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A conservative revolution: Julius Bernstein and his trip toward a membrane theory. A focus on bioelectrical processes in Mid-Nineteenth Century Germany

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ABSTRACT

This paper aims at illustrating the historical circumstances which led Julius Bernstein in 1902 to formulate a membrane theory on the resting current in muscle and nerve fibres. It was a truly paradigm shift in research into bioelectrical phenomena, if qualified by the observation that, besides Bernstein, many other electrophysiologists between 1890 and 1902 borrowed ideas from the recent ionistic approach in the physical chemistry domain. But the Bernstein's subjective perception of that paradigm shift was that it represented a mere re-interpretation of the so-called "pre-existence theory" advanced by his teacher Emil du Bois-Reymond in the first half of the 19th century.

Key words

Bernstein • Molecular Theory • Ions • Membrane Theory

Introduction

According to the current neuroscientific opinion, Julius Bernstein's membrane theory on resting current in muscle and nerve fibres, initially put forward in 1902, with later refinements on the mechanism underlying negative variation, or action potential, added in 1912, represented a paradigm shift in research into bioelectrical phenomena, and laid the groundwork for a true revolution in electrophysiology headed by Andrew F. Huxley, Alan L. Hodgkin, Howard J. Curtis, and Kenneth S. Cole some 40 years later. We would like to underline Bernstein's subjective perception of that paradigm shift. Specifically, his idea that an electrochemical definition of the problem was a mere interpretation of the so-called pre-existence theory his teacher Emil du Bois-Reymond had advanced in the first half of the 19th century and to which Bernstein would, albeit with reformulations, remain essentially loyal.

Bernstein's molecular theory

According to Heinrich J. Boruttau, a Göttingen physiologist writing in 1904 a review about the history of electrophysiology, "the discussion on the *question of the origin of bioelectrical phenomena*" seemed to have entered into a "new stage": du Bois-Reymond's *molecular theory* "by the end of the century had been replaced by a nearly unanimous acceptance of Ludimar Hermann's *theory of alteration*" (Boruttau, 1904, p. 427). For Boruttau the last remaining exponents of molecular theory were Bernstein and Isidor Rosenthal (1899, pp. 238-239). Hermann, who was one of the du Bois-Reymond's

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brilliant students, held that the electromotive effects of animal tissues were attributable to chemical changes in living substance that manifested themselves as atrophy and necrosis. This "alteration theory" claimed that the contractile substance is able to respond to injury with an electromotive reaction, in accordance with the law that the injured part will behave electronegatively with respect to the intact segment. Thus, the electromotive force of resting current *arises from the injury itself* and can be detected at the "demarcation surface", i.e., at the contact surface between the tissue undergoing atrophy and the physiologically intact tissue. According to this view, excitation has the same effect as injury, which justifies the term "demarcation current" Hermann coined to denote negative variation.

Proposing his "molecular theory", du Bois-Reymond asserted that muscle fibres were composed of "small longitudinally arranged particles" which he viewed as "electromotive molecules" ordered in rows and immersed in a conducting fluid (du Bois-Reymond, 1848, pp. 682-683). He called them "peripolar" because they had a positive charge in the equatorial zone and a negative charge in the two polar areas. In this theory, it was implied that contractile tissue had all the conditions for electrically respond to any injury or stimulation.

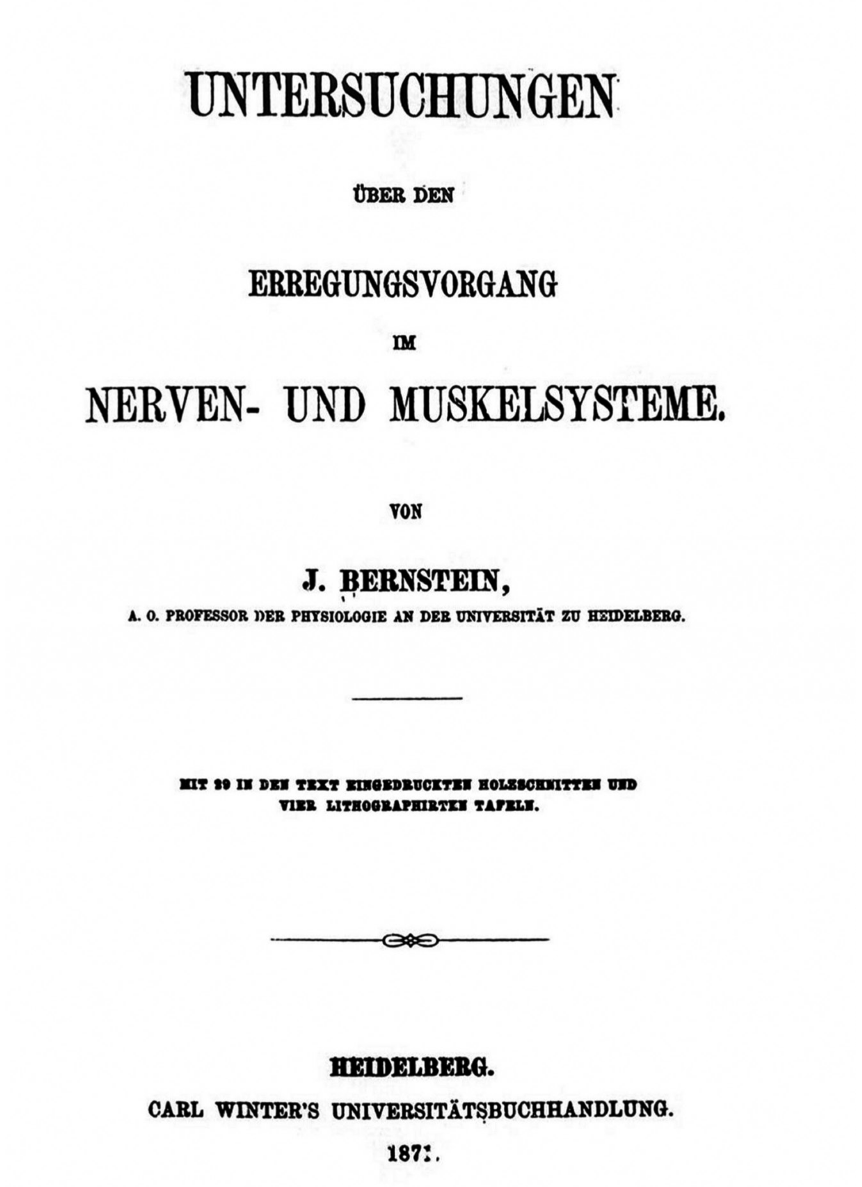
Bernstein, the other eminent du Bois-Reymond's scholar, not only rejected Hermann's alteration theory but also criticized his rival for having termed the bioelectrical phenomenon "demarcation current", which implied acceptance of a specific interpretation. Basically, this was a theory-laden expression – to use a present-day epistemological concept – that was emblematic of the way in which a scientific term's connotation goes beyond a phenomenological datum to incorporate a certain theoretical interpretation: in this case, the alteration theory. So Bernstein preferred "negative variation" for a datum that could be experimentally controlled. According to his molecular theory "from this arrangement of molecules a current must run from the longitudinal to the transverse section in an applied electric arc", and this current run "through the conducting fluid of the muscle fibre or its moist sheath" (Bernstein, 1894, p. 358). This explains why Bernstein defined it "pre-existence theory" in reference to both the original molecular theory and his versions dating from the 1870s and 80s. "The theory of muscle and nerve currents as proposed by du Bois-Reymond presupposes – Bernstein said – a pre-existence of electrical voltages in the molecules in the muscle fibre".

