extremely well respected in the field of aeronautical and aerospace engineering.

Because his mother was suffering from glaucoma, Dr. Fung became interested in the mechanics of the eye in the late 1950s. He was convinced that understanding of the human functions could be improved by analyzing forces, motion and stress and strain in the human body. In 1966, he organized a landmark symposium and published a book on Biomechanics [5]. He advanced the viewpoint that if scientists can determine the structure and mechanical properties of a living organ, then by the principles of physics, they can predict the functions of that organ.

Dr. Fung's Move to UCSD

In 1966, Dr. Fung visited Dr. P. F. Scholander at the Scripps Institution of Oceanography of UCSD, together with Dr. Benjamin Zweifach, who was on a sabbatical leave at CalTech from New York University. Dr. Sol Penner, then Chair of the Department of AMES (Aeronautical Mechanics and Engineering Science), wanted to initiate a program of Bioengineering at UCSD. This matched perfectly with Dr. Fung's emerging interest in bioengineering. Following Dr. Penner's recommendation, UCSD invited Drs. Fung and Zweifach to start a new Bioengineering Program. This new initiative developed rapidly into an outstanding program with biomechanics and microcirculation as the central themes. In the 1980s, Dr. Fung coined the term "tissue engineering" as a new direction for bioengineering. This not only has developed into a new integrative research theme at UCSD Bioengineering, but also has become the focus of bioengineering efforts in many programs in the world. These two disciplines-biomechanics and tissue engineering-have been two major thrusts in bioengineering.

In his studies on biomechanics and mechanobiology, Dr. Fung integrates biology and mechanics at multi-scales, from organs to genomics. He correlates structure and function in terms of remodeling, geometry, and growth, with emphases on temporal and spatial features and active *vs.* passive responses. He combines experiments (with innovative technology and rigorous execution) and theory (with creative formulation and elegant analysis), and makes effective iteration and feedback between them. Dr. Fung established the foundation of biomechanics in a variety of organs and tissues, including the lungs, heart, blood vessels, skin, as well as other organs and tissues. His groundbreaking studies on tissue remodeling under stress provide the foundation of tissue engineering and regenerative medicine.

Residual Stress in Biomechanics

Dr. Fung has numerous accomplishments in biomechanics. One of his very fundamental and innovative contributions is his research on residual stress, which is the stress that remains after the removal of external forces. He developed the ingenious approach by determining the residual stress from the opening angle after cutting open a biological structure in two different directions. An example is shown in Fig. 1 for an aorta that have been removed and hence without pressure load; a ring is first obtained by cross cuts, and this ring is then cut open in the radial direction to result in a zero stress state [6]. The opening angle provides a measure of the residual stress in the vessel wall due to the geometry and wall constituents. It is truly amazing that such an important parameter in biomechanics can be measured with such a simple experimental procedure, requiring only a pair of scissors. Fig. 2 shows that the ileal artery and ileal vein have strikingly different residual stress as shown by their opening angles [7]. This opening angle measurement has also been applied to the heart ventricles [8], trachea [9], and other organs and tissues.

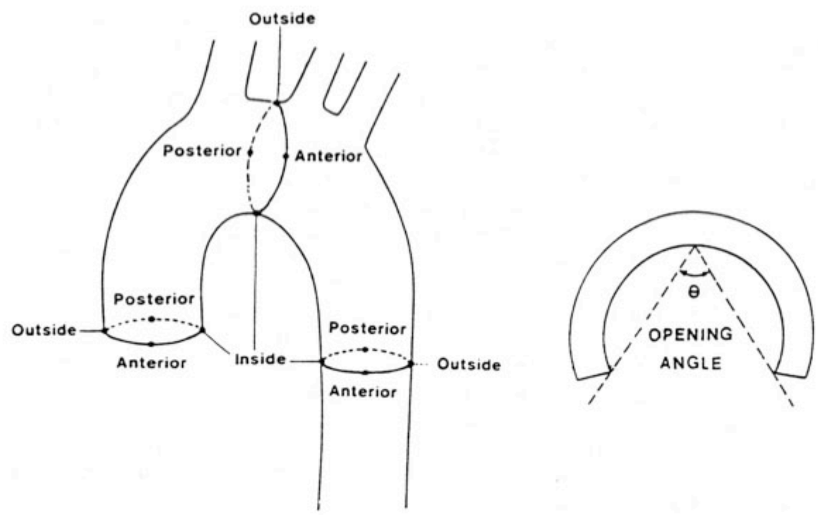

Figure 1: Left: Sketch of an aorta with an indication of the cutting positions. Right: Schematic cross-section of a cut vessel segment at zero-stress, defining the opening angle. From [6]

