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COLLEGE IN BIOPHYSICS: EXPERIMENTAL AND THEORETICAL ASPECTS OF BIOMOLECULES

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What is Biophysics?

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I- WHAT IS BIOPHYSICS?

The most important phenomenon in Nature for us, is Life. It is also very complex and in order to understand life and living processes several branches of science are needed. Biophysics uses biological and physical concepts for the study of life.

One of the greatest physicists of our century, Erwin Schroedinger wrote a beautiful little book which he named What is Life? (see reference).

Though this book is now outdated it can be read with benefit by the modern scientist.

Not only physics but especially biochemistry are essential to answer the question . So today, Biophysics is understood as a broad interdisciplinary area encompassing biology, physics, biochemistry, mathematical and computational modeling among many others. It is thus a very rich part of modern science with tremendous opportunities for basic and applied research. In the past century, physicists occasionally used models, theories and techniques to describe biology and life sciences. On the other hand, biologists, physicians, pharmacologists and other life scientists, rarely looked for physical concepts and instrumentation to help solve their problems. Until the mid-twentieth century biology has been largely a descriptive field.It is only in the last half of this century that this gave way to a more complete, integrated approach, in which we talk about biophysics as an independent branch of science. This in turn resulted in new courses for the education and training of biophysicists at the undergraduate, graduate and post-doctoral levels. Today if you want to become a biophysicist you can find opportunities in numerous research institutions. The Biophysical Society in the US was founded in 195?; several journals publish articles primarily related to biophysics and annual congresses on biophysics are held in many countries with international biophysics congresses every few years. Each year there are symposia dedicated to various subfields of biophysics. Biophysics, like most scientific disciplines, has numerous subfields. This can be understood if we observe that living organisms have a huge range of sizes from viruses to whales to giant sequoia trees. Living species exist in ecosystems as small as a bacterial colony to as large as the Amazon tropical forest. All of these systems follow the laws of nature. Physics, chemistry and mathematics are needed to describe and understand living things in a quantitative way. It should not be surprising that a broad field like biophysics touches many other fields, such as genetics, genetic engineering, biochemistry, medical applications of physics,etc.

MODERN MOLECULAR BIOPHYSICS

Modern biophysicists try first to understand the microscopic phenomena of life, that is, the molecular basis of life. From an understanding of the microscopic they try to explain macroscopic systems like cells, tissues, organs and even entire organisms and ecosystems.

Because of the complexity of life, this is not easy. It has been successful for only a few fundamental problems. For example, in genetics the molecular basis is the famous dioxyribonucleic acid - DNA - molecule. This molecule contains a chemical language which can code genetic information from viruses to humans. From an understanding of genetics one can progress to the study of changes in the genetic information that leads to biological evolution. Another example is to first study the microscopic basis of nerve conduction and then progress to an understanding of information transfer in our nervous system. In nerve conduction, the atomic and molecular mechanism of charge transfer across the neuron cell membrane was studied. Electric nerve signals (action potentials) were found to be due to transport of ions across nerve cell membranes. Other auxiliary molecular mechanisms provide energy and information processing to neural systems. Many "molecular diseases" have been identified and found to be related to defects or malformations of specific molecules! A single error in the composition of the hemoglobin molecule - the oxygen carrying part of our red blood cells - leads to the serious hereditary disease sickle-cell anemia. Many other molecular diseases have been found. Today, thanks to molecular biophysics, we are seeing the emergence of Molecular Medicine. The most ambitious molecular biophysics project up to now is the Human Genome Project. Many laboratories world-wide are mapping the molecular details of human DNA. This will lead to an immense amount of knowledge that will help us understand the nature of the human health and illness. Molecular research in biophysics led to another revolution - genetic engineering - in which DNA itself is modified or "engineered" to perform different biological functions. Some of these functions never existed before in Nature!. One espetacular example was the introduction into a bacteria of a piece of DNA coding for insulin. This is a substance needed to control sugar in the body. Proper insertion of the fragment "educated"the bacteria to use its chemical factory to make insulin. This mode of production led to a more economical form to produce this drug. This is one aspect of biotechnology, using genetical engineering, an example of applied Biophysics.