In his 1871's *Untersuchungen* Bernstein mentioned du Bois-Reymond's use of a "purely physical method" and defended his teacher against opponents who had claimed an "unreal and incomprehensible nervous agent that was more like a mythological divinity than a force of nature" (Bernstein, 1871, p. 2). Bernstein reasserted the identity between excitation of a nerve fibre and negative variation, which propagates in wave form and can be observed experimentally.

Moreover, proposing again the core idea of du Bois-Reymond, Bernstein maintained that the nerve vital properties suggested that "inside the nerve fibre [there is] a particular molecular arrangement" (Bernstein, 1871, p. 35) and that excitation of the nerve fibre is to be conceived of as a movement of molecules, for which he offered no further hypotheses, however (Bernstein, 1874, p. 58). Bernstein rejected the idea that muscle current and negative variation were caused by chemical processes alone, as Hermann's theory stated, in opposition to purely electrical causes, as postulated by du Bois-Reymond. Whether chemical or electrical in origin, muscle current and negative variation "depend on an orderly arrangement of small particles, without which none of these processes can take place" (Bernstein, 1871, p. 236).

Bernstein and the electrochemical version of molecular theory

In 1888 Bernstein returned to the idea of a "linear arrangement of molecules" in excitable tissues, now setting it within a different context that was not specifically electrical. Instead, he framed it as a chemical process linked to a metabolic concept of resting and excitation states. To explain this change of mind, we must enter another student of du Bois-Reymond, Eduard Pflüger, who was in this turn of time his assistant in Berlin. In an article on the theory of respiration he emphasized the biological importance of carbon in binding similar atoms into chains and networks, wherein the formation of organic molecules or "living proteins" proceeded in a process of continuous growth owing to polymerization.



UNTERSUCHUNGEN

ÜBER DEN

ERREGUNGSVORGANG

IM

NERVEN- UND MUSKELSYSTEME.

VON

J. BERNSTEIN,

A. O. PROFESSOR DER PHYSIOLOGIE AN DER UNIVERSITÄT ZU HEIDELBERG.

MIT 29 IN DEN TEXT EINGEDRUCKTEN HOLZSCHNITTEN UND
VIER LITHOGRAPHIRTEN TAFELN.

HEIDELBERG.
CARL WINTER'S UNIVERSITÄTSBUCHHANDLUNG.
1871.

Fig. 1. - The title page of the 1871 extensive monograph in which Bernstein reported the results of his electrophysiological investigation with the differential rheotome.

In this highly materialistic context, into which the conceptual frame of Justus von Liebig's chemistry was set, Pflüger saw in isomery and polymery the basic properties of protein molecules.

Pflüger underlined that a characteristic of living material is that it can be decomposed by oxygen, linked somehow to the molecular arrangement that causes the involved atoms to oscillate (Pflüger, 1875, p. 327). Drawing on Pflüger's theory, in 1888 Bernstein formulated an "electrical molecular theory" to give "a special interpretation" of his former conception based on internal molecular processes and the concept of excitability as an oxidative process. This was an attempt to incorporate chemical concepts derived from Pflüger into an interpretation of bioelectrical phenomena.

From Pflüger Bernstein adopted also the idea of a living protein molecule, composed of a stable core with oxidizable atomic groups arranged on its longitudinal sides, and side chains of oxygen atoms which, in addition to binding the adjacent molecular cores, have properties that make them extremely unstable the farther the chain extends from the core. At the resting state, the tissue will have a low metabolic rate which becomes more or less strong following a stimulus; therefore, the oxidative process that breaks the molecular bonds is simply the "chemism" of the state of excitation. At this point, Bernstein could interpret in metabolic terms the two phases of negative variation:

"The ascending segment of the stimulus wave represents the symptom of liberation of chemical voltage in the living fibre and the descending segment represents the symptom of restoration of voltage; in other words: the ascending segment signifies dissimilation of the muscle and nerve tissue, the descending segment signifies its assimilation" (Bernstein, 1888, p. 98).

During this time, roughly over the span of a generation, an apparently "radical change" emerged in Bernstein's interpretation of bioelectrical phenomena. Essentially, these years marked a shift from a purely physicomechanical concept, based on du Bois-Reymond's original paradigm, to a nearly chemical view of the conditions of resting and excited states of nerve and muscle tissues. Yet, subjectively, Bernstein felt he had remained loyal not only to his concept of nerve and muscle fibres as sequences of atoms or peripolar molecules, but especially to his belief in the pre-existence of electrical voltage in the resting state, voltage generated by the particular arrangement of atomic groups in chains.

"Our theory – he concluded – may be called a theory of pre-existence insofar as it assumes that in the molecules there exists a pre-existing disposition of atomic groups such that, after laying bare an artificial transverse section of a series of molecules, electrical voltages follow, which previously existed in a bonded state" (Bernstein, 1888, p. 62).

The birth of electrochemistry and its implications for physiology

In 1902 membrane theory arose at the intersection of as many different fields of inquiry. These developments concern the work by Moritz Traube in physical chemistry around the mid-19th century; the later experiments in plant physiology by the botanist Wilhelm Pfeffer; and the theory of osmosis in solutions proposed by the Dutch physical and organic chemist Jacobus van t'Hoff in a 1887 article that appeared in the first volume of the *Zeitschrift für physikalische Chemie*, which also included a paper on electrolytic dissociation by Svante Arrhenius. These two articles marked the birth of the new discipline of physical chemistry, which culminated with an explanation that Walther Nernst will advance the following year for the potential difference generated in the so-called concentration cells.

Traube in 1867 gave a mechanistic explanation for a vital phenomenon he considered of utmost importance: cell formation and growth. Cell growth was understood by analogy to a mechanical model with which a semipermeable precipitate membrane of contact between two solutions could be produced.

Ten years later, Pfeffer continued working in this direction, focusing his studies on plant organisms with a view to explain, again, in mechanistic terms, the vital phenomenon of plant metabolism in terms of an osmotic exchange between the inside and the outside of the cell. Pfeffer saw a similarity between the physical structure of living cells and of artificial inorganic cells specifically built to measure osmotic pressure.

He solved the problem of Traube's fragile precipitate membrane by constructing an artificial "cell" structurally similar to a plant cell and with a semipermeable membrane. Pfeffer's work on diosmotic phenomena inevitably attracted interest from botanists, eminent among which was the Dutch botanist and geneticist Hugo de Vries who was working on plant cell turgor and maintained correspondence with his friend van't Hoff. Moreover, working on the theory of solutions, van't Hoff set up an osmometer equipped with a semipermeable membrane, in order to achieve quantitative determinations for the osmotic pressure. In this context he proposed an analogy between gases and solutions, but he noted certain discrepancies with the gas laws, specifically, with Avogadro's law. It was Arrhenius who explained this discrepancy proposing that in solutions it was matter of a dissociation in *ions* of the solute molecules. This "ionistic theory" was corroborated experimentally by Arrhenius which tested the relationship between osmotic pressure and electrolytic dissociation. Due to Wilhelm Ostwald's

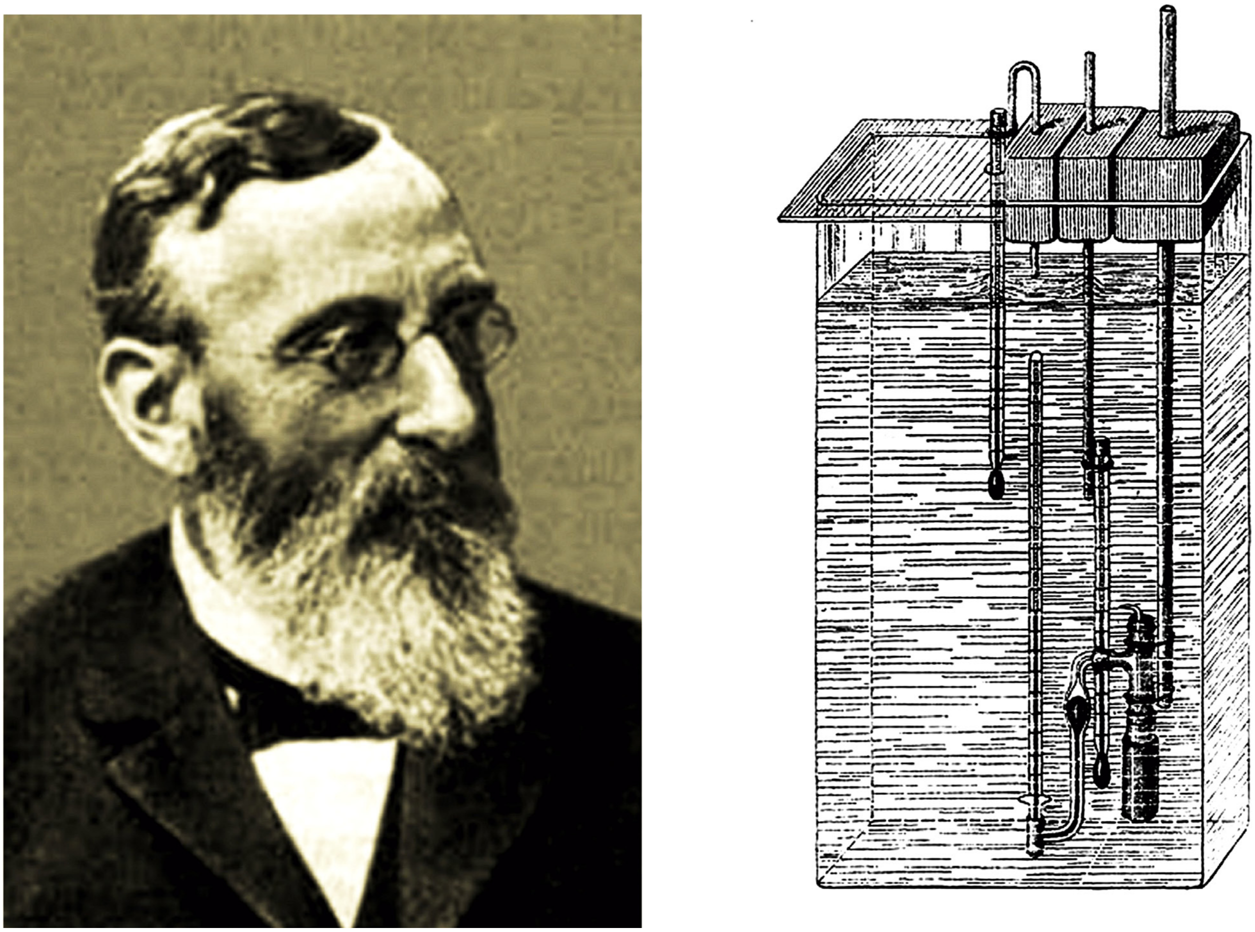


Fig. 2. - Plant physiologist Wilhelm Friedrich Pfeffer (1845-1920) with, on the right, an image depicting his osmotic cell.

forceful propaganda this ionistic approach gained a certain acceptance not only in chemists's community, but also in a number of physiologists, who were working on the biolectrical phenomena.

In a paper on the effects of the semipermeable membranes, Ostwald came out with a statement, destined to be quoted a lot of times:

"It is perhaps not too bold to conjecture that through the properties of the semipermeable membrane discussed here an explanation could be found not only for electrical current in muscles and nerves but also for the puzzling effects of electric fish in particular" (Ostwald, 1890, p. 80).

The theory of electrolytic dissociation opened the way for a rethinking of the function of galvanic cells and particularly of the concentration cells that Hermann von Helmholtz had studied in an exclusively thermodynamic ambit.