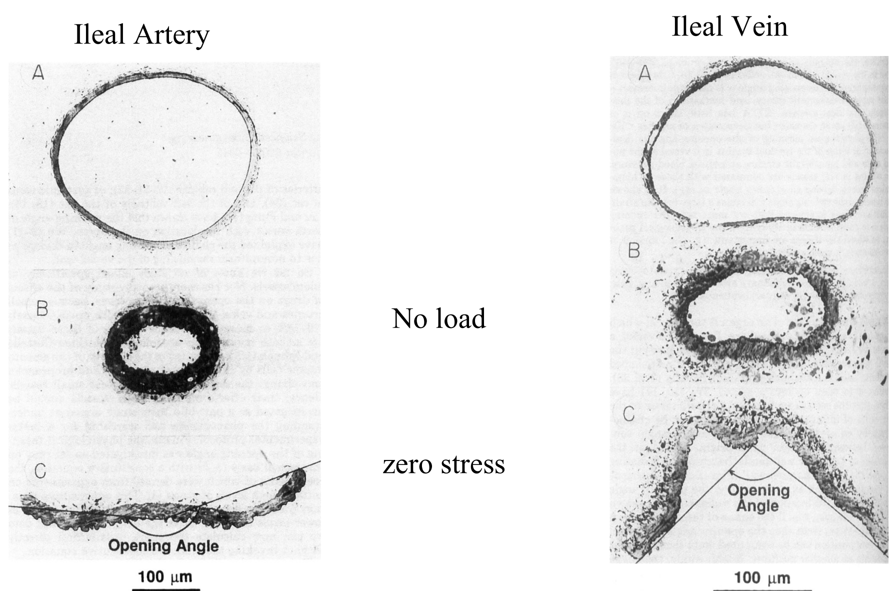

Figure 2: Differences in residual stress of an ileal artery (left) and an ileal vein (right) as reflected by their opening angles. From [7]

With a combination of experimental and theoretical approaches, Dr. Fung has determined the 3-D stress distribution in an artery [10]. He has also determined the stress-strain relations of collagen and elastin [11,12], which are the interstitial constituents of the vessel wall (Fig. 3), thus elucidating the relationship of the biomechanical behavior of a blood vessel to that of its molecular constituents and establishing an important step in multi-scale and integrative bioengineering.

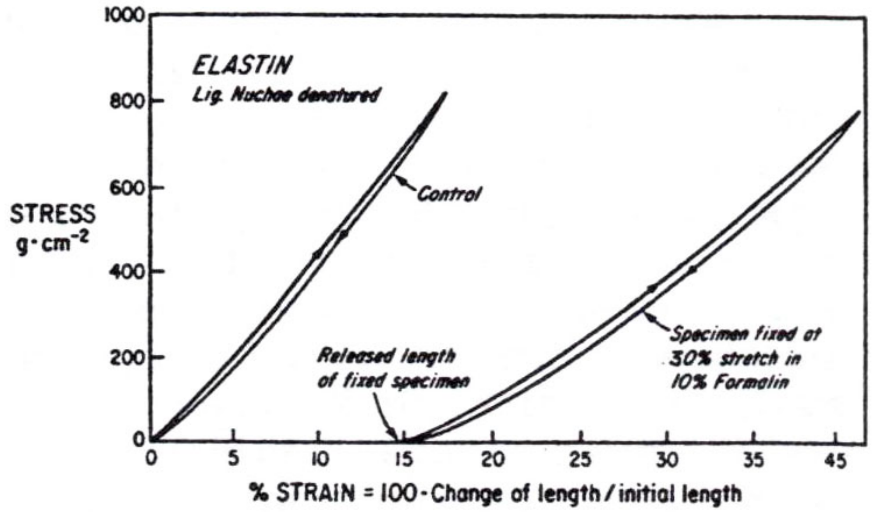

Figure 3: Stress-strain relationship of elastin from a ligament under control state and after fixation at 10% stretch in 10% formalin. From [11,12]

Biomechanics of Pulmonary Microcirculation: Coupling of Circulation and Respiration

Dr. Fung has made outstanding contributions on the joining of circulatory and respiratory systems at the microvascular level. In his pioneering work with Dr. Sidney Sobin and other colleagues [13,14], the innovative concept of sheet flow through the pulmonary capillaries between the posts spanning sheets of alveolar wall (Fig. 4) was formulated with rigorous experiments and elegant analysis. The sheet-flow theory has been used to compute the alveolar sheet thickness and hence the alveolar sheet flow as a function of the capillary-alveolar pressure differential (Fig. 5) [15]. Application of this theory to experimental data provides a quantitative understanding of the interplay among many factors, including alveolar blood flow and blood volume, as well as their regional differences and transit time distributions. These results allowed the understanding of the effects of arterial, alveolar and venous pressures, alveolar area, mean A-V path length, and alveolar membrane tension on alveolar flow dynamics [16]. Their findings opened up a new paradigm for research on the pulmonary microcirculation in health and disease. Dr. Fung applied morphometric technique to study the topographical arrangement of arterioles and venules in the cat lung [17], and generated novel findings on the distribution pattern of these two types of pulmonary microvessels (Fig. 6). The results indicate that, on the average, each terminal precapillary arteriole supplies 24.5 alveoli, and that each terminal postcapillary venule drains 17.8 alveoli.

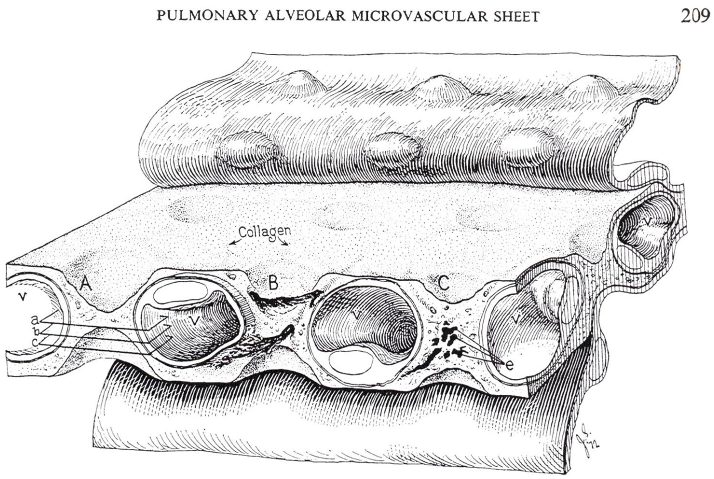

Figure 4: Schematic drawing of a pulmonary alveolar microvascular sheet. From [13]

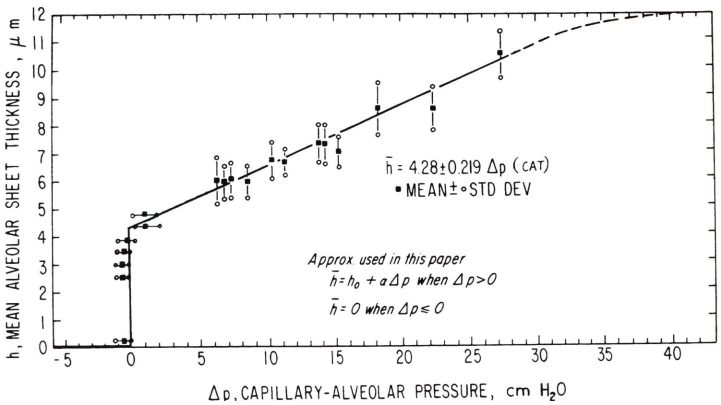

Figure 5: Mean alveolar sheet thickness as a function of capillary-alveolar pressure difference. From [15]

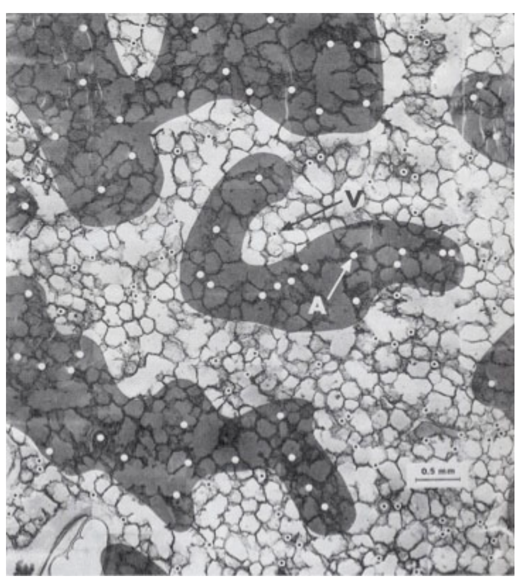

Figure 6: A montage of photomicrographs of a cat lung. Branches of pulmonary blood vessels which are not capillaries and have diameters less than 100 mm are individually identified. Arteries are marked with white dots; veins by black dots. A darker transparency covers the arterial regions. From [17]

Biomechanics of Blood Cells

Dr. Fung has used elegant engineering analysis to investigate the mechanics and geometry of human red blood cells (RBCs), including stress analysis in RBC swelling [18], determination of RBC 3D geometry by interference microscopy (Fig. 7) [19], and the use of extreme theorem to analyze the extreme value statistics of RBC geometry [20]. At the time of these important studies conducted by Dr. Fung, my main area of interest was the mechanism of RBC deformability in relation to blood rheology, and I benefited immensely from his groundbreaking studies and valuable advice.

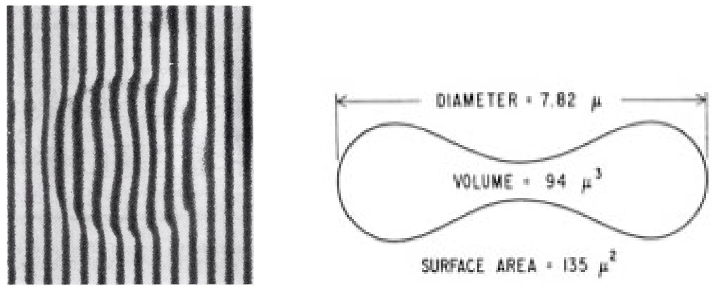

Figure 7: Determination of RBC 3D geometry by interference microscopy. Left: Holographical picture of a human RBC. Right: the geometric dimensions of a biconcave discoid human RBC determined by using the interference microscope. From [19]

Dr. Fung extended his studies on blood cells to their behavior in blood vessels, especially at branch points. He elucidated the mechanism of stochastic nature of flow in capillaries by experimental studies and engineering analysis, showing that a small difference in flow partitioning between two daughter branches at a bifurcation can have a dramatic nonlinear effect on blood cell distribution [21] (Fig. 8). He used a lab model system to demonstrate the important role of RBCs in modulating the interaction of white blood cells with the vascular endothelium [22]. He showed how high RBC concentration can push the WBCs toward the vessel wall and enhance WBC-endothelial interactions. These findings have important implications in the role of hemodynamics in WBC behavior in the microcirculation in health and disease, including inflammation. Dr. Fung has computed the blood flow pattern in vessels beyond a local constriction [23]. The complex flow behavior in such regions, including flow reversal, reattachment and stagnation (Fig. 9), has been shown to have major effects on endothelial structure and function in the post-stenotic region as well as branch points, thus playing a significant role in atherogenesis.

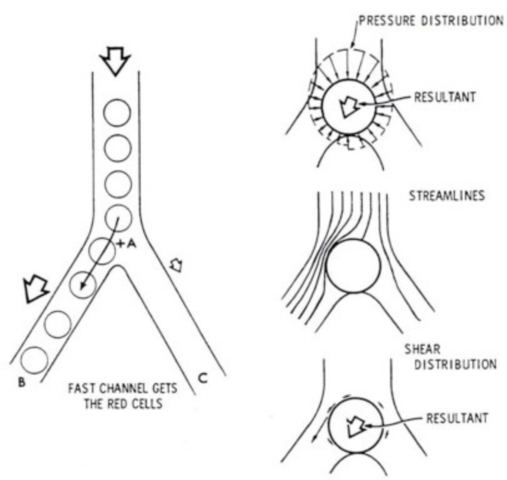

Figure 8: Stochastic nature of flow in a capillary branch point. The distributions of pressure and shear determine the streamlines, which cause the preferential entry of the blood cells into the branch with high flow, leading to unequal distribution of cells in the daughter branches. From [21]

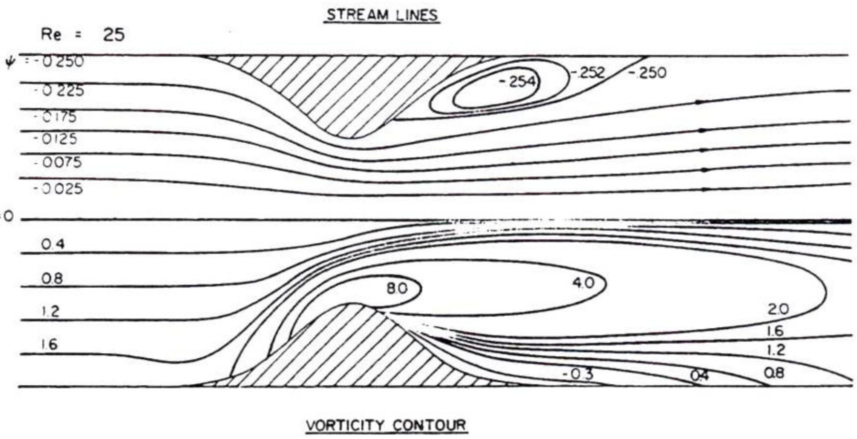

Figure 9: Computation of streamlines in flow beyond a narrow constriction. From [23]

Cardiovascular Remodeling

Dr. Fung applied mophormetric analysis to determine the geometric features of the coronary artery circulation in the pig right ventricle under normal condition and in hypertensive state [24]. These results have generated important information on coronary artery remodeling in cardiac hypertrophy.

As a result of his pioneering work on residual stress and remodeling, Dr. Fung formulated the concept that the remodeling of a blood vessel is best described by changes of its zero-stress state and that growth results from changes in cellular and extracellular mass and configuration (Fig. 10) [25]. These concepts have led to his proposal of specific ways to test the biomechanical properties of a tissue-engineered vascular graft in order to match the hemodynamic conditions it encounters *in vivo*.

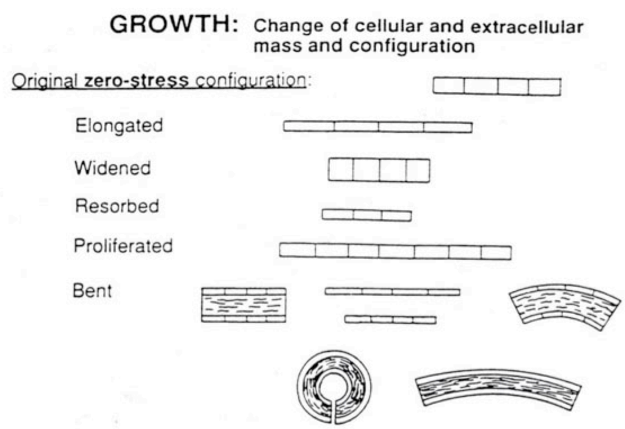

Figure 10: Diagrammatic illustration that the remodeling of a blood vessel is best described by change of its zero-stress state, which results from changes in cellular and extracellular mass and configurations, as depicted in these drawings. Redrawn from [25]

Genetic Basis of Pulmonary Artery Remodeling in Hypertension

Dr. Fung has made a systematic study on the time course of the remodeling of the pulmonary artery of normal and hypertensive rats in response to hypoxia (Fig. 11) [26]. With the advent of molecular and genomic approaches to investigate biological problems, he studied the changes in gene expression under such hypoxia-induced pulmonary hypertension by using the DNA microarray technology [27]. He was able to match the time course of changes in the expression of a variety of genes with the alterations of specific structure and functions in the pulmonary artery, as exemplified in Fig. 12. This important study provides a genetic correlate of functional abnormalities in pulmonary hypertension. Based on these and other findings, Dr. Fung proposed that "DNA Replication and transcription involve molecular motion through a viscous medium to reach the appropriate site, and the lengthening takes place through the balance between the chemical energy of binding and the kinetic energy of molecular motion. Therefore, these processes involve accelerations, strains and strain rates with directions. They need to be treated as force vectors and stress tensor".

