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On the physical nature of biopotentials, their propagation and measurement

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HIGHLIGHTS

- Biopotentials come from ion diffusion polarizing the organ border.
- Language of excess charge and polarization nicely complements the theory of membrane potential.
- Living tissue resembles an electrically isolated conductor, filled with electrolyte.
- Debye–Hückel theory for electrolytes well describes propagation of biopotentials.
- Polarization theory may help to improve simulation in neuroscience.
- Many macroscopic experimental cases may be described using single theory.

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ABSTRACT

This paper discusses various consequences of the fact that the physical nature of process of generation, propagation and measurement of biopotentials is inherently ionic. Source of macroscopic biopotential is the temporary deficit of charge captured by ionic channels, which polarizes the organ border. Electric properties of the living tissue seem to be dominated by the electrolyte which polarizes easily and fast. Current theory of biopotential which treats the body as a volume conductor of certain conductivity is an idealization, which does not consider polarization of tissue. Polarization in quasistatic approximation may be reliably described using the well-known Debye–Hückel theory for electrolytes, derived directly from Boltzmann equation and Poisson equation. The polarization theory for biopotential generation, propagation and measurement is conceptually simple and enables to model wider range of experimental conditions, such as dependence of the potential on ionic strength. Modification of the basic numerical assumption for biopotential modeling: the electroneutrality condition is proposed. The accuracy of the theory is verified by comparison with existing experimental results, which shows very good accuracy. This paper shows the importance of a proper physical description to interpretation of biopotentials. The topic is of special importance to electrophysiology and neuroscience, but affects all biopotential measurements, theories and numerical studies.

1. Introduction

A measurement in experimental physics is not always easy to interpret. This led Albert Einstein to an observation, that: “Whether you can observe a thing or not depends on the theory which you use. It is the theory which decides what can be observed”. This statement applies exceptionally well to current theory of biopotentials. Their measurement and

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modeling is important for (neuro)biology and electrophysiology [1]. According to Google Scholar, since 2000 this keyword has appeared 11,815 times, with growing tendency [2]. Mathematical modeling of biopotentials is used: (a) to explain how features of the source are mapped to a body surface, where they are commonly measured or (b) to show how can the body surface potentials be used to reconstruct the source activity [3]. Despite all great scientific achievements, supported by numerous numerical packages of computational biology, some of the basic assumptions of existing theories seem to be quite distant from the physical reality of the living body. Foundations of classical theory of biopotentials (CTB) in source and surrounding tissue were laid at times, when microscopic structure of organs and tissues was yet unknown. Certain ideas, that have been formulated at that time, are still in use. Purpose of this paper is to show that referring to physics and anatomy of electroactive organs, such as heart and brain, may simplify their analysis and interpretation.

The organization of the paper is as follows. First, the classical theory of biopotentials is introduced. It explains the generation, propagation and measurement of biopotentials under assumption that the living tissue may be represented by a volume conductor. Specifically, the biophysical foundations for biopotential are discussed and the explanation of their physical nature is proposed. Then, the polarization theory for biopotentials is proposed. It is explained how it enables to relax the principle of electroneutrality. Generation, propagation and measurement of biopotentials are explained in terms of the new theory, which is rather based on displacement current than on conductance current. Preliminary experimental validation is performed, based on a comparison with existing experimental data. Finally, all the limitations of the study and some possible benefits of the new theory are discussed, and conclusions are drawn. The paper represents the opinion of a physicist on widespread ideas, actively used in biological and clinical society.

2. Classical theory of biopotentials

The classical theory of biopotentials is composed of three associated classes of models: (1) the Hodgkin–Huxley class of models for membrane potential [4], immersed in the (2) monodomain or bidomain model, which starts from membrane potential and allows to reconstruct the activity of the whole organ (a.k.a. the source), and finally (3) the Laplace equation, which describes passive propagation between the source and the surface of the body [1]. The bidomain model assumes, that the conductance may be split into two pathways: the first one leads through the intracellular space with its specific resistivity and the second one takes place in the extracellular space. In geometric sense both regions occupy the same space and are connected to each other by the current, which is obtained from any immersed model for membrane potential. The bidomain model for source activity may be combined with that for passive propagation, so that the potential is derived directly from membrane potentials [5]. All models, which describe the relation between the membrane potential and the surface measurements, described in [1], are further referred to as volume conductor models.

2.1. Cell membrane

Models of dynamics of membrane potential V_m generally follow Hodgkin–Huxley model [4], in which the membrane is treated as a loaded capacitor:

$$C_m \frac{dV_m}{dt} = -\sum_j I_j(t) + I_{stim}(t) \tag{1}$$

The sum runs over all channel types and corresponding ionic species, I_{stim} is an applied stimulation current and C_m is membrane capacity.

Note, that Eq. (1) defines only the change of potential, regardless of its initial (resting) value. In Hodgkin–Huxley class of models, this resting value is the result of channel conductances and their respective reversal potentials [6]. Interestingly, the resting value for the membrane potential used in Eq. (1) is not derived from any first principles, but it is defined by Nernst law (2a), which in case of membrane potentials, was derived from experiment [7]:

$$V = \frac{RT}{zF} \ln \frac{c_{out}}{c_{in}} \tag{2a}$$

$$\Delta E = U \cdot ze = kT \ln \frac{P_{out}}{P_{in}} \tag{2b}$$

Here c stand for concentration of ions of valence z inside and outside the cell, R is gas constant and F - Faraday constant (electric charge of one mole).

Nernst law has an interesting physical background, namely a textbook model of statistical physics: model with two energy levels. The energy difference ΔE expressed as difference U of (external!) electric potentials, acting on ions on both sides of membrane, leads to equilibrium ratio of occupation probabilities for both "inside" and "outside" states, which is a direct consequence of the canonical ensemble. The ratio of probabilities has a form (2b), which after multiplication of the denominator and the numerator by N_A becomes Eq. (2a).

Eq. (2a) is typically derived from the condition for equilibration of fluxes: the diffusive flux, caused by concentration gradient and the drift flux, caused by potential gradient. It may be extended to many ionic species under the name of

Goldman–Hodgkin–Katz equation [7,8]. In electrochemistry Eq. (2a) is derived by applying the condition of equilibration of electrochemical potentials at both sides of the membrane.

In case of a biological membrane, the potential gradient U is not external: it is commonly expressed as a result of an electric field E within the membrane, integrated across the membrane, and the source of this field, like the displaced charge, is not directly discussed. In fact, Nernst equation describes an equilibrium in the vicinity of a membrane, where the potential is derived only from the difference in concentrations and neither from Coulomb potential of ions themselves nor from bulk concentration of charge.

All these facts lead to the conclusion, that Eq. (2a) does not directly define the electrostatic potential outside the cell, understood as a superposition of Coulomb potentials, resulting from a specific ionic mixture. This equation only states, that specific concentration ratio in the vicinity of a membrane acts as a certain potential gradient and may be treated as such. In multi-ionic systems the value of potential has no 1:1 correspondence to any specific composition of ions: according to Goldman–Hodgkin–Katz equation there exist infinitely many microstates defined by a set of ionic concentrations and channel conductances, which yield the same value of U. Description of a membrane in terms of its potential resembles description of physical system in terms of its energy: there are many microstates which lead to the same energy. Importantly, Endresen et al. have noted, that V_m is not a simple superposition of Coulomb potentials of ionic concentrations, as it depends on the concentration ratio and not on surplus charge (c.f. [9]). If concentrations on both sides of the membrane are, 10^n times larger, the resting value of V_m as defined in the Nernst equation, will not change. In the Hodgkin–Huxley theory, V_m is a central quantity, which *de facto* controls channel conductances. Note, however, that in many widely accepted models, such as smooth muscle cell model by Königsberger [10], dependence on V_m is shown to be insufficient, and direct dependence on $[Ca^{2+}]$ must be added to properly describe channel dynamics; e.g. for calcium induced calcium release (CICR) channels. In fact $[Ca^{2+}]$ is these models is considered twice: once as such and once as a component of membrane voltage. This is somehow justified by the fact, that $[Ca^{2+}]$ plays an important regulatory role, however it is impossible to discern, whether a formula for certain ionic current reflects the regulatory or the electrostatic role of $[Ca^{2+}]$.

Another weakness of the Hodgkin–Huxley class of models, which we experienced in our research, is their inability to model heterocellular coupling of cells with different resting potentials. The tendency of cells to equilibrate resting potentials, through potential coupling, dominates over all other dynamical effects and leads to oscillator death [11]. One of oscillators enters fixed state and ceases to oscillate, and this is not what is observed in experiment. A better theory of heterocellular coupling needs to be developed.

Great popularity of Hodgkin–Huxley class of models and associated volume conductor models, left little space to models addressing the physical foundations of biopotentials [9,12–14]; notably the electrodiffusive models of the membrane or tissue [12,14]. They start from the dynamics of individual ionic fluxes in order to provide the value of action potential, on the expense of somewhat higher computational expense, compared to that of lumped Hodgkin–Huxley models. Definitely, the value of these models lays in fact, that they are derived from first principles.

3. Volume conductor model

Models, which consider the relation of a cell with the surrounding tissue (volume) [1,5] are commonly built on a foundation laid by Wilson and coworkers [15]. Main assumptions of these models are as follows: (1) Generation of the signal (the source) is independent from its propagation (volume conductor), (2) The volume may be represented by a pure resistance, (3) What is observed in an electrogram is a result of activity of the source, which resembles the field of a dipole, which is spatially oriented. Hence, the interpretation of the ECG is primarily geometric.

In consequence there is large variety of interpretations of the electrocardiogram (ECG). The fact, that the ECG resembles a difference of membrane potentials, which seems to be quite obvious, was interpreted either as a result of the excitation wave, composed of depolarization and repolarization (a.k.a. the source and the sink) [15], or as the difference between the potential of endocardium and epicardium [16], or as a result of the equivalence of the heart to a set of oriented dipoles [15] or as the difference between the local and the remote component [17]. So far, the model, which is closest to physical reality, is the equivalent source model, which considers the organ border to be an equivalent source of biopotential [18]. However, still it is based on the volume conductor model, the validity of which is discussed below.

