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Julius Bernstein (1839–1917): pioneer neurobiologist and biophysicist

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Abstract Julius Bernstein belonged to the Berlin school of "organic physicists" who played a prominent role in creating modern physiology and biophysics during the second half of the 19th century. He trained under du Bois-Reymond in Berlin, worked with von Helmholtz in Heidelberg, and finally became Professor of Physiology at the University of Halle. Nowadays his name is primarily associated with two discoveries: (i) The first accurate description of the action potential in 1868. He developed a new instrument, a differential rheotome (= *current slicer*) that allowed him to resolve the exact time course of electrical activity in nerve and muscle and to measure its conduction velocity. (ii) His "Membrane Theory of Electrical Potentials" in biological cells and tissues. This theory, published by Bernstein in 1902, provided the first plausible physico-chemical model of bioelectric events; its fundamental concepts remain valid to this day. Bernstein pursued an intense and long-range program of research in which he achieved a new level of precision and refinement by formulating quantitative theories supported by exact measurements. The innovative design and application of his electromechanical instruments were milestones in the development of biomedical engineering techniques. His seminal work prepared the ground for hypotheses and experiments on the conduction of the nervous impulse and ultimately the transmission of information in the nervous system. In 1912, shortly after his retirement, Bernstein summarized his electrophysiological work and extended his theoretical concepts in a book *Elektrobiologie* that became a classic in its field. The *Bernstein Centers for Computational Neuroscience* recently established at several universities in Germany were named to honor the person and his work.

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1 Introduction

Julius Bernstein belonged to the prominent school of physiologists in Germany that was represented by Emil du Bois-Reymond, Hermann von Helmholtz, Ernst von Brücke and Carl Ludwig. They called themselves "organic physicists" and played significant roles in creating modern physiology during the second half of the 19th century.

Bernstein was trained and educated under du Bois-Reymond in Berlin, then worked with von Helmholtz in Heidelberg, and finally became Chair of Physiology at the small university of Halle (near Leipzig), where he stayed until his retirement. His work was mainly concerned with what we would now call "biophysics and neurobiology", i.e., the physiology of nerves, sense organs, and muscles. Nowadays his name is primarily associated with his "Membrane Theory of Electrical Potentials" in biological cells and tissues and with the innovative design of his "Differential Rheotome" that allowed the first, exact measurements of bioelectric signals. Who was Julius Bernstein? And why was he a pioneer in neurobiology and biophysics?

Here, I first provide some biographical information on Bