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## BIOELECTRONICS: A BACKGROUND AREA FOR BIOMICROELECTRONICS IN THE SCIENCE OF BIOELECTRICITY

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### Introductory remarks

Continuing the tradition set by L. Galvani the science of bioelectricity aims at considering all the essential aspects of the relationship between various manifestations of electricity and the processes of life. One of the fields of these studies is the border area between electronics and biology called bioelectronics.

Bioelectronics (biological electronics = electronics and electrodynamics of biological systems and processes) may be defined as the area of the applications of concepts and methods of both physical and applied electronics to living systems and their components in order to: firstly, identify the electronic properties of and electronic processes in these systems, and, secondly, to show what and how important role they may play in the life phenomena. The activity in the latter area may be also labeled as physiological electronics. As the works characterizing bioelectronics are lacking, the aim of the present article is to describe it, yet from a specific angle, namely, to show it as an area, where a new branch - biomicroelectronics - is taking shape. However, a closer description of this only seemingly new area of study will be the subject of a separate paper (1).

The development of bioelectronics, attaining its greatest rate in the sixties, has been suffering a noticeable slowing-down in recent years. It results from the meta-theoretical reasons, on the one hand, and from various obstacles related to the subject of study, on the other. The main source of the difficulties of the latter category is the structural and functional complexity of biosystems which decisively comes into play when one has to deal with the multicellular and multiorganismal systems.

Facing seemingly insurmountable obstacles when trying to unequivocally relate the electric, magnetic, and electromagnetic properties and phenomena in biological materials and biostructures with biological processes, the investigators have increasingly been paying attention to the simpler as

well as simplified (artificial) objects. This is accompanied with a drift of the originally bioelectronic research to the technology-related studies. This, in turn, results in shifting them closer and closer to the areas which though closely related to bioelectronics, as e.g. biomaterial -based microelectronics, biotechnological electronics or microelectrobionics, are different from bioelectronics itself.

As far as the former category of difficulties is concerned, one may notice that there is also a lack of meta-theoretical studies devoted to the methodology of bioelectronics, its, specific object of investigation, and the range of aims it is supposed to take. Also the historically arisen contamination of the meaning of the word "bioelectronics" is of no smaller significance. These subject-related and metatheoretical questions will shortly be dealt with in the second part of this article.

## The fronts of research in bioelectronics

At present, one may distinguish at least three directions of the research in the electronic properties of biosystems and their significance to life processes (Fig. 1). The first one may be identified with a biology-oriented derivation of quantum chemistry, known also as quantum biochemistry. It directly aims at the description of the electronic structure of biomolecules and at deducing from it their physico-chemical properties. Indirectly, this discipline attempts at revealing the connection that exists between the electronic structure of biomolecules (2) or various pharmaceuticals (3, 4) and their biological significance. The basic (5) works by A. and B. Pullmans may be regarded as decisive steps initiating and shaping this area (6-8) of study. Its fruitful continuation of it is due mainly to P-O. Löwdin (9) and J. Ladik (10,11).

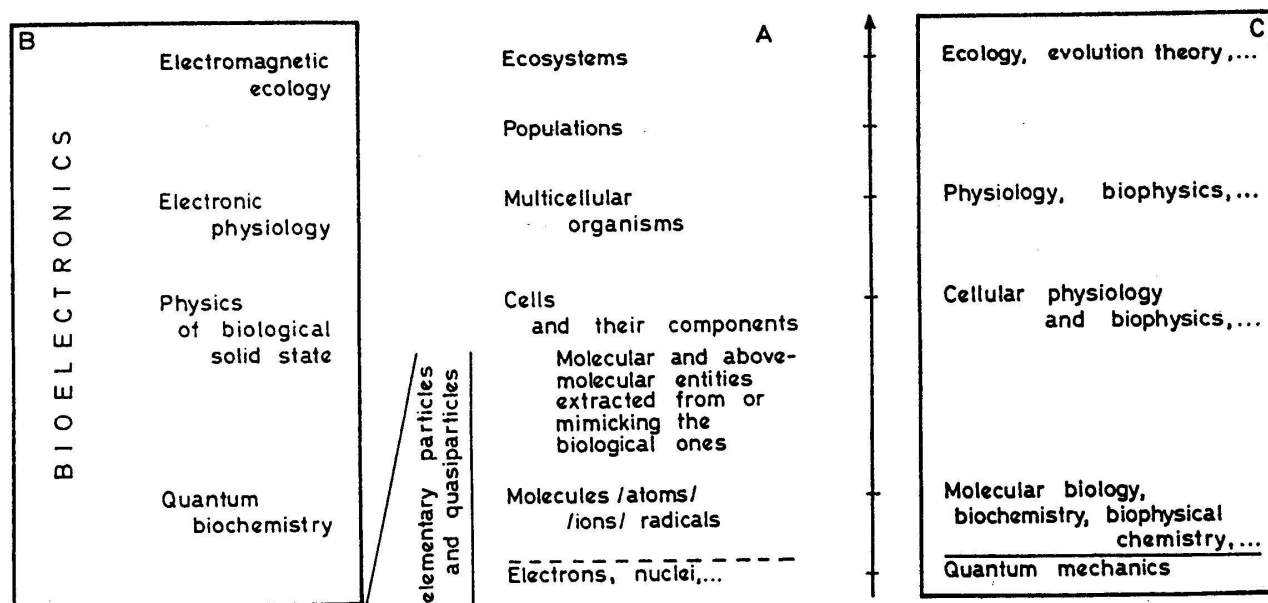


Fig. 1. The levels of organization of living systems (A) and the examples of the disciplines in the domains of the well established biological sciences (C), and in bioelectronics (B) dealing with the phenomena which manifest at these levels.

The second direction was initiated some fifty years ago (12-15) by the suggestion that the charge and energy migration in biosystems may be realized by the mechanisms essentially the same, as those active in the non-biological solids. The basic feature of the studies in this field has been paying attention to the properties of biomaterials which are physical- or technological elec-

tronics-related, especially to the conductivity of the electronic type and the phenomena connected with this kind of electrical conduction. The results of the research carried out along these lines have been exhaustively summarized in (16-51).

Apart from the investigation oriented at the phenomena and the properties essentially connected to the long-range migration of the electronic charge carriers, new vistas of research were opened when such properties as piezo- (32-41, 43), pyro- (38-41), ferroelectricity (42-46) extraordinary dielectric properties of biomaterials (47-48), liquid crystallinity (49-52), and the electret state (53-55) became the targets of investigation. For works reviewing the above mentioned fields of study see (56-58).

Motivated by both the need of learning about the electronic phenomena involved in the realization of the processes of life and by the demands of the current technology for the construction of cheap and efficient systems for, e.g. the conversion of light into electricity, many attempts have been undertaken at investigating these phenomena in the model and reconstituted systems. As in the natural biological units extremely large number of factors contribute to the observed phenomena, the modeling approach makes it possible to assess which group from this multitude of components plays the essential role in a given process. On the other hand, the attempts at the reconstruction of an electronic property in a previously disassembled system, allow one to tell which of the studied properties are the result of a direct summing up of the properties of the units belonging to the lower level of organization, and which are the properties of the system as a whole.

As far as the investigation in this area is concerned, the works on the electronic conductivity and photoelectric phenomena in pure lipids of biomembranes, bilayer lipid membranes (17, 59-62), modified bilayer lipid, (24, 63-65), reconstituted chloroplast and visual receptor membranes (62, 64-66), as well as piezoelectricity in the oriented biomolecular films (67-69) may be mentioned here as the examples of the investigation carried out in this domain.

The third front of bioelectronic studies consists of the attempts at explaining in the terms of physical as well as applied electronics the mechanisms (mainly of electronic nature) underlying important biological phenomena (70-80, 92 -101) and at the describing the influence of various factors on the living structures that are considered - implicitly or explicitly as electronic-chemical systems capable of life (81-91). This kind of approach to the physical basis of the phenomena of life is best exemplified in the publications of such authors as: R. O. Becker, F. W. Cope, A. Szent-Györgyi, P. H. Callahan, and W. Sedlak (56, 85, 90, 92-100, 124-125).

## The factors limiting the development of bioelectronics

Slowing down of the rate of the development of bioelectronics that became evident in recent years may be traced back to the difficulties arising from the complexity of the structure and functions of biosystems and to some multidisciplinary circumstances.

As far as the first category of these difficulties is concerned, it may be observed that the higher the level of the organization of the system, the bigger the number of factors and mechanisms which should be taken into consideration, when trying to satisfactorily explain how a high-level physiological response is connected to an external factor "by a chain of physico-chemical events. As a result, when dealing with the most complex systems, a very rich body of important data is gained at the price of their high controversiality, as far as a clear-cut connection between the influencing factors and the physiological response is concerned. On the other hand, the research done on the most simplified systems (e.g. on models) allows one to clearly point out the properties and chains of events coupling the influencing factor/s) with the observed phenomena. However, a serious limitation on the degree of adequacy between the conditions and mechanisms operating in the living, highly complex systems and the model ones is the usual price paid for this clarity.

One of the main meta-theoretical difficulties of this discipline stems from the lack of the re-

flection on the methodological status of it, which results among other things in the multiplicity of meanings which may be ascribed to the very word "bioelectronics". The following (1) part of this study is meant to satisfy this need, yet only on the example of biomicroelectronics, which shares most of its essential features with bioelectronics. The semantic difficulties will be shortly characterized in the closing section of this paragraph.

## The difficulties related to the object of study

1. Quantum biochemistry has been suffering substantial difficulties arising from the limitations on the ability to perform extremely large number of calculations in a finite time, which is required for getting satisfactorily precise results, especially when dealing with large biomolecules. The results of satisfying exactness are obtained only then one deals with relatively small, isolated molecules or polymers consisting of simple repeating units. The calculations get more involved, if one wants to take into consideration the presence of such ubiquitous molecules as water in biosystems.

To overcome these restraints many methods simplifying the calculations have been applied and specific types of model molecular systems have been dealt with as, e.g. polypeptides or polynucleotides composed of repeating units of well defined amino-acid or nucleotide sequences (102-104). No doubt, the results obtained make a progress mainly in methods of revealing the properties of more and more complex molecular and supramolecular systems by various means provided by quantum chemistry, yet the ultimate target of these calculations - the properties of the real molecules in their natural milieu - remains still distant. It may be added, however, that the results of quantum mechanical calculations even at their present level of exactness may well satisfy the needs of e.g. quantum pharmacology (i.e. the application of the theories and methods of quantum chemistry to the molecules of interest to pharmacology), biomolecular electronics, and may bridge quantum chemistry with the solid state microelectronics of biosystems.

2. As far as the results obtained with the application of the methods of solid state electronics to biomaterials are concerned, it should be realized that a typical procedure of searching for electronics-related properties of biomaterials involves: isolation, purification, and preparing the sample for the electrical measurements. Mitochondria, chloroplasts, rods and cones of the visual receptor, bacterial chromatophores, cellular nuclei (as well as the molecular and supramolecular components of these units), tendons and bones have been the most frequently used objects in such investigations. The preparation of these structures for the electrical measurements involves such denaturing steps as drying, forming the samples with the application of high pressure, and covering their surfaces with conducting materials.

Sometimes the measurements are carried out in temperature ranges extending far beyond those, which are typical for normal functioning of a given biostructure. Less drastic methods involve, e.g. the measurements done on the suspensions of isolated cells and their substructures in electrolytes of known, yet not physiological, composition. It is therefore not surprising that the results obtained in such circumstances may be put to doubt as to whether they really reveal the properties of biostructures themselves.

Although the above mentioned measurements have indeed shown that the investigated biomaterials have interesting properties (from the electronic point of view), it seems that considering these results as a proof for the occurrence of these properties in real living structures is extremely risky. The procedures of the isolation and preparing the samples for measurements may well eliminate or impart some properties in the samples tested. Therefore, it must be admitted that if bioelectronics were developed solely according to this methodology, it would give no substantial progress in the learning of the electronic features of living structures'. It does not mean, however, that this type of strategy may not be useful for biology-oriented electronics, one branch of which is bio-

molecular electronics.

The research done on biomaterials prepared in the way that only well controlled changes are induced, is a variant of the above strategy which is closer to the biological situation. In such a case, one proceeds from a satisfactorily described and controlled physical situation - still being far away from the one which is characteristic of the native structures - to a more natural one. The works on the influence of such factors as variable content of water on the nature of charge carriers and the value of electrical conductivity (105-107), or the influence of these factors on the characteristics of piezoelectric polarization (108-110) are good examples of studies approximating the biological situation. They were often undertaken for the sake of bridging the knowledge of the electronic properties of denaturated biostructures with the information gathered on the physiologically active ones.

The modeling strategy has also important drawbacks to it, which should be kept in mind when assessing its contribution to the learning about the electronics underlying or co-determining the processes of life. In many experiments it has been shown that the electronic processes and properties do really occur in the model systems, yet there still remain serious doubts whether these same do occur and are of significance in the intact biosystems. In this connection it should be remarked that when undertaking a study on a model system, a given property is paid the prevailing attention and measures are usually taken to eliminate those factors which in normal conditions would mask or even block the manifestation of it. In doing so, the conditions for the appearance of the property may even be created, although they may not be present in normal physiological context.

There is also another risk arising from this same source. Namely, in the result of the above mentioned adjustment procedure, a given electronic property may reveal itself with a much greater degree of expressiveness in the model system, than it does in the natural one. Therefore, no matter how great significance the knowledge gained on model systems may have for, e.g. biomolecular electronics, for bioelectronics itself it may be of questionable value, if the real biological context was not paid due consideration.

5. The situation is not much better when one is dealing with the electronic properties and their physiological role in intact single organisms or with populations of them. In this case, it should be stressed that they differ substantially from those of the inanimate nature and from those constructed by man, with respect to their unique and complex composition, structure, functions, and - what is of not lesser importance - their history. Even greater is the difference when groups of organisms well fitted to their environments are the subject of investigation. Due to this complexity the identification and establishing the role of the electronic properties and processes in an individual organism or in populations of them must remain debatable.

As far as the interaction between the environment and organisms that is realized via the "electronic link" (i.e. those in which electronic properties of and/or electronic phenomena in biosystems play a significant role) is concerned, it has been shown that it may only be revealed, if the relevant changes are followed on a sufficiently numerable groups of organisms or sets of biological events. This is the fundamental requirement for a justified application of various statistical evaluations. First of all, the statistical method which is applied must be appropriate, i.e. it must be fitted to the size and the quality of the collected raw data; secondly, there should be no bias in collecting and/or interpreting the data; thirdly, the obtained correlations must be satisfactorily significant; fourthly, it should be kept in mind that the obtained correlations alone do not prove that there is a direct or causal relationship between variables. Therefore, the existence of a causal relationship between, e.g. the disturbances in the state of health in a given population (111-114) and the incidence of an "electronics-related" factors may be questioned (115) either on the procedural grounds or the basis of principles mentioned above.

Taking together all of the above mentioned restricting factors, it should be stressed that the research carried in each of the above mentioned directions is not, and should be not, considered as isolated from the context formed by the other ones. To be relevant to bioelectronics, it should be

directed by (as still not clearly expresses and accepted) general theories, hypotheses, and empirical strategies aimed at the identifying the electronic features of biosystems and relating them to the role they might play in the physiological, ecological, and evolutionary processes. Otherwise, the results obtained - especially those gained on the complex biosystems - would be purely descriptive, not allowing one to understand why the observed events could take place and which new phenomena and properties should be searched for.

## Semantical difficulties

Bioelectronics, similarly as biophysics, may narrowly be understood as the mere application of the electronic apparatus and measuring techniques to the living objects. It may also be defined as an application of biosensors, i.e. devices that incorporate a biologically derived sensing element in intimate contact with or integrated within an electronic transducer in biomedical analytics (115). In this way it is reduced to the role which only accidentally may touch upon the very electronic features of biosystems.

On the other hand, if bioelectronics is understood as a systematic study of the electronic properties and processes underlying and co-determining the course of life processes, or - in analogy to the dynamical biochemistry - as physiological electronics, a question about the type of electronics relevant to these investigations may immediately be asked. The reason is that there are at least two basic and many derived types of electronics. The first one is the so called physical electronics (incorporating both classical and quantum electrodynamics), the other - the applied one.

Physical electronics deals with all the phenomena in solids, liquids, gases, as well as in vacuum which involve free electrons, and especially with various mechanisms coupling their movement to the energy conversion, storage and transfer. Being able to describe these phenomena on the basis of the first principles of physics, this type of electronics is an independent branch of physics providing the "basis for the applied electronics.

To satisfy concrete practical demands, applied electronics studies and constructs devices of various degrees of complexity which work usually on the basis of coupling various non-free-electronic processes to the movement of mobile electrons. In this way, it covers a much wider spectrum of properties and mechanisms than does the physical one, compelling it therefore to pay special attention to the study of the phenomena underlying the functions of electronic devices. These very circumstances enforce broadening of the original scope of electronics to include such studies as, e.g. the magnetic properties of materials, their piezo-, pyro-, and ferroelectricity, the electret, plasma, and liquid crystalline states in or of them, as well as photons and various quasi-particles in all aggregation states of matter. It is this extended meaning of the term "electronics" that bioelectronics should be linked to.

There are also some historical precedences of either ascribing another meaning to "bioelectronics" or labeling with another name the field of study characterized above. Here, some widely known examples will be mentioned solely for the sake of recording these difficulties.