Volume conductor theory describes the relation of a cell with its surrounding tissue, which passively conducts the signal [1,19]. Intracellular and extracellular volume are two overlapped domains, which share the same volume, represented by two resistance nets interconnected by membrane currents. At each point the difference between the intracellular and the extracellular potential is equal to V_m. The idea that resistance elements are a suitable choice for the description of extracellular electric activity [1] originates from early cardiac potential research: when an additional conductor was used to shunt the epicardium and the skin, the skin potential got altered to the extent dependent on the conductance of the shunting medium [20]. Since than, in the so-called volume conductor theory [21], the tissue outside the studied organ is treated as a continuous conducting medium Ω of certain resistivity [1].

Biopotentials in a conducting medium, characterized by local conductance $\sigma(\vec{r})$ are represented by a scalar potential $\phi(\vec{r})$, which may be solved using Laplace equation (LE), with suitable boundary condition (which will be discussed in depth in the next chapter):

$$\nabla[\sigma \cdot \nabla\phi] = 0|_{\Omega} \tag{3a}$$

$$\sigma \cdot \nabla\phi \cdot \vec{n} = -\sigma\vec{E} \cdot \vec{n} = -\sigma\vec{E}_n = 0|_{\delta\Omega} \tag{3b}$$

Here $\vec{n}$ is a vector normal to surface. Solving Eq. (3a) in spherical coordinates yields a complex formula for potential as function of distance - c.f. (9.38–9.39 of [1]).

3.1. Electroneutrality

An important assumption, utilized in the Laplace theory (3a) is the electroneutrality of the tissue surrounding the organ. It is typically argumented, that there is no net charge in the tissue, which is thus effectively electroneutral [1]. As the electroneutrality has to be conserved during cell activity, there must be no current through the boundaries $\delta\Omega$. Equivalently, the normal component of potential gradient, related to currents via σ - c.f. eq. (Eq. (3b)) must vanish on the boundary $\delta\Omega$.

For cardiac potential propagation, the condition of electroneutrality is imposed both on the heart surface (source) and on the torso surface. The only nonzero components of $\nabla\phi$, allowed by the theory, are those, related to boundary surface currents. This assumption is used practically everywhere. Numerical packages used to solve Laplace problem using Galerkin method in a FEM/BEM setup share the same assumption, as all of them start from Laplace equation for volume conductor. There may exist certain currents within the source [5] but they have to be confined to its boundary [1].

There are few assumptions of the theory that may be questioned: (1) that the boundary condition implies that the electric field normal to the surface vanishes at $\delta\Omega$ and (2) that the volume of tissue does not contain any net charge (which justifies the use of Laplace equation), while in the same time the medium is modeled as a pure resistance. The electric field propagates through this resistance, producing some current, as the conductance is nonzero. The alternative explanation, given in the next chapter, allows to relax the condition (3b) without violating the electroneutrality principle.

4. Measurement

Final part of the biopotential theory is measurement of ϕ, typically done using metal or metal-salt-gel (e.g. Ag/AgCl) electrodes. In both cases, the ions approaching the electrode polarize it but do not enter the electrode [22]. The border of electrode is a natural barrier to ionic conductance.

Note, that the quantity measured under the name of biopotential is the change of potential with respect to certain baseline. If there is some static charge distribution within the body, e.g. double layer potentials of all membranes , it generates certain stationary potential $\Phi_0(\vec{r})$. Value of $\Phi_0(\vec{r})$ is disregarded as a constant component [18].

There are certain effects which are not handled by the [1,23] lead field theory, which describes the measurement in spirit of CBT. Firstly, it neglects the fact, that there is no continuity of ionic current at the electrode border, as there is a charge exchange process, in which ionic current in gel is converted to electron current in metal.

Secondly, it does not allow to model the fact, that the presence of an electrode partially polarizes the tissue below it: this effect is responsible for electrode repositioning noise, which is a great problem for ECG monitoring and specifically for EEG: input impedance of modern EEG amplifiers reaches even 1 TΩ [24] in order to minimize currents related to polarization effects. Values of cardiac potential between nearby points (and consequently the gradient of the source field) do not change so much; they depend mostly on distance from the source [1], so they cannot produce such a noise. The repositioning noise is not predicted by the lead field theory. Influence of other bodies, which may polarize the tissue is not regarded as well.

Actually one of technical principles of ECG measurement, is to avoid touching the patient during measurement. In fact the quantum physics approach applies here: the act of measuring affects the measured system. Presence of the electrodes or other polarizable bodies, such as the body of other human, distorts the body potential map. If we measure epicardial potentials through the open thorax, we have no guarantee that the potential is the same as within an intact pericardium. Interestingly, in biology, the signal measured by the electrode is interpreted as electric potential, while in electrochemistry, after calibration, it is a measure of concentration (potentiometric method). In fact, due to Nernst law, from the point of view of electrochemistry, it is all the same.

This analysis leads us to the question: what is the actual quantity measured by the electrode? This question is addressed below.

5. Polarization theory of biopotentials

In order to build a self-consistent theory for initiation, propagation and measurement of biopotentials, physical nature of conductance in the living tissue has to be addressed, to formulate minimum physical assumptions of the process.

5.1. Assumptions

Important assumptions concerning the conductance in the living tissue come from the analysis of anatomic structure of electroactive organs. Each electroactive cell is immersed in the extracellular fluid. For extracellular currents, all the ions which leave the ion channels are released into the extracellular volume. This volume is smaller than the volume of a cell. When certain number of ions is released from larger volume to smaller volume, the concentration change is different on both sides of the membrane. Thus the concentration is not conserved, which seems counterintuitive. The same is true for intracellular currents.