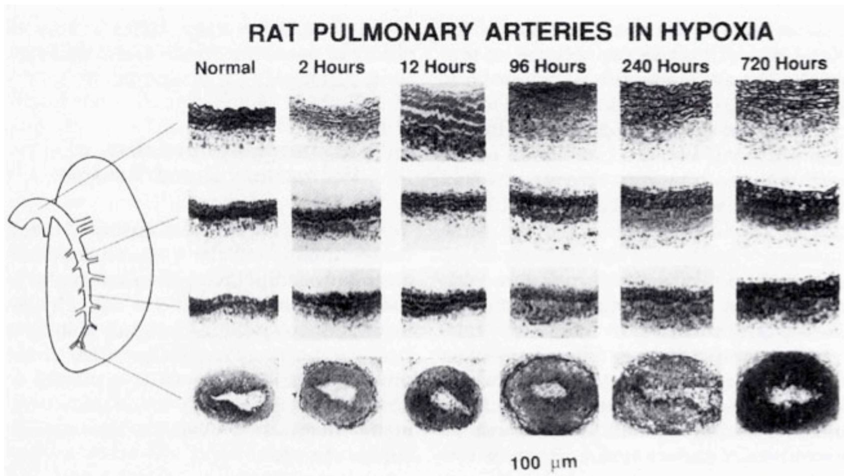

Figure 11: Photographs of histological slides from four regions of the main pulmonary artery of a normal rat and hypertensive rats with different periods of hypoxia from 2 to 720 hours. From [26]

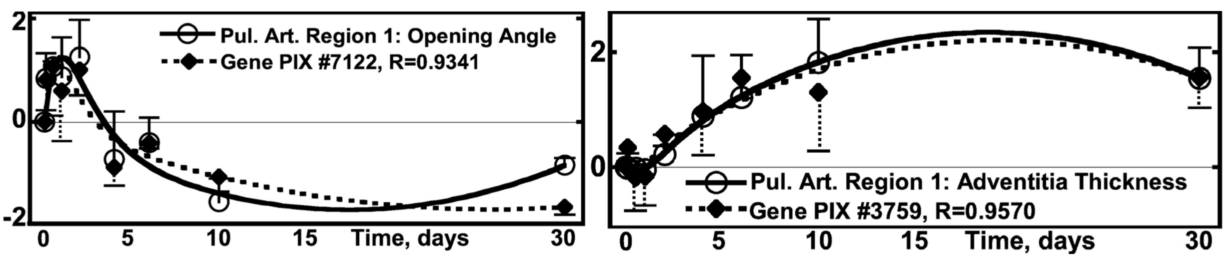

Figure 12: Matching of gene activities, as determined by microarray analysis, and physiological functions and structure of the pulmonary artery obtained after different periods of hypoxia. Note the high levels of correlation between the opening angle of region 1 of pulmonary artery with gene Pix #7122 and between the adventitial thickness of region 1 of pulmonary artery with gene Pix #3759. Similar high levels of correlation were obtained for other functional/structural parameters and other genes. From [27]

Development of Instrumentation for Biomechanics

Dr. Fung's ability to solve complex bioengineering problems is accompanied by his innovation in designing sophisticated instrumentation to meet the experimental needs. Examples are the development of the innovative device "Biodyne" [28] for testing the mechanical properties of a variety of biological materials (Fig. 13) and the instrumentation to study the biomechanics of the skin [29], peristaltic transport [30], peeling force in a biological graft [31], as well as other ingenious instruments designed in cooperation with the late Gene Mead and other colleagues. These instruments allowed the performance of innovative experiments on the biomechanical properties of the skin and the adhesive strength of biological grafts; these findings have important bearing on the translational studies on the development of skin graft for clinical application in burns and other disorders. The instrument for the investigation of peristaltic transport led to the elucidation of the biomechanics of this process in the ureter [30], intestine [32] and other organs.

