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MEDICAL PHYSICS? BIOPHYSICS?

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The training of medical students and biophysics research at the Semmelweis Medical University in Budapest

The terms, medical physics and biophysics, have these days definitions that are internationally accepted and, as a crystal physicist, I should not like to be called upon to modify or improve them. My qualifications for the following reflexions stem essentially from the fact that for more than 30 years I have been teaching in the Institute of Biophysics of the Semmelweis Medical University Budapest and I have been a professor there for the past 10 years. During this time I have been able to participate in the evolving interaction between physics and both medicine and biology.

Medical training in Hungary was carried out for more than 200 years at the university of sciences, whereas since the beginning of the fifties, it has taken place at independent medical universities. These nevertheless, include a number of different faculties with specialists from many disciplines.

Physics as Basic Education

My first encounter — nearly 50 years ago — with medical training had been as a student of physics, when first-year students of physics and medicine together followed a course on basic experimental physics. As an enthusiast for my subject, I thought it obvious that medical students should study the natural science considered by me to be the most general, i.e. "pure" physics, on a level higher than is taught in secondary schools. (I am still today deeply convinced of the thought-forming power of physics.)

Thus, when in 1949, I was appointed to the *Institute of Medical Physics* my aim was to create an enthusiasm for physics itself amongst our first-year medical students. At the same time to ensure my own concern with medicine, I was presented by the director of the Institute with a "medical physics" problem. (A dentist in Budapest, whose routine work in the state dental surgery had been the extraction of teeth, had developed the theory that saliva entered into the space between teeth and, because of its physico-chemical properties, acted as a protection against caries. I had to investigate this hypothesis.)

A year later, another physicist, I. Tarján succeeded Gy. Koczkás as director of the Institute. Originally a crystal physicist (and my own tutor), he would be described today as a biophysicist. He took in hand the organization and continuous development of the teaching activities of the Institute and set as his first objective, the extension of the knowledge of its teaching staff (consisting of physicists, chemists, physicians, pharmacians). He wanted to train specialists who were good in their own field, but able to perceive the ideas of others.

Physics as a Tool in Medicine

In the teaching programme, the primary aim became the teaching of those parts of physics which impinge directly on the work of a general physician, and our first goal was to define an appropriate curriculum, selecting those areas of physics best suited to teaching the structural and operational principles of apparatus used in medicine, mainly through practical work. When we found that some part of the course was not understood by the students, we developed exercises which took the form of individual measurements in the laboratory. In this way we transferred to practice e.g., the Abbé-theory on microscopical image formation or the functioning of flip-flops. An appreciation of quantitative measurements, individual work, the development of experimental skills, all figured in the aims of these practical exercises.

Our two fields of research in crystal physics that we were pursuing, crystal growth and the investigation of crystal defects, enlarged our teaching ability and led us deeper into biophysical research. In biology, analogous problems — at least as a rough approximation — are the self-organization and the role of structural defects in biological macromolecules. Moreover the influence of our practical experience in the growth of crystals was also far from negligible. Being in close contact with both physicians and physicists, we worked out as early as the beginning of the fifties — inter alia — methods for the production of crystals for use in the measurement of radioactive emissions which are used world-wide even today. In doing so we stimulated the medical application of radioisotopes and nuclear physics research in Hungary. We succeeded in equipping our student laboratories with up-to-date apparatus for work in nuclear physics and dosimetry and we introduced such exercices as e.g. the absorption measurement of nuclear radiations, measurement of γ-spectra, double isotope labelling, radiocirculography in connection with blood circulation and cardiac action etc. (I might mention that Hungarian industry produces several items of equipment relevant to nuclear medicine under licence to us.)

Transition to an Integrated Approach

Despite the fact that our teaching and research were entering the medical spheres as such, the name medical physics was still right for us at that time. In the big mixed

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team concerned with medicine and medical training we were identified essentially as physicists. It is difficult to state when, as obviously it was not in one step, the strengthening of our medical-biological knowledge resulted in a more direct contribution to the formation of medical and biological understanding. This came about through a more exact approach to the teaching of the physical concepts involved in biological processes. There were fields in which we were the pioneers even of the right *medical* approach at our university; for example, in place of the auditory theory of Helmholtz, we introduced the results of Békésy. We taught the physical bases of audiometry, the phon and son scales showing the problems of the psychophysical application of the Weber-Fechner law. Step by step we made everything that we did serve biology and medicine: studies of the structure of matter, thermodynamics, electronics etc. while simultaneously we aimed at the formation of the right scientific attitude.