To the author's knowledge, it was L. O. Vincent who for the first time used the term "bioelectronics" (117) to label the field of the study of the equilibrium in the human organism in terms of proper relationship between such properties as pH and rH of the body fluids. In the A. Szent-Györgyi contributions, one may observe a shift from the sense closely related to solid state physics - "new biochemistry" (14, 157 - through the application of quantum mechanics to biochemistry, "quantum mechanical biochemistry" (92), then a composition of solid state physics and chemical bioenergetics - "submolecular biology" (93) which was paralleled by the E. Ernst's solid state physics-related proposal of "subatomic biology" (118) - to the investigation of the charge transfer processes in biosystems - called by him "bioelectronic s" (94) or "electronic biology" (95).

The rather awkward term "the physics of biological solid state" coined by F. W. Cope (56),

seems to fit well the range of studies of physical and/or technological electronics-based bioelectronics. The term "quantum biology" used by P-O. Löwdin (119) - proceeded by relating it to the study of the interactions between ionizing radiation and living organisms by F. Dessauer (120) and by A. and B. Pullmans' "quantum biochemistry" (7) or "electronic biochemistry" (6) - is tightly connected with the quantum chemistry of biologically active molecules, and only indirectly refers to the phenomena on the above-molecular levels of biological organization. R. W. Adey (121) suggests that "quantum biology" would refer to the area of the investigation on the influence of electromagnetic fields on the molecular and cellular bio-structures, as well as on the means of electromagnetic communication in and between these entities.

The discussion of the meaning of the more specific terms, as: "supramolecular biology", "magnetobiology", "electric biology", "electromagnetic biology", and the "electrodynamics theory of life", along with the above mentioned ones, would go beyond the scope of the present work.

## Closing remarks

After the appearance of bioelectronics as a new direction in the way to look at the properties of biosystems and the mechanisms underlying the life phenomena, a noticeable interest in it has developed and many hopes were raised. As usual in such cases, only some of them proved well founded. In response to the difficulties met at various fronts of investigation, as well as to the not yet fulfilled hopes of solving such directly to the practice coupled problems, as: carcinogenesis, satisfactory knowledge of the mechanisms that control differentiation and regeneration in higher organisms, or the degree of the dependence of the state of organism on the spectral composition and intensity of external electromagnetic radiation, many more specific strategies were developed and new research targets were defined. Correspondingly, the original scope of bioelectronics has changed to some extent, and some techniques and research targets too broadly set have been abandoned. It may also be added that many results remain controversial, hypothetical, and some are erroneous. However, this state of affairs is not an exception among the situations in other fields of the scientific endeavor.

As a closing remark, it should be added that it was not the purpose of this article to assess the correctness of the results or the viability of the hypotheses and theories in bioelectronics. Its basic purpose was to show the outline of the conceptual structure of this branch of the science of bioelectricity, the main strategies of elucidating the connections between the living matter and its electronic properties, as well as to identify the difficulties which at present seem to be the most serious obstacles to its development. The full description of bioelectronics as a subdomain in the science of bioelectricity still remains to be done. However, as the miniaturization of the technical electronic devices reached the level of single molecules and the presence of molecular electronics is the fact of life (122), it seems that appropriate time has come to speak about biomicroelectronics (biological microelectronics). As a matter of fact, it has been virtually present in most of the studies done in the field of bioelectronics and it was alluded to its existence at least as early as in the sixties (99, 123-125). Describing the scope, purposes, and methods of this area of investigation is the aim of the article (1) that follows the present one.

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## BIOELECTRONICS: A BACKGROUND AREA FOR BIOMICROELECTRONICS IN THE SCIENCE OF BIOELECTRICITY

(Summary)

Bioelectronics is a branch, of science of bioelectricity dealing with biological systems and life processes from the angle of either physical or applied electronics with an aim to describe the electronic properties of biosystems and to establish their role in physiological phenomena, including the coupling that exists between the biological systems and their environment. Quantum biochemistry, physics of biological solid state, and the studies in the dependence of organisms on the external factors which may be realized with the involvement of the electronic features of bio- structures have been the three domains mainly contributing to the bio-electronic research. Because of the difficulties stemming from the complexity of organisms as well as from the lack of methodological and semantical studies, bioelectronics as a whole seems presently to be in a phase of slowing down its development. This does not hold true, however, as far as the development of biomicro-electronics a new subdomain in bioelectronics, is concerned. In fact, this biology-oriented counterpart of molecular electronics has been inherent in most of the bioelectronic studies since the very beginning of this discipline.