EMERGENCE OF BIOPHYSICS

Let us now look back on how biophysics emerged from biology, physics and other sciences: Galileo considered the problem of how tall a tree can grow. In the last centuries a few scientists started to look for applications of physics to biology. Since we cannot name all of them let us mention some of the giants. Most biophysicists agree that Helmholtz (years?) was one of the first scientists to pioneer in this historical task. He made significant contributions to our understanding of hearing and vision. One of the first to use molecular techniques in biology with the help of physics was Albert Szent-Gyorgyi. This extraordinary man - who also discovered vitamin C - investigated how muscles contract. By mixing isolated biomolecules in a test-tube and adding calcium ions he saw the mechanical action of the muscle fibers!Max Perutz, Dorothy Hodgkin, Linus Pauling ,Max Delbruck and Francis Crick are some of the pioneers in molecular biophysics. A study of the lives of these scientists can provide motivation to study biophysics.

THE EVOLUTION OF BIOPHYSICS

Important contributions to the science of biophysics were made by the discovery or invention of new experimental techniques and instruments. The most important early development was the invention of the microscope by (1st name?) Anton Leeuwenhoek(1673)with which cells, microbes and other microscopic organisms could be seen and studied. A more profound step forward was the discovery of X-rays in 1895 by W. Roentgen. X-rays permited the study of submicroscopic structures, such as biomolecules and biopolymers - proteins, polynucleotides and poly sacharides. Pioneering work with x-ray studies of biophysics was done by Max Von Laue and W.H. and W.L. Bragg(father and son!). The invention of the electron-microscope in (1927) permitted the study of membranes, tissues and cell organelles never before seen in detail. The use of x-rays for structure analysis permitted an improvement of 10,000 times in the detail that could be seen compared to a conventional microscope. New areas of modern physics such as nuclear physics and quantum physics were also applied to biology. Nuclear physics led to nuclear and radiation biophysics. Quantum physics led to the electron microscope and devices like lasers and very sensitive magnetic sensors, such as the SQUID (superconducting quantum interference device) which can detect the minute magnetic fields produced in the brain. With the tunneling microscope we can virtually see individual atoms and molecules! The field of spectroscopy in physics led to new areas of research in biophysics .This happened for instance with Electron-Spin and Nuclear Magnetic Resonance spectroscopies with enormous significance to the study of biology and biochemistry. These in turn led to new imaging techniques in biology and medicine including magnetic resonance imaging (MRI) which is now at the frontier of modern medical imaging. A most important step for the advancement of biophysics was the invention of the computer and the associated development of informatics and electronics. This made possible the extensive and detailed calculations necessary for modeling , imaging and automation in biophysical instrumentation. To do research in molecular biophysics computers are essential: first because the structure of biomolecules is investigated with the help of computers; second because calculations involving models in biophysics are practically impossible without the help of computers; and third because most modern instruments in the biophysics laboratory involve electronics and computer- control.

FORM AND FUNCTION AND LIFE MACHINES

Life exists on earth for some 3 or 4 billion years. It started with atoms and molecules existent in the pre-biotic(pre-life) environment. The Universe started much earlier(some 20 billion years ago if the Big Bang model is correct). These atoms were made in the cosmic furnace as it gradually cooled. Evolution of the Universe and Evolution of Life are two fascinating and connected themes. Abdus Salam, Nobel prize winner for his contributions in fundamental physics, has even proposed that in the very beginning of the Universe forces appeared capable of distinguishing left from right. These forces may have induced left and right assimetry in biological molecules(aminoacids) fundamental for proteins of today. If this is right, we may say that there is a "memory"of the origin of the Universe in biomolecules!(see reference below). One of the atoms made in the cosmic furnace was carbon, and this would prove to be essential for living systems. Others are O,H,N,P,Ca,Na,K S ,Mg ,Zn and Fe.These atoms gradually assembled into molecules like water,carbon dioxide, fosfates, and this corresponds to the inorganic evolution of molecules. Then came the organic chemistry evolution with molecules like metane,organic carboxylic acids ,acetilene and then to organic polymers of higher molecular weight. The fourth evolutionary step after the stellar,atomic and organic evolutions was towards biomolecules: that is molecules having form(structures) that allowed them to perform basic and later more sophisticated life processess (functions).