Taking the heart as the first example, in order to understand the properties of such source of biopotential, the anatomic structure of the heart has to be taken into account.

The heart is almost completely surrounded by non-conducting tissue: i.e. the dense fibrous pericardium: layer of connective tissue outside of the pericardial sac, which under normal quasistatic conditions does not permit any drift of ions to the surface of the thorax in finite time. Fibrous layer has a conductance ca 50 μS/m [25] which gives specific resistivity of 20 kΩ m. As the mean resistivity of thorax is appr. 10 Ω m [1], the fibrous layer conductivity is 3 orders of magnitude less than the thorax, which justifies the opinion that under (short and reversible) action of cardiac potential it does not permit any non-negligible current flow. In case of brain such natural border is the skull, with brain–skull conductivity ratio 19.7 [26].

Hence, the contact of the organ boundary with tissue volume does not really resemble a ohmic contact, as implied in the volume conductor theory. It rather resembles a plate of capacitor covered with a non-conducting dielectric layer, possibly accompanied with a certain amount of conductivity (imperfect dielectric). This dielectric may be polarized, but does not conduct a physical current, i.e. drift of ions.

In fact, the electrolyte in the extracellular volume (being a dielectric with dissociated salt) is easily polarizable, which has an effect nearly equivalent to that of the conductance, but the microscopic reality is completely different and polarization is definitely not equivalent to conductance.

The conducting tissue past the organ border responds to V_m as an imperfect dielectric inside a capacitor, but isolated from the capacitor plate. In fact, this behavior is consistent with the classical theory of biopotentials. The electroneutrality condition (3b) implies, that there may be no normal component of the field (potential gradient) at the organ border, as at nonzero σ it would lead to current flow. If we assume the contrary: that at the organ border $\sigma = 0$, then presence of $\vec{E}_n$ at the organ border does not cause any current flow and hence does not violate the electroneutrality principle, as the domains are physically disjoint. If $\sigma = 0$ is set, which is quite realistic, the condition (3b) might be relaxed. This could lead to better quality of computational models, which is a constant concern in this field, as the reverse Laplace problem is ill-posed [1]. And the idea, presented here, that the polarization of the organ border results in a nonzero $\vec{E}_n$, is quite natural. It is, in fact, introduced in late version of CTB as the idea of current dipoles [1], which have, however, no plain physical explanation [1].

The framework of the classical theory, described above, leads to certain inconsequences in interpretation of the ECG. If the depolarization of the tissue is modeled using Laplace theory [1], which permits only surface fields and currents, the part of the ECG curve relevant to depolarization of the septum is interpreted as a depolarization wave traveling perpendicularly to the septum, towards the free wall of left ventricle, which is not consistent with the measured isochrones of ventricular activation. The theory which was originally developed for planar atrial activity waves and neurones modeled with cable theory does not behave well in a true 3-D object, such as heart ventricles. In fact, the arguments for planar waves were extrapolated to volume sources [5,15]. Concerning the septum we adopt the idea expressed in the equivalent source model theory, that the activity of the septum contributes to the activity of the epicardium [18].

From anatomical point of view it seems more legitimate to treat the tissue as an isolated conducting medium and not as a pure medium without Ohmic barrier, but with a questionable condition (3b) imposed on source field. Consequently, there seems to be reasonable anatomical evidence for the fact the tissue may be treated as a conducting medium with negligible current inflow, and outflow and conserved charge.

The crucial difference between the conducting and the polarizable medium is its response to constant external electric field. In the conducting medium constant electric field leads to direct current. In polarizable medium, once all possible mechanisms of polarization are saturated, the polarization current drops to zero, regardless of the presence of external polarizing field. The current field induced by potential gradient (3a) is not a perfect candidate for a central quantity, to describe subsequent biopotential changes. It is proposed here, that the role of a source is played by charge itself, which makes the experimental scene much easier to model and to interpret. It also opens the scene to diffusive models, as shown below.

5.2. Source of biopotential

Let us consider a single cycle of activation of the electroactive tissue, such as the heart. From physical point of view it constitutes an active medium, which is ready to accept the igniting activation wave. Before the beginning of a cycle, the source of biopotential is in the state of thermodynamical equilibrium, which results in a certain static Coulomb potential $\Phi_0(\vec{r})$, certain static distribution of charge and certain dielectric/electrolyte polarization. We assume that the

static presence of all charges within the extracellular space before the cycle contributes only to $\Phi_0(\vec{r})$ and not to the action potential.

As a cycle begins, each cell activated by a wave of activation releases ions utilizing various passive and active conductance mechanisms. If we integrate Eq. (1) over time, in order to obtain the value of $V_m(t)$, the r.h.s. gets integrated over time as well. This latter time integral has a sense of $Q(t)$: the amount of charge deficit in the extracellular space at any time instant t. This fact is so obvious that it is strange that it has never been noted.

Deficit of charge decreases the concentration in the relatively small extracellular space and the outer layer of the organ (organ border) becomes unloaded: i.e. loaded with lesser surface charge, of certain planar density $\sigma_0(t)$ (lower than the resting value). When the wave of activation of cells travels through the tissue, it manifests itself by temporary unloading of the organ border. Depolarization of membranes within the source leads to depolarization of the border of the whole organ.