Towards the membrane theory

In the 1890 article, Ostwald cited Traube's work on diffusion and osmotic pressure, where the semipermeable membrane would act like an "ionic sieve". Ostwald stated that "There exists a permeability or an impermeability of membranes not so much for certain salts as rather for certain ions". Only certain ions rather than others (positive or negative) cross the membrane, and the semipermeable membrane becomes the site of potential differences.

Because by selective passage the number of ions on one side of the membrane increases, resulting in a different concentration on either side, Nernst was able to explain the formation of the potential difference at the membrane through an equation in which the essential elements involved in the cell were mathematically related. Ostwald proceeded to an application of this equation in physiological ambit and now Nernst's merit was to have characterized this context in terms of an ionistic theory.

The first to have attempted a quantitative determination of the potential difference in reference to a living tissue by means of the Nernst's formula was Vasilij Jur'evich Chagovec of the Imperial Military Academy at St. Petersburg, who described the protoplasm as an electrolytic solution in which the salts were in the conditions Arrhenius had predicted. He was the first to apply mathematical equations of the ionistic theory to these phenomena.

Then the Finnish physiologist Maximilian Oker-Blom also viewed muscle tissue physiologically as a concentration cell. He held electrochemical views: the semipermeable membrane works like a sieve which permits the selective passage of the ions.

Around the same time, Charles E. Overton, under Max von Frey at the Department of Physiology, University of Würzburg, had studied the osmotic properties of plant cells before turning his attention to the muscles of vertebrates.

According to Overton: "Only the sodium ions are important for the processes of conduction of excitation and muscle contraction, whereas the anions and the non dissociated molecules play no part or at most have a minor role" (Overton, 1902, p. 368).