The basic functions are: self-reproduction, information storage, energy storage,catalytic(or enzymatic) action and structural(in the geometric and mechanical sense) function. To make a long story short, they became life-machines, and after 4 billion years we have only 4 basic types of biomolecules! With these we build all living beings on earth! Energy is basically suplied by Sun-light coupled to special life-machines with photosynthetic properties. The rest is information processing(evolution by the life-machines themselves under the influence of the environment (ecosystem). All this under the Laws of Nature since the Big-Bang when present laws began to structure and operate.

The four basic types of biomolecules are described in Table I together with their relevant forms (structures) and functions. They are sometimes called biopolymers or macromolecules,except for lipids, relatively small molecules. Natural proteins are made of only 20 aminoacids monomers,all levogyrous, turning polarized light to the left.The polynucleotides (DNA and RNA) can code for all life processess.Lipids build membranes, the fundamental structure that defines individuality of cells and tissues. Polysacharides(as well as some proteins) have binding and structural properties that make them fundamental for plants,algae and animals.For instance all plants contain cellulose, a polysacharide, as basic building material.Two important observations should be made: water is linked to all of these biomolecules with important functions because of its large electric dipole and hydrogen binding properties. It constitutes 70% by weight of most living beings. Its role is still to be completely understood in biophysics. The other important point is that all these molecules are vibrating and changing their instantaneous structure in time. They vibrate at frequencies of 10 trillions times per second! Only recently, with the advance of very fast lasers, biophysicists were able to make dynamical measurements in biomolecules. This is a tremendous research frontier, for perhaps many of the important biological functions can only be understood by the dynamical properties. Enzymatic action and electron transfer in vision and photosynthesis are possible dynamical biophysical functions. So ,only in this short paragraph, we identified two new frontiers: biophysics of water and of biomolecular dynamics.

TABLE I- The 4 types of Biomolecules .

BIOMOLECULE	COMPONENTS	EXAMPLES
PROTEINS	AMINOACIDS	COLLAGEN(SKIN),HEMOGLOBIN(RED CELLS)
POLYNUCLEOTIDES	NUCLEOTIDES	DNA(GENETIC CODE),RNA(REPLICATION)
POLYSACCHARIDES	SUGARS	CELLULOSE(PLANTS),CHITIN(ANIMALS)
LIPIDS	FATS,FOSFATES	CELL MEMBRANES IN GENERAL

FRONTIERS OF BIOPHYSICS

What are some of the other frontiers of biophysics for which the creativity of young scientists soon to enter the field will be needed? The topics we selected are drawn from an enormous list. Biophysics is a dynamic and ever-expanding field since it involves the phenomena of life itself! A few fundamental frontiers in biophysics are the following:

-What is the basic biophysics of the origin of life - how it started on Earth or in the Universe? A pioneer in this field was A.I. Oparin who wrote"The origin of Life"(see bibliography).Problems and questions for this area range from: What were the first biomolecules? What was the nature of the "molecular evolution" up to present day life-processes? How can we look for "archeological" molecules? How can we understand why the aminoacids (the fundamental building blocks of proteins and other polypeptides) are all left-handed? That is, their molecular structure is such that they turn the plane of polarized light always to the left (levogyrous). How can we reproduce in the laboratory the original pre-biotic conditions? The question of life in the universe is fundamental to the question of the origin of life on earth because life could have originated in another part of the Universe and then "migrated" to the earth. -Another important frontier in biophysics is the study of the brain. How does it functions not only in humans but in other animals? The fundamental problem here is to understand the hardware - cells called neurons are the main circuitry of the brain , how are they connected? and the software how do they communicate with each other? New concepts from information theory, statistical physics, molecular electronics such as neural networks, artificial intelligence, and neural biochemistry are introducing new insights to this fundamental problem. The very notion of how we think, how we create, how the so-called higher brain-functions (emotions, for instance) came into existence, are part of this research. There are profound philosophical problems involved: What is the difference between mind and brain? Anyone wishing to embark on a fantastic scientific adventure, perhaps the most ambitious of all - the brain trying to understand the brain - might choose this area of biophysics for a longterm research program..

-The prime energy source that makes life possible on earth is sun-light. The study of this area of biophysics is called photosynthesis. It is an area investigated by photobiology - a branch of biophysics. What are the processes by which a photon from Sun-light interacts with plant cells so that energy is stored in chemical substances in the cell? Thanks to biophysicists we now know enough to sketch the basic molecular process: a light photon of a specific wave-length is absorbed by a chlorophyll molecule and an electron is transferred to other molecules in a very short time. This time was measured by special spectroscopic and pulsed laser techniques. The photon energy is transformed into electrical potential energy of the molecules and chemical reactions occur which further transform this energy into chemical potential energy in the plant-cell. Besides studying such photosynthetic processes in detail the fundamental questions in this area are: Can we make artificial plants? What are the common processes between photosynthesis and vision where the photon energy is transformed into an electric signal in the brain? Can we use the sophisticated processess of molecular electronics of vision and photosynthesis to build new biocircuits(biochips) and develop a new field of molecular electronics?

-In bio-technology important frontiers range from the field of molecular medicine to research on the human genome . The human genome project, already in existence, is a megaproject with a cost estimated in billions of dollars. The knowledge to be gained will be of fundamental importance for attacking the problems of molecular genetics and molecular biophysics. Its goal is to obtain the full library of genetic data bank ,of men and women, from which predictions can be made about the possible occurrence of many diseases, like some forms of cancer or other molecular diseases. For agriculture germplasm banks have already been established for preservation of species and defense of biodiversity. Molecular methods for genetic transformation and engineering involve subtile biochemical and biologi cal methods as well as brute force physical shooting of DNA pieces into a cell with an air-gun or an electric disruptive discharge.

-Last, but not the least, let us mention the research frontier to understand complexity itself. Living systems are constituted of an enormous number of atoms,molecules, organelles and cells. Complexity nevertheless leads to simplicity if we recognize that despite the vast number of components, living processes evolved harmonically in time and space. This is certainly due to cooperative effects. A complete human being starts with just one fertilized cell. Billions of our body cells are formed each hour while others die or are destroyed.The main question is, can we obtain from the laws of statistical physics, thermodynamics and chemistry the basic concepts underlying self- organization? How is it that a large biomolecule such as a protein, remembers to fold exactly to its original form even if it is denatured by thermal or chemical means? What induces bacterial colonies to organize themselves in almost perfect crystalline arrangements? A little philosophical discussion is appropriate here. There are two fundamental but not quite opposing concepts. One is order, the other is disorder. Chaos is complete disorder. Complete order would be the absence of defects in a structure and consequently also absence of motion because motion would produce defects after a short time. There are no systems in nature that exhibit absolute order. Even at absolute zero temperature the laws of quantum physics require a so called zeropoint energy.This is related to the Heisenberg uncertainty principle of quantum mechanics. On the other hand other laws of physics require that a completely disordered structure(i.e., chaos) will start to show local fluctuations and out of these fluctuations some order is introduced or pumped into the system. There are now many examples in fluid dynamics and chemistry in which self- organization appears in apparently chaotic systems. Life can be thought of as due to pumping information inside a cell. For this, energy is needed but energy by itself has no information content . Energy is essential to make living systems selfsustaining. All living systems are dynamically in search of equilibrium between order and disorder. Too much order or disorder will cause death. It is interesting to remember that in greek mythology the first God to be created was Chaos. And the modern scientist will complete:everything else then came out of chaos with the help of the Laws of Physics with their elements of order and harmony.