The impermeable membranes at the outer layer of the organ form a barrier, which prevents wide diffusion of ions. Such a wide diffusion would limit the ability of the cells to promptly complete the activation cycle.

The ions diffuse in EF only within a single muscle strand, in the volume limited by sarcolemma. Deeper layers within the source have a further way to the outer organ layer, but all the cells are coupled via the EF: it the ions cannot propagate freely, they will polarize the sarcolemma, with similar effect. The physical process involved in these changes is a diffusion-limited process which leads to an equilibrium. This equilibrium in polarization is reached faster than the propagation of activation, which is a complex process, which spans from the molecular to the cellular level, involving changes of protein conformation, opening the ionic channel, the dynamics of ionic channel and the resulting diffusion of ions. Process of polarization spread is on the molecular level, as discussed in the next chapter.

Initial depolarization of cells seems to move to the outer layer of the organ (inner layer, is affected as well - c.f. [27]). This depolarization is represented as a nonzero deficit charge density $\sigma_0(t)$, which may be obtained directly from integration of membrane currents.

Interestingly, the quality of the classical biopotential theory seems to come from the definition of capacity: proportionality between membrane potential and charge. In fact, the classical biopotential theory seems to be absolutely right, stating that the membrane potential is a cornerstone for the theory, but is seems, that the above is true due to the fact, that the potential happens to be strictly proportional to the momentary amount of deficit charge, which depolarizes the tissue.

5.3. Biopotential propagation in tissue volume

Although the source has already been successfully described using electrodiffusive model [14], even in the most modern numerical packages, the tissue volume is still described using bidomain model [14]. However, as a matter of fact, the medium outside the organ border is of the same nature as the tissue inside the organ; the only difference is the entirely passive conductance in the tissue volume. In consequence, the electrodiffusive models [14] may be extended to the tissue volume as well. In order to achieve this, we must start from the physical processes related to biopotential propagation. The response of the tissue to biopotentials seems to be dominated by the response of electrolyte: it is well known, that the conductance is strictly related with the amount of water in tissue and tissue perfusion [1,28].

Propagation of potential in a polarizable dielectric medium has two components: dielectric and conductive.

Dielectric component is polarization of all available dipoles: water molecules, proteins or suspended cells. Water at room temperature has $\varepsilon_r = 80$: any external field within the electrolyte is 80 times weaker, as the tissue gets polarized. This process is of nanosecond scale, as at low fields water molecules mostly get reoriented. Also any Coulomb interaction is 80 times smaller, which promotes dissociation [29]. This process is limited by the availability of dipoles: the bioengineers know, that the ECG is observed also in the air outside the body, but it quickly vanishes, as there is much less dielectric matter to polarize [30]. The bones are also very poorly (but still) polarizable, however it is typically attributed to their reduced conductance [1].

At the end of this process, each layer of tissue, including the measurement electrode, is polarized,

Conductance component is polarization of tissue fluids (intra and extracellular). Ironically, an isolated conductor, such as volume of electrolyte, behaves as a perfect dielectric of $\varepsilon_r = \infty$. All electric charges in an isolated conductor displace, in order to neutralize the external field. The process has a time scale of nanoseconds, which may be concluded from the dielectric and conductance spectrum of tissue (time constants may be read directly from resonant frequencies [31]). A quantity which naturally limits this process is the availability of ions, expressed as their concentration, or more generally, as the ionic strength of the electrolyte (see below). Unlike the true metal, in which the role of the polarizable medium is played by the electron gas, in a living body the role of physical plasma is played by cations: Na^+ dominates in the extracellular fluid and K^+ dominates in cytosol. Any stronger effect, such as deformation of charged proteins is possible but not probable at low endogenous fields.

At the end of this process, all available free ions in the electrolyte become separated and polarize the opposite borders of the volume considered, be it the sarcolemma, the skin, the skull or the pericardium.

The fact, that the ions possess the hydration shell does not prevent them from participation in conductance. The hydration shell is an object of complicated structure [32], which does not completely neutralize charge of an ion: note e.g., that despite the presence of hydration shell, salted water is a good conductor.

Relation between both components: conductive and dielectric within the framework of the classical theory was often discussed [28,33], final theory, however, favors the conductance (hence the name: volume conductor theory). The initial argument for disregarding the capacity in the classical theory was the observed similarity between tissue response to DC and AC [15], but note that the argument was only qualitative, and bridge measurements utilized the AC anyway [15]. Both components produce an outcome which is quite similar: the state of polarization and corresponding charge density gets transported from the inner to the outer border of the volume. The only limiting factor is the availability of water dipoles and free ions. It may appear contradictory at the first glance, but the more polarizable is the tissue, the less is the subsequent potential drop. If the density of charges in electrolyte is high enough, as in conductor, the electric fields is pushed out of the volume. As the electric field is equal to potential gradient, $\vec{E} = 0$ implies $\Phi = const$. Hence, potential drop in such a volume is zero.

If the organ is immersed in an easily polarizable tissue, the biopotential it produces is not reduced even at large distances from the source. The existence of a biopotential is limited mainly by a geometric factor, as discussed below. It is also known, that the biopotentials depend on the properties of tissue outside the source; regions of high conductance (or capacitance) attract the lines of electric field [1]. If the medium is uniform or if the distance is close, as for cardiac precordial leads, the biopotential is a localized phenomenon: i.e. the charge from the border of organ under the electrode is directly propagated to the electrode. Hence it is understandable, that electrodes that are close in space may record a different signal (as for precordial leads in ECG or scalp electrodes in EEG).