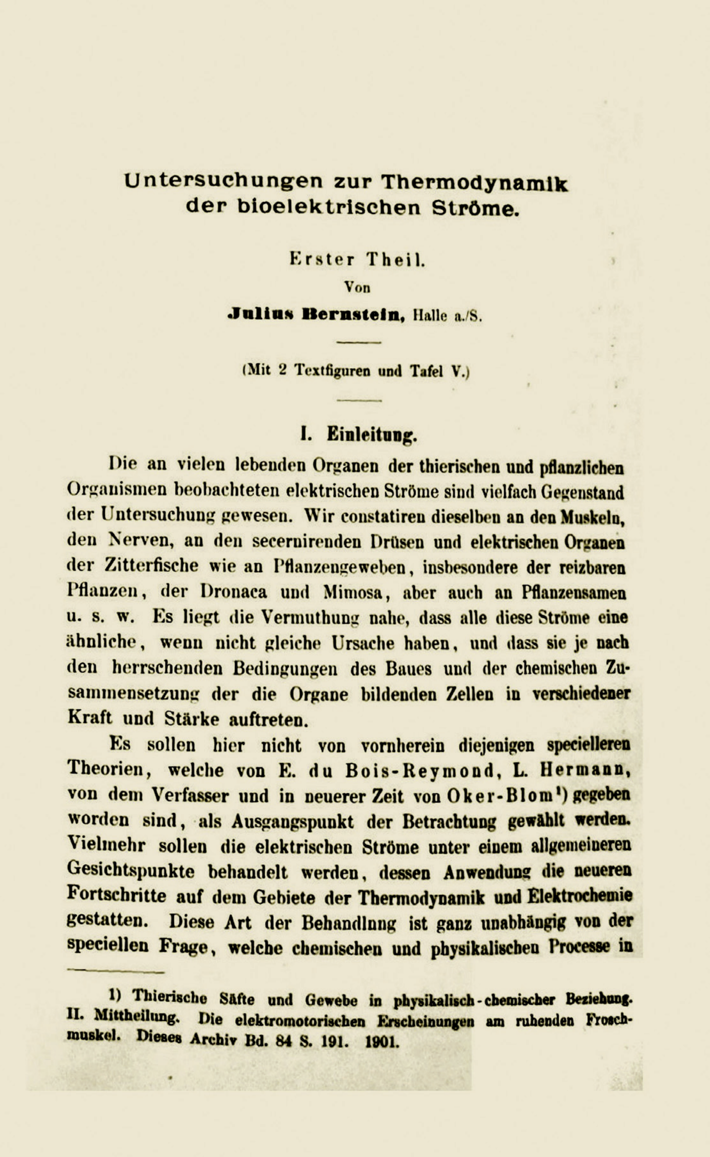
A conservative revolution

Between 1890 and 1902, a number of independently working researchers, including Napoleon Cybulsky (Jagellona University, Krakow), Boruttau, Oker Blom, Overton and also English physiologists such as W. Strong and John Smith Macdonald, were applying ionistic concepts to nerve and muscle physiology. In 1901, Oker-Blom had criticized Bernstein, accusing him of "inapt" use of the term "electrochemical membrane theory" to describe his 1888 theory. Oker-Blom wrote: "Starting from du Bois-Reymond's molecular theory, Julius Bernstein announced a modification in 1888 which he inaptly called the 'electrochemical theory of excitation processes and electrical phenomena of nerves and muscles'" (Oker-Blom, 1901, p. 193).

Returning to Bernstein, in February 1902, Bernstein and Armin Tschermak published an article on energy expenditure during muscle contraction based on experiments conducted between 1899-1901 (Bernstein and Tschermak, 1902). The studies on the thermodynamics of bioelectrical currents, in which the membrane theory was first mentioned, date from March-May 1902, which renders absurd the idea of a sudden change of course in the short time between the publication of the two articles that year, insofar as the first appeared in February and the experiments for the second began no more than a month later. Timothy Lenoir's hypothesis that "radical changes" had occurred over these few months, with the substitution of the molecular for the membrane theory, therefore appears implausible (Lenoir, 1986, p. 35). On the contrary, the theorizing on concentration cells as models of nerve-muscle preparations, to which Nernst's equation could be applied, might be dated earliest to 1900 when Bernstein referred to Nernst's *Theoretische Chemie* in a new appendix included in the second edition of his *Lehrbuch* (Bernstein, 1900), and exposed new ideas on the electrical conductivity of solutions and ion mobility. In his 1902 article, in which he first explained the membrane theory, Bernstein mentioned Ostwald's famous statement of 1890, where he underlined the crucial role of the semipermeable plasmatic sheath, and claimed that a chemical process cannot be considered as a direct source of electrical energy, "muscle current belongs to a series of concentration currents" (Bernstein, 1902, p. 539) and so depends only on a diffusion process.

Bernstein expanded on Ostwald's idea of the semipermeable membrane as a determinant factor in the generation of current in biological cells: the potential difference observed in biological cells resulted from the membrane blocking the passage of an ion of the electrolyte: 2 different potentials form at the longitudinal and the transverse sections, respectively: "Let us imagine that these electrolytes diffuse freely from the transverse section of the fibrils into the surrounding fluid, whereas their diffusion at the longitudinal section is inhibited by the living sarcoplasmatic sheath, because it is more or less impermeable to their ions, for example, to the anion; then, on the fibril surface there will form a double electrostatic layer, the inner of which would carry a negative charge and the outer one a positive charge" (Bernstein, 1902, p. 542).

Despite the appearances, Bernstein's arrival at the membrane theory from the molecular theory through the "electrochemical theory" did not constitute so drastic a change in course as to Lenoir's eye.



Untersuchungen zur Thermodynamik der bioelektrischen Ströme.

Erster Theil.

Von

Julius Bernstein, Halle a./S.

(Mit 2 Textfiguren und Tafel V.)