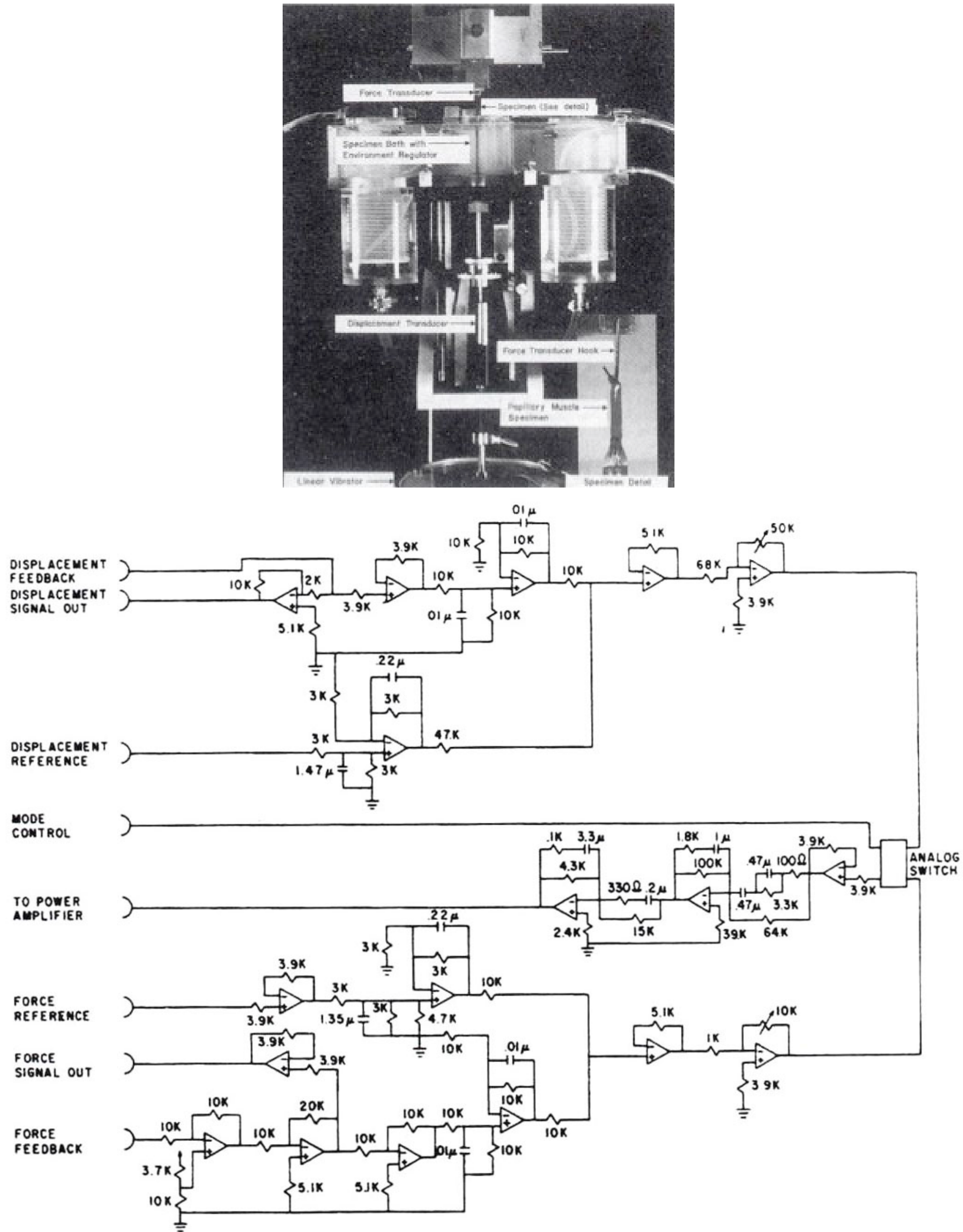

Figure 13: A device for testing of mechanical properties of biological materials: the "Biodyne". From [28]

Translation of Biomechanics to Industry and Clinical Medicine

Dr. Fung's superb research accomplishments have major impacts in opening new areas and laying the foundation for important translational application to industry and clinical medicine. Dr. Fung was a consultant for many industrial firms when he was in the field of Aeronautics. His research has formed the foundation of industrial applications in a variety of bioengineering fields, including the tissue engineering of cardiovascular, urinary, musculoskeletal, and cutaneous systems. His studies on the biomechanics of the skin contributed importantly to the development of skin substitutes to treat burn patients. He has contributed to the development of tissue-engineered vascular graft with mechanical matching to the native vessels. His research contributes to the advancement of diagnosis and treatment of a variety of important diseases, including pulmonary disorders such as pulmonary hypertension and emphysema, cardiovascular diseases such as myocardial infarction, heart failure, atherosclerosis, and systematic hypertension, dysmotility of the digestive and urinary systems, musculoskeletal disorders, burns, and many others.

Contributions to Education

Dr. Fung has made outstanding contributions to bioengineering education as well as research. He built the superb graduate and undergraduate programs at UCSD, which have educated graduates who have made important contributions to bioengineering endeavors in academic bioengineering, medical schools, hospitals and industry. A large number of his Ph.D. students and postdoctoral fellows hold key faculty positions in universities in the United States and abroad, and many are heads of departments of bioengineering. In the most recent National Academy of Sciences-National Research Council survey of graduate education published in 2010, UCSD Bioengineering was ranked number 1 in graduate education. This is largely attributable to Professor Fung's vision and leadership.

Dr. Fung's educational influence extends beyond his teaching in the classrooms and laboratories at UCSD. He defined the pedagogy of biomechanics by writing several authoritative books [e.g., [25,33,34] that are widely used as textbooks in this country and abroad and are read by virtually everyone in the field. These books have been translated into many foreign languages and updated in several editions, setting the standard for all textbooks in bioengineering. His great contributions to education and training in China were mentioned in the early part of this article. He played a major role in the birth of biomechanics and biomedical engineering in China by training the leaders, giving lectures, and organizing meetings there (such as the China-Japan-US Conference on Biomechanics that he initiated).

Dr. Fung is strongly devoted to the education of the younger generation. This is well illustrated by my personal experience as an Assistant Professor at Columbia attending the Microcirculatory Society (MCS) meeting in Atlantic City in 1965. When I went to a restaurant for dinner with my wife and two daughters, Dr. Fung was at a neighboring table with members of MCS Council. He came over to our table and sat down to chat (Fig. 14) for nearly an hour until the MCS Council members and we all left. At that time, I had met Dr. Fung only once very briefly. His kindness to spend time with young people was really impressive and greatly appreciated. I still remember vividly that wonderful experience more than fifty years later.