5.4. Propagation of biopotentials: quantitative model

As it was shown, not only the build-up, but also the propagation of biopotential seems to be a diffusion-dependent phenomenon. Consequently, instead of quite arbitrary theories, such as the bidomain theory, in which the tissue is modeled as a pure resistivity, regardless of its real nature, equilibrium statistical physics of the electrolyte may be used to describe spatial distribution of biopotential. And the actual solution to this problem appears to be long known.

Propagation of biopotential in macroscopic region Ω, filled with tissue, fits well into the general setup of Debye–Hückel theory, which was introduced to describe properties of electrolyte in the vicinity of charged surface [34]. If we treat epicardium or pia matter as a charged surface, the tissue outside of it, subject to electric field from the loaded surface, may be described using Poisson equation:

$$\varepsilon_0\varepsilon_r\nabla^2\Phi(\vec{r}) = -\rho(\vec{r}) = -\sum_{j=1}^{N}\left[q_j n_j(\vec{r})\right] - q_e(\vec{r}) \tag{4}$$

Index j index j runs over all ionic species. Each of species is characterized by spatially variable concentration $n_j(\vec{r})$ and its valence q_j. On the contrary to the classical theory, we do not assume, that the volume of thorax/scalp does not contain charge, even if net charge is zero. Presence of the charge in the medium is crucial, as it enables polarization of the isolated conducting medium. The second of discussed mechanisms: the dielectric polarization, is represented by ε_r in Eq. (4) - see below. Charge $q_e(\vec{r})$ in Eq. (4) is an external charge density, which is the source of the polarizing field. In case of biopotentials, the source is the loaded organ boundary $\delta\Omega$, or under even more crude approximation, we may represent it by an equivalent point source at $\vec{r} = 0$: $q_e(\vec{r}) = Q\delta(\vec{r})$, where δ denotes Dirac delta. In a quasistatic limit, the equilibrium concentration $n_j(\vec{r})$ follows the Boltzmann canonical distribution: $n_j(\vec{r}) = n_{j0}exp(-\frac{q_j\Phi(\vec{r})}{kT})$ where n_{j0} represents concentration. Utilization of the equilibrium theory to a dynamical phenomenon seems legitimate, as the polarization process is at least six orders of magnitude faster than the gradual polarization of the organ. Linearization of (4) leads to Debye–Hückel equation:

$$\nabla^2\Phi(\vec{r}) = \frac{1}{\lambda_D^2}\Phi(\vec{r}) - \frac{q_e(\vec{r})}{\varepsilon_0\varepsilon_r} \tag{5}$$

where λ_D is the Debye length: a constant expressed in units of length, as the Laplacian of Φ is in V/m^2 units. Electroneutrality condition is used in the theory to remove the constant term in linearization.

Debye length is defined as:

$$\lambda_D^2 = \frac{\varepsilon_0\varepsilon_r kT}{\sum_{j=1}^{N} n_{j0}q_j^2} = \frac{\varepsilon_0\varepsilon_r kT}{2N_A e^2 I} \tag{6}$$

The sum over ionic species resolves to the ionic strength I, commonly used in biophysics, which is btw. not considered by the classical theory for biopotentials. The ionic strength must be, however, renormalized; otherwise sub-femtomolar concentrations would be required: this is discussed below.

For a simplest case of point charge, the solution of Eq. (5) is a spherically symmetric potential:

$$\Phi(\vec{r}) = \frac{Q}{4\pi\varepsilon_0\varepsilon_r r}e^{-r/\lambda_D} + \Phi_0 \tag{7}$$

where Φ_0 represents an integration constant.

In fact, the simplest possible model setup is used here: spherically symmetric potential in uniform volume, surrounding the point charge. The more realistic description should address the following issues:

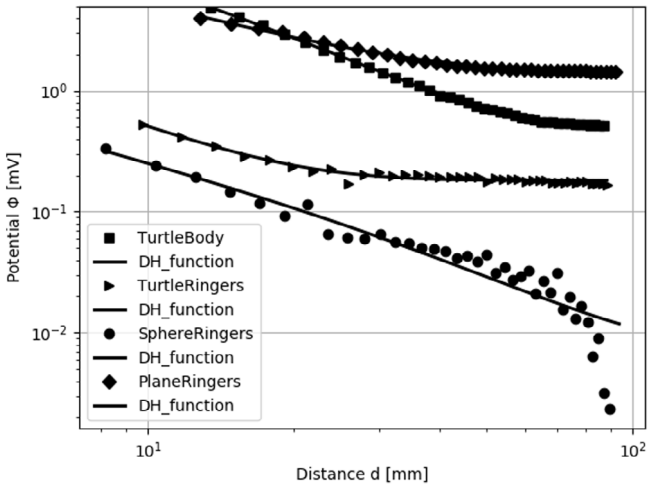

Fig. 1. Digitized curves from [35] (points) and results of Levenberg–Marquardt fitting for each experimental setup (lines).