The road to biophysics on which we had started led further. A good part of our course on biophysics was devoted to the relation between molecular structure and function, the bio-physics of stimulation processes and sensory function, bio-cybernetics etc. Especially emphasized e.g. was the concept of modelling of biological phenomena and processes. We discussed concretely the electro-diffusional and electrical models of biopotentials; equilibrium and non-equilibrium thermodynamical transport models, cable models etc. Similarly we turned to the model of an analogous signal processing system in the discussion of sensory function. We applied our solid state physical "connexions" and approach to the discussion of the structure of macromolecules of biological interest (nucleic acids, proteins, membrane). Thus we gradually reached the stage when it became justified to change the name of our institute from Institute of Medical Physics to Institute of Biophysics.

As an example of our physics approach to the teaching of biological processes, let me cite the case of electrical signal generation in, e.g., muscle fibre, invoking the concepts of rest and action potentials.

Rest Potential

The rest potential in medical terminology is the potential difference measured across a cell membrane, i.e. from the intra- to the extracellular space. The earliest interpretation of this potential was the equilibrium thermodynamical model of Donnan (Fig. 1), in which the living cell is characterized by the presence of mobile and immobile ions on both sides of the membrane. The mobile ions are mainly the K^+ and Cl^- ions, the immobile the protein and phosphate anions and to a first approximation the Na^+ ions as well.

As membrane is impermeable to the immobile anions, they line up on one side, and some of the cations line up on the other, thus forming an electrical double layer. This gives rise to the so-called Donnan voltage, or the membrane potential of Donnan. Because some of the mobile ions are bound by the immobile ions, the concentration of the mobile ions is different on the two sides of the membrane, so that we are dealing also with a concentration cell, which in equilibrium, creates a voltage equal to the membrane potential but in the opposite sense.

From electrochemical considerations the membrane potential between the extra and intracellular space is:

$$\phi_e - \phi_i = (RT/F) \ln (c^e_{Cl} / c^i_{Cl}) = (RT/F) \ln (c^i_K / c^e_K)$$

where c is concentration, and the superscripts e and i denote the extracellular and intracellular space.

A comparison of the potentials calculated from the above equation with the measured values is shown in the Table, from which it can be seen that the Donnan model is only a first approximation. Its obvious deficiency is that it oversimplifies the real conditions by, e.g., considering the cell and its environment as a thermodynamically closed system in equilibrium.

The development of a non-equilibrium thermodynamical (transport) model is due amongst others to Hodgkin, Huxley and Katz. Its basis is that between the external and internal side of the membrane, concentration differences exist, causing a continuous transport of ions, whose migration is inhibited to a differing degree. This produces an electrical double layer at the surface. The model gives:

$$\phi_e - \phi_i = -\frac{RT}{F} \ln \frac{\sum_{k=1}^{n} p_k^+ c_{ke}^+ + \sum_{k=1}^{m} p_k^- c_{ki}^-}{\sum_{k=1}^{n} p_k^+ c_{ki}^+ + \sum_{k=1}^{m} p_k^- c_{ke}^-}$$

where c_{ki} and c_{ke} represent the intra- and extracellular concentrations of the k-th ion and p_k its relative permeability constant. From this one obtains a rest potential of 61 mV for the sepia giant axon and 90 mV for the frog nuscle, which are in good agreement with experiment.

Action Potential

If now we impose a potential across a membrane by applying a square shaped pulse so that current flows from the intra- to the extra-cellular space, we observe a decrease in the numerical value of the rest potential. Increasing the pulse size causes a progressive increase in de-polarization (or hypopolarization) until a certain threshold value is reached at which point a disproportionate excitation is observed (Fig. 2).

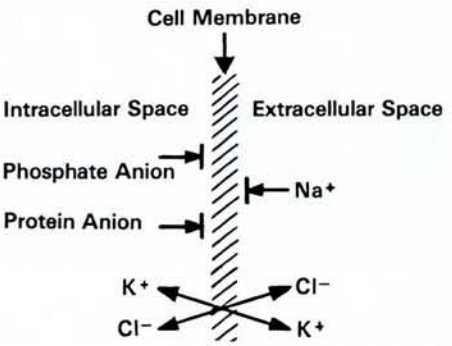

Fig. 1 — Representation of a cell membrane.

Similar voltage changes, called the action potential, are seen whenever an excitation process of biological origin is started in an individual fibre. The change in general lasts about 1 ms. Moreover, one finds that every stimulus which reaches or goes beyond the de-polarization threshold, irrespective of intensity, initiates an action potential of the same shape and size.

The formation of the action potential can be interpreted in the following way. Any change of the membrane potential causes a change of the permeability of the membrane, so that in the beginning, up to the de-polarization threshold, the permeability of the membrane increases at first mainly for the Na^+ ions. In consequence the Na^+ ions begin to flow along the concentration gradient into the intracellular space. The presence of these ions leads to a decrease of the negative potential of the intracellular space towards zero, and further increases the permeability of the membrane to the Na^+ ions. A self-amplifying process is thus begun (Hodgkin-cycle) which lasts until the migration of K^+ and Cl^- ions (also enhanced during depolarisation) takes over. Occuring later than the increase in Na^+ ion flow, it finally becomes dominant and the action potential decreases, overshooting to a give a temporary "positive after-potential".