I. Einleitung.

Die an vielen lebenden Organen der thierischen und pflanzlichen Organismen beobachteten elektrischen Ströme sind vielfach Gegenstand der Untersuchung gewesen. Wir constatiren dieselben an den Muskeln, den Nerven, an den secernirenden Drüsen und elektrischen Organen der Zitterfische wie an Pflanzengeweben, insbesondere der reizbaren Pflanzen, der Dronaca und Mimosa, aber auch an Pflanzensamen u. s. w. Es liegt die Vermuthung nahe, dass alle diese Ströme eine ähnliche, wenn nicht gleiche Ursache haben, und dass sie je nach den herrschenden Bedingungen des Baues und der chemischen Zusammensetzung der die Organe bildenden Zellen in verschiedener Kraft und Stärke auftreten.

Es sollen hier nicht von vornherein diejenigen specielleren Theorien, welche von E. du Bois-Reymond, L. Hermann, von dem Verfasser und in neuerer Zeit von Oker-Blom[1]) gegeben worden sind, als Ausgangspunkt der Betrachtung gewählt werden. Vielmehr sollen die elektrischen Ströme unter einem allgemeineren Gesichtspunkte behandelt werden, dessen Anwendung die neueren Fortschritte auf dem Gebiete der Thermodynamik und Elektrochemie gestatten. Diese Art der Behandlung ist ganz unabhängig von der speciellen Frage, welche chemischen und physikalischen Processe in

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1) Thierische Säfte und Gewebe in physikalisch-chemischer Beziehung. II. Mittheilung. Die elektromotorischen Erscheinungen am ruhenden Froschmuskel. Dieses Archiv Bd. 84 S. 191. 1901.

Fig. 3. - The title page of 1902 article in which Bernstein first expounded his "membrane theory".

On this point there is precise evidence published in a note in the third edition of Bernstein's *Lehrbuch*, where he stated: "The 'electrochemical molecular theory' in the previous editions of this book was an interim transition (*Übergang*) to the membrane theory, insofar as this theory also assumed polarization of the fibers, but, according to the model of du Bois-Reymond's theory, transferred it to the molecules without being able to indicate the cause" (Bernstein, 1910, p. 330, note). Again, as mentioned in his 1902 article, Bernstein wanted to underline that, compared with Hermann, "The essential difference between the two theories resides in the assumption that [owing to the injury by cutting] the electrolytes forming in the transverse section take part in the current by means of alteration, and that these electrolytes pre-exist in the living fibre or fibril. But this theory of pre-existence rests essentially on the membrane theory" (Bernstein, 1902, p. 560).

The double layer also had to be pre-existent: it "must be present also in the undamaged fibre, but it could manifest only after injury or due to excitation (negative variation). This assumption would have the appearance of a theory of pre-existence; accordingly, as the semipermeable membrane carries out an essential role, in brief, I shall call it 'the membrane theory'" (Bernstein, 1902, p. 542).

We now dispose of the elements for justifying our title: a conservative revolution. Bernstein's paradigm had not undergone substantial changes since the first experiments (1868) on the temporal course of the negative variation, conducted within the framework of du Bois-Reymond's theory. His main concern was to defend what he thought was the fundamental aspect of his teacher's doctrine, i.e., the theory according to which muscles and nerves present with all the necessary conditions for generating phenomena of animal electricity. Having elucidated the role of the semipermeable membrane as a primary cause of the generation of potential difference, Bernstein underlined that the membrane theory was to all effect a theory of pre-existence. Du Bois-Reymond sought to explain bioelectrical phenomena without the use of agents or *sui generis* forces, but rather along the lines of physicomechanical theories circulating at that time. Some 50 years later, Bernstein took on the same task, demonstrating that the bioelectrical phenomena had to be framed within the emerging discipline of electrochemistry, since this branch of science proved able to unify the most diverse fields of inquiry. As an interpretive mechanism, this unification enabled Bernstein to conserve what he considered was his teacher's basic lesson: the idea of pre-existence.

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