1. The source of potential is not an excess point charge but rather the epicardium surface which is loaded (polarized) in its resting state and becomes depolarized when the intracellular currents begin,
2. The net amount of charge, transported through the membrane wall in the myocardium should be calculated for any time instant.
3. This charge polarizes/depolarizes the epicardium. An equivalent time-dependent charge source has to be constructed, resembling the one used in [18],
4. The charge density in the epicardium is not only the result of the true source distribution, but also of the capacitive properties of the outside tissue. A capacitor of higher capacity attracts more charge than that of lower capacity.
5. The tissue outside the heart is non-uniform so the potential wave will spread in an anisotropic manner,
6. The tissue is not a macroscopic volume filled with electrolyte of certain ionic strength, with certain solid structures immersed in it. It is composed of many macroscopic domains which, in turn, may be composed of microscopic domains. Each macroscopic domain will be polarized and this will also affects its microscopic domains. Also the domain walls may be oblique to the direction of potential propagation, which also may introduce anisotropy. It has to be verified if this fact can be represented as renormalization of ionic strength, close to the ideas used in soil modeling. The renormalization has to take into account the physical extent of simulated volume.
7. The Debye–Hückel equilibrium for each domain has to be calculated separately. Then, altered electric charge density at the domain wall acts as a source of polarization for another domain, somewhat alike to the Huygens principle. If the lack of charge causes incomplete polarization and potential drop, this will induce incomplete polarization of all other distal (outer) domains.
8. A special part of the tissue is the circulatory system, filled with low-resistance plasma. The ions have many possibilities to equilibrate gradient within this macroscopic volume. Note, however, that it was shown, that clipping the aorta does not affect the shape of the ECG [20].
9. A realistic shape of heart, torso and internal organs has to be taken into account.

It may be seen, that direct application of the polarization theory requires many partial theoretical studies, introducing different aspects of the theory and making it, step by step, more realistic.

5.5. Model validation

In order to perform basic validation of the model, we decided to use experimental plots of cardiac potentials measured in turtle by Eyster and coworkers [35]. The experiments included four types of experimental conditions: in turtle body (TB), turtle body replaced with Ringers solution (TR), sphere (SR) and plane (PR) of Ringers solution [35]. Under each condition cardiac potentials were measured and the potential difference was plotted. Turtle was selected, as the shape of the tissue approximates a sphere. The experiment is unique, as most probably it would not be allowed by any modern ethical committee. The curves of Fig.3 of [35] have been digitized using WebPlotDigitizer [36] and Eq. (7) was fitted using Levenberg–Marquardt algorithm [37]. As the potential in Fig. 1 does not always fall to zero, additional parameter Φ_0 was added to fitting to account for that fact.

The level of agreement between the experimental data and the Debye–Hückel model, shown in Fig. 1, seems to be quite satisfactory. The values of fitted parameters are given in Table 1. The values of the χ^2 statistics are three orders of magnitude smaller than critical values; even in the case, when the model results are only an approximation, as for

Table 1
Results of fitting Debye–Hückel model to data of Eyster et al..

Model	$Q/4\pi\varepsilon$	Λ_D [mm]	Φ_0 [mV]	χ^2
TB	105.91 ± 1.54	23.30 ± 0.51	0.47 ± 0.01	0.015
TR	8.83 ± 0.83	10.02 ± 0.82	0.18 ± 0.00	0.02
SR	2.97 ± 0.15	50.20 ± 14.45	0.01 ± 0.01	0.05
PR	53.84 ± 2.22	29.99 ± 2.53	1.38 ± 0.02	0.030

the case of a plane (PR), where 2-D Laplacian should be used instead of 3-D. The same would hold for better measures, e.g. power discrepancy.

6. Discussion

The novelty of the presented theory does not lay in the fact, that it builds up a brand new theory for biopotentials. Instead it shows, that we may reduce the problem of propagation of biopotentials in the living tissue to another problem which has been solved a long time ago: the Debye–Hückel theory for electrolytes.

This fact is important to many particular fields in modern bioengineering and electrophysiology. Problems such as: estimation of cross-talk between electrodes in EEG, physical description of intracellular potential coupling, role of temperature and ionic strength in generation and propagation of biopotentials, including the propagation of ECG, can now be solved within the framework of macroscopic electrodiffusive models, which may be reduced to the basic Debye–Hückel theory, but may also be extended to nonequilibrium problems. It shows, that the role of diffusion in biopotential description may be much better developed.

Taken the rising popularity of biopotentials, modeling the activity of a whole organ in language of diffusive processes for ions, emerges as an important problem.

Note, that the complete description of processes of generation, propagation and measurement may be done in the language of only one theory: polarization theory, with diffusion-based polarization of electrolyte. If we compare the results of the polarization theory with the results of the classical theory, both of them lead to formally similar spatial variability of potential ((7) vs. chapter 9 of [1]), however the latter is conceptually much mode complex. Its interpretation seems to be much more complicated as it uses many arbitrary parameters, such as intracellular and extracellular specific resistance (c.f. chapter 9 of [1]). The assumption, that the tissue is a purely conducting medium has determined the direction of biopotential analysis for years. If we assume, that the key role is played by polarization of tissue, which is able to transfer polarization of epicardium to polarization of skin, all the assumptions, including electroneutrality condition, are in place, and the theory describing the tissue shows to be in a complete agreement with Maxwell's equations.

If we assume, that the organ border is nonconducting, the assumption, that the normal component of the source potential gradient must vanish, may be relaxed, which can potentially improve the stability of numerical procedures used to solve the backward propagation problem.