The amplitude of the action potential may exceed by 3-5 times the stimulating voltage, but it must be noted that the stimulation threshold varies as a function of the action potential. Once initiated, until the maximum is reached a further stimulus can not start an excitation process, and the fibre is in the so called absolute refractory state. After the peak, the threshold is abnormally high for some time (relative

Rest potentials as measured and calculated for K^+ and Cl^- for three tissues.

Tissue	Rest Potential (mV) Measured	Calculated K^+	Calculated Cl^-
Giant axon of sepia	62	91	56
Frog muscle	92	103	89
Rat muscle	92	95	86

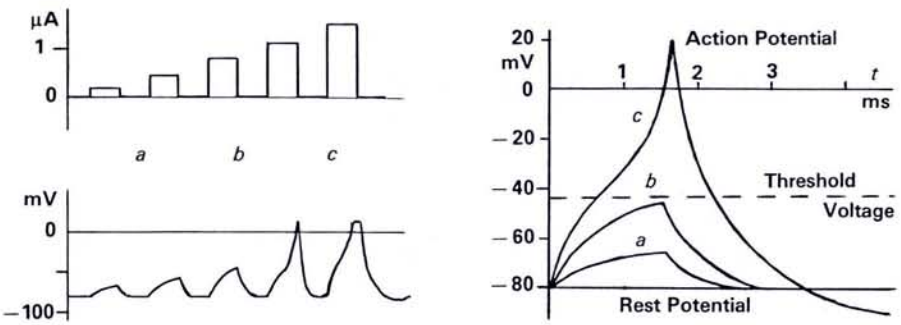

Fig. 2 — Response of a membrane to the application of a square wave potential of increasing value.

refractory state), and only a suitably high stimulus can start a new action potential.

Sensory functions

For the perception and processing of different stimuli in the sensory functions special systems are employed, but once the stimulating energy is transformed in the primary processing, all stimuli produce uniform action potentials on the appropriate sensory nerve. In hearing, for example, the receptor cells are the hair-cells in the cochlea which are affected by shearing forces. Vibrations induce in them an electric voltage, the so called microphone potential, which generates action potentials on the nervus-cochlearis endings at the hair-cells.

The intensity of the stimulating sound conditions partly the number of hair cells where the microphone potential is formed, and partly the amplitude of the microphone potential. The number of hair cells determines the number of active nervus cochlearis fibres that are affected, while the microphone potential (in the relative refractory state) determines the frequency of action potentials produced.

It is evident that in such processes the interaction between physics and biology and therefore its relevance to medicine is very strong.

Biophysical Research

As well as our teaching, we have a serious programme of research which aims to reveal and characterize quantitatively the relation of structure and biological function — on a molecular level. Order-disorder, structural defects and their consequences, phase transitions etc., are problems of the same importance in biological macromolecules as in the field of crystals. In this context, we study the damage to nucleoproteids (bacteriophages) and their constituents (nucleic acids, nucleotid based crystals) produced by physical and chemical agents (UV light, alkylating agents etc.). In parallel we study also the changes in the structure and function of biological and model membranes brought on by various external effects (temperature, electric field, ion-concentration change, pharmacons).

The research methods and the way of reasoning have a great similarity to solid state physics; only the studied objects are different. Theoretical methods which are particularly promising are the stochastic and statistical mechanical methods and beyond these, quantum chemical calculations.

Let me mention just two of the most recent results of interest found in our two fields of research.

1) *Bacteriophages.* The viruses of phages are macromolecules consisting of nucleic acid and protein and they can be treated as a model of the cell nucleus. In connection with the supermolecular structure of the T7 phage and the destruction of this structure under the effect of programmed heating, we have obtained information on the detailed interaction between the nucleic acid compared to its regular ordering shown in solution. According to our experiments, this distortion effects in some cases e.g. the sensitivity to damage by UV of the nucleic acid.

2) *Artificial Membranes.* We are studying the so-called artificial membranes which are a model of cell membranes. They are of special interest because they can be produced to a pre-set composition and the changes created in them by various external effects can be studied in exactly reproducible conditions. By the aid of our statistical mechanical model worked out for lipid bilayers, we have interpreted the first order phase transition from crystalline to liquid crystalline state. We have shown that the permeability of lecithin membranes in the liquid crystalline state can be related to the intra- and intermolecular defects present in the membrane. Also we find that hydrostatic pressure increases the phase transition temperature of membranes.

This is just part of the work that is undertaken and which is in constant development. Biological systems provide a challenging and expanding field for the physicist.