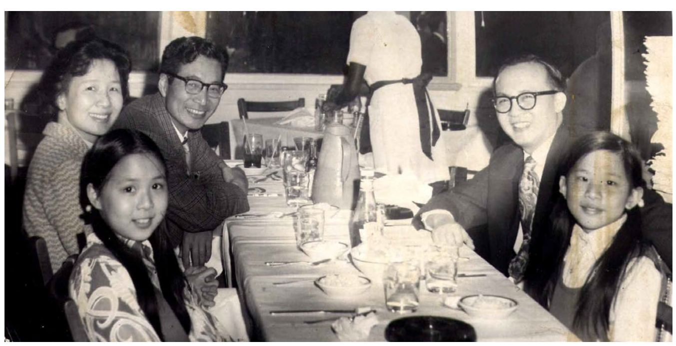

Figure 14: Dinner at Captain Stern's restaurant, Atlantic City, NJ. April 16, 1965. From back to front: Left: Professor Fung, K.C. Chien, May Chien, Right: Shu Chien, Ann Chien

Services to Professional Organizations

Dr. Fung has devoted himself to the advancement of Bioengineering by serving in many key positions in professional organizations. He was President of the American Academy of Mechanics and Biomedical Engineering Society (BMES), Vice President of the International Society of Biorheology, and Chairmen of the Third International Congress of Biorheology, the Second World Congress of Microcirculation, and the First China-Japan-USA Conference on Biomechanics. He was also Chairman of the Applied Mechanics Division in the American Society of Mechanical Engineers (ASME), U.S. National Committee for Biomechanics (now Honorary Chairman), and World Council for Biomechanics (now Honorary Chair). Dr. Fung has been a member of Microcirculatory Society Council, American Physiological Society Council of Circulation, American Heart Association Council on Basic Science, and World Congress of Biomechanics Steering Committee.

Awards and Honors

Dr. Fung's outstanding contributions to research and education in bioengineering are broadly recognized. He is a member of all three U.S. National Academies (National Academy of Sciences, National Academy of Engineering, and Institute of Medicine), as well as a Foreign Member of the Chinese Academy of Sciences and a member of Academia Sinica (Taiwan).

Dr. Fung has received all the major awards in his fields of endeavor, including the Eugene Landis Award from Microcirculatory Society (1975), the Theodore von Kármán Medal from American Society of Civil Engineers (1976), Lissner Award for Bioengineering from ASME (1978), Centennial Medal from ASME (1981), Worcester Reed Warner Medal from ASME (1984), Poiseuille Medal from International Society of Biorheology (1986), Excellence in Research Award from UCSD (1987), ALZA Award from BMES (1989), Timonshenko Medal from ASME (1991), Borelli Award from American Society of Biomechanics (1992), the Lifetime Achievement Award from the Association of Chinese Scientists and Engineers of California (1992), Distinguished Alumnus Award from California Institute of Technology (1994), Melville Medal from ASME (1994), Bioengineering Award from the Japan Society of Mechanical Engineering (1995).

Dr. Fung has received three of the most prestigious awards: In 1998, he received the Founders Award, which is the highest honor given annually by the NAE to recognize "outstanding engineering accomplishments by an engineer over a long period of time and of benefit to the people of the United States". In 2001, he received from President Clinton the United States National Medal of Science (Fig. 15), which is given to individuals "deserving of special recognition by reason of their outstanding contributions to knowledge in the physical, biological, mathematical or engineering sciences"; he is the first bioengineer to receive this prestigious honor. In 2007, he received the Russ Prize, which is awarded by the NAE "biennially to a researcher whose achievements are of critical importance in advancing science and engineering, ultimately improving the human condition".

Figure 15: Professor Fung receiving the U.S. National Medal of Science from President Bill Clinton in 2001. From left: President Clinton, Mrs. Fung, Professor Fung

Dr. Fung is a Fellow of the American Academy of Mechanics, American Institute of Aeronautics and Astronautics, ASME, American Institute of Medical and Biological Engineering, and Cardiovascular Section of the American Physiological Society. Dr. Fung is the recipient of Honorary Doctoral degrees and Honorary Professorships from many universities in China (including Hong Kong) and U.S.A. He has been invited to give many named lectures and plenary lectures, and he is an Honorary Member of several scientific organizations.

In honor of Dr. Fung, the ASME established the "Y.C. Fung Young Investigator Award" in 1986, the Chinese Association of Biorheology and Chinese Society of Biophysics, with funding from the International Society of Biorheology and the International Society of Clinical Hematology, established the Fung-Chien Young Investigators Award, and UCSD established the Endowed Chair "Y.C. Fung Professor of Bioengineering" (Fig. 16).

Figure 16: Professor and Mrs. Fung and Shu and K.C. Chien at the ceremony celebrating the Y.C. Fung Chair Professorship at UCSD on September 15, 2006

Dr. Y.C. Fung as a Renaissance Man

Dr. Fung and his lovely wife Luna Hsien-Shih Yu married in Pasadena, California, in December 1949 (Fig. 17). Luna is an excellent mathematician with BS from Central University in China and MS from CalTech. They have two wonderful children Conrad and Brenda. After 68 years of a marvelous marriage, Luna unfortunately passed away in April 2017.