All the parameters of Table 1 have a direct bearing to measurable values: ε_r, Q and λ_D related with ionic strength I. When the sphere is filled with Ringers solution, the potential drop is much lower, which means, that the value of potential, which comes from the source, appears at other terminal (skin) nearly unchanged. This is consistent with the experiments when the bulk tissue was shunted using medium of high conductance [20]. On the microscopic level, it was observed, that the microscopic electric field outside the isolated cardiac cell disappears very close to the cellular wall [38], which is quite different to the classical numerical predictions [39], but absolutely understandable for the electrolyte (past the double layer). For microscopic simulations λ_D has an order of magnitude of nanometers and represents the rate, at which the potential drops at membrane surface. For macroscopic simulations, the values of λ_D are larger: the potential vanishing within nanometer range would not be measurable. Note, that for the macroscopic systems, the r.h.s. of (4) is not large, as the net charge in bulk material is indeed close to zero, which leads to relatively high values of macroscopic λ_D. Macroscopic λ_D represents a summed effect of all individually polarizable components, such as cells, interiors of other organs, intravascular volume and other areas, which are easily polarizable, but may be electrically isolated themselves - c.f. Fig. 2. Ionic strength in Eq. (6) cannot be inferred directly from the value of λ_D, as this would lead to unrealistic sub-femtomolar concentrations. In electrochemistry and soil chemistry a generalized version of concentration is used under the name of activity, in order to account e.g. for the low volume of solvent, kind of solvent, concentration of electrolyte and many other factors. This kind of procedure has to be applied to a living tissue in order to quantify the relation between λ_D and the effective ionic strength I, affected e.g. due to the presence of a complex organic structure, which limits the free movement of ions and alters the effective volume of solvent.

Note, that in description of the capacitive component, there is the room for improvements. In the definition of λ_D, the ε_r appears in the numerator, so that a better dielectric leads to the larger λ_D, thus the potential drops faster. In the previous chapters it was shown, that both mechanisms act in parallel, and the proper place for ε_r would rather be the denominator. This apparent inconsequence comes from the fact, that the ε_r of the solvent strongly affects the dissociation constant, which is the result of minimization of Gibbs free energy. Hence, in a classical setup for Debye–Hückel theory, the dielectric constant defines what amount of the concentration of ions gets actually dissociated and what amount remains in

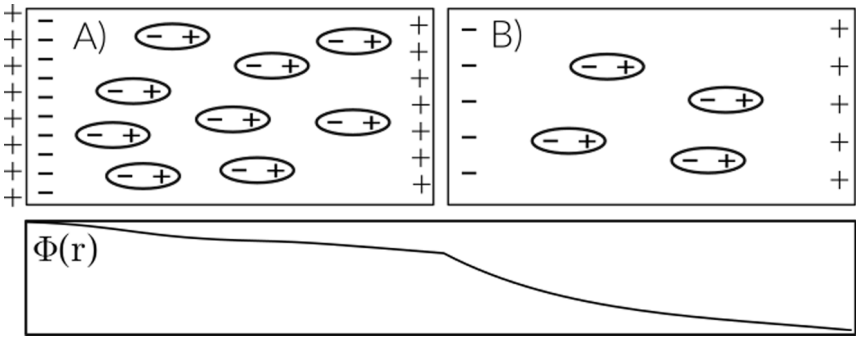

Fig. 2. Polarization and potential drop in region of good (A) and poor (B) polarization: high and low λ_D, respectively. Volume electric field (potential gradient) and resulting voltage drop in (A) is low, due to all mechanisms of tissue polarization. High voltage drop in (B) (bone, air) is caused by low polarizability, which may be mistaken for high impedance.

the undissociated form. The same effect regulates dissociation in biological solutions, as the mechanism is universal. Hence polarization of solutions with constructive role of capacitance remains an interesting theoretical problem to address.

Concluding, statistical physics, seems to give a clear, concise explanation of initiation and propagation of biopotentials. Electrodiffusive models [14] of statistical physics may benefit from integration with the macroscopic polarization model, which may be used instead of the bidomain theory. Note, that treating the biopotential as a result of depolarization caused by charge deficit seems to be closer to the physics of the system than attributing it to electric current of abstract nature (electron, ionic).

The fact, that the potential may spread only using displacement current and does not require true conductance is a novelty in theory of biopotentials. And it seems, that once again Einstein, who claimed, that it is the theory, which decides, what is actually measured, happened to be a man ahead of his time.

7. Conclusions

This paper defines foundations for polarization theory for biopotential generation, propagation and measurement. Current theory for biopotentials is sufficient for operational purposes, but adopting a more realistic physical scenario may lead to new, yet undiscovered, effects, interpretations (basic and clinical) and applications of biopotentials. Description based on electric field in a volume conductor is an idealization, which should be confined to the actual measurements of the underlying ionic currents in the tissue and their effect: i.e. the polarization of tissue, which is well described using Debye–Hückel theory for electrolytes. Modification of the basic numerical assumption for biopotential modeling: the electroneutrality condition is proposed, which may potentially improve the quality of inverse problem calculations. This contribution opens field to further numerical and theoretical verification of the polarization theory. The relative simplicity of the theory facilitates its utilization in electrophysiology, bioengineering and neuroscience.

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