BIOPHYSICS SUBFIELDS

In a general way Biophysics may be classified in Classical and Molecular Biophysics. Classical Biophysics is more related to macroscopic systems and in the past was given in medical and biological curricula as part of physiology. One would find topics such as biophysics of the circulatory , vision,hearing and nervous systems as well biomechanics(forces and stresses in muscles and skeleton). Also topics in physical instrumentation like in electric-cardiography,electric-encephalography,phonoaudiology were part of biophysics disciplines in particular in medical schools. As discussed previously, modern biophysics is now mainly concerned with microscopic aspects using the molecular approach.The main guiding principle is that of duality between structure and function. The biological function is fundamentally related to the structure of the biological system.This has profound implications: molecules are life-machines designed to perform functions like enzymatic action,information and energy storage,recognition and communication with other molecules. Some of the more important subfields of biophysics are:

Photobiology(interaction of light energy with living systems),Biophysics chemistry(colloids,interface and electrochemical potentials), Membranes biophysics(properties and transport across biomembranes,including thermo dynamical and statistical modeling and use of techniques like electron spin and nuclear magnetic resonances, fluorescence spectroscopy and others). Structural Biophysics(structure and function of biomolecules using techniques like X-ray,electron and neutron diffraction,nuclear magnetic resonance spectroscopy,pulsed laser techniques and others like tunneling microscopy). Theoretical Biophysics(physico-mathematical modeling of fundamental biophysical processes in genetics,bioenergetics,electron transfer,biocybernetics,evolution , information and energy transfer and complex systems.)

OTHER AREAS CLOSE TO BIOPHYSICS

There are many important areas of science close to Biophysics. We will mention only a few for their closeness and importance:

-Medical Physics-This is a very rich and expanding area ranging from Physics of the body, imaging techniques, radiation dosimetry, radio and lasertherapies, biomagnetism , bioelectricity and many other subfields. See reference on bibliography.As for Biophysics an American Med.Physics Assoc. was founded in the US in 19(?).An important reference source is the J.Med. Physics(?)

-Bioengineering- In this field engineering is applied to biological problems and related instrumentation and materials needed to solve them. Important applications involve electronics engineering,computer and information sciences, control theory and techniques.Sub-fields are robotics,artificial vision and speech,biomaterials engineering.Materials Science applications for example range from special ceramics, polymers and metal alloys used for implants, surgical and medical equipment in general. It is also a very dynamical and rich area close to Biophysics.

-Molecular Pharmacology and Immunology- As implied in the fundamental principle of Form and Function briefly discussed above,the understanding of the action and effects due to the molecular structure of drugs is of paramount importance. With the advent of molecular engineering drugs can be obtained and modified by new techniques.The sub-field of drug-design for example is now a very active area of research and industrial development. Antibiotics,hormones,neural-transmiters,anti-rejection medicine, cancer chemotherapy are some of the areas of intense research today.

BIOPHYSICS AS A PROFESSION

Biophysics is involved in research and development for all these areas basic and applied, with its arsenal of techniques, methods and concepts. Because of this we may say that Biophysics offers excellent professional opportunities both in academic areas (Universities and Research Institutions and Labs) or in Technology and Industry. In fact many physicists, chemists and biologists are drifting to Biophysics in search of new career opportunities.

Being a biophysicist means participating in this vast scenario either as an actor or perhaps ,with luck, as one of the genial authors of this never ending play.

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BIOGRAPHIES:

In this Encyclopedia, look under the names of scientists mentioned, practically all Nobel Prize Winners.