Figure 17: Cake cutting during the wedding of Professor and Mrs. Fung, 1949

Conrad has two sons Anthony (Tony) and Michael, and Brenda has a son Nicholas Manos (Fig. 18). Tony finished his undergraduate study in Bioengineering at UCSD and is now enrolled in the graduate program. I have the pleasure of having him as a Teaching Assistant in the Introduction to Bioengineering course. He is intelligent, knowledgeable, creative, dedicated, and caring for the students, following the tradition of his grandfather. Michael is studying Neuroscience at Vanderbilt University and will apply for medical school next year. He is an avid opera singer and will sing in the Vanderbilt chorale in Prague this summer. Nick graduated from USC majoring in marketing. He lives in Long Beach with his wife Claire.

Figure 18: The Fung family in their La Jolla home in November 2014. Seated from left: Nick Manos, Luna and Y.C. Fung, Michael Fung. Standing from left: Tony Fung, Brenda Fung Manos and Conrad Fung

Dr. Fung enjoys being with long-time friends (Fig. 19) and with young people (Fig. 20).

Figure 19: A good laugh with friends: Seated (from left): Mrs. Shirley Yih, Mrs. Luna Fung, Mrs. Ching-hua Wu, Ms. Hsien-Tzai Yu, and Mrs. Zhe-Ming Zheng. Standing (from left): Drs. Zhe-Ming Zheng, Chia-Shun Yih, Theodore Wu, and Y.C. Fung

Figure 20: Professors Fung and Schmid-Schönbein with Bioengineering students (2016)

Dr. Fung is not only a superb scientist and engineer, but also a wonderful artist. He has excellent commands in Chinese calligraphy and poetry. He has marvelous talents in making Chinese chops (or seals, for people's names); the imprints of these can be found in the front pages of many of his books. Thus, Dr. Fung excels in Science, Engineering, and Art. He is a renaissance man, a peer of Leonardo DaVinci (Fig. 21).

Yuan-cheng Fung

A Renaissance Man

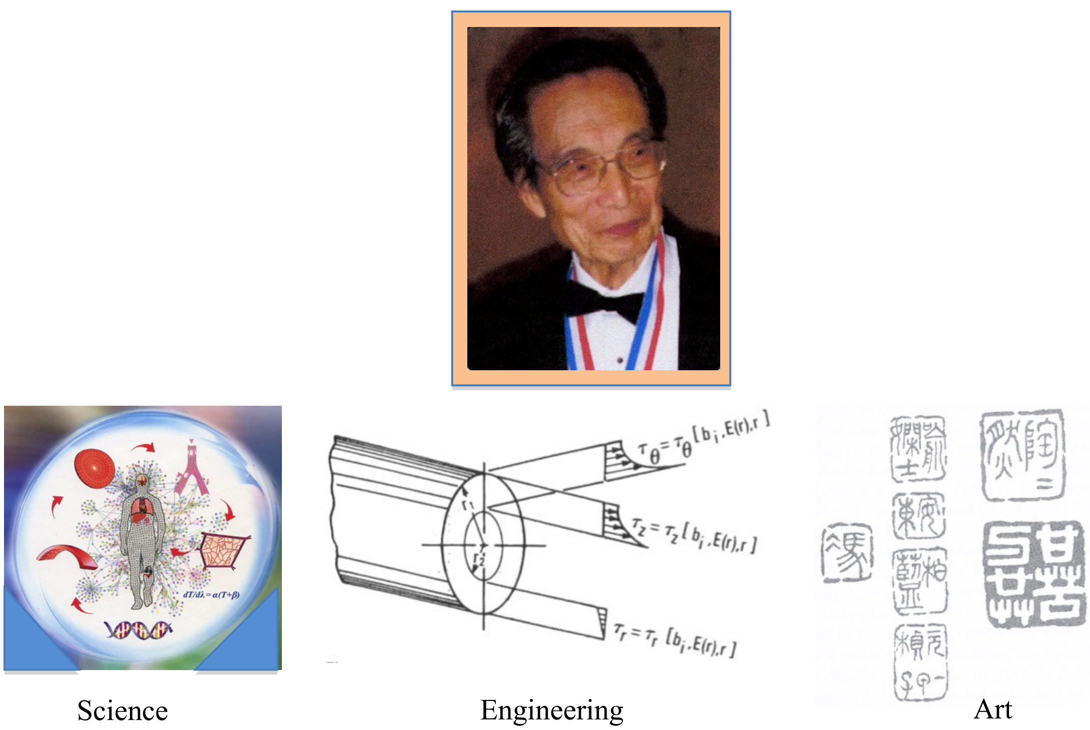

Figure 21: Professor Yuan-cheng Fung, the Renaissance Man who excels in science, engineering and art. From [1]

Congratulatory Note

Dear Bert, on this marvelous occasion of your 100th Birthday, K.C. and I would like to express our warmest congratulations and best wishes for your Best Health and a Happiest Birthday; Many, Many Happy Returns.

Acknowledgement: The author thanks the World Scientific Publishing, Co., Pte., 352 Ltd, Singapore, for giving the permission to use the materials presented in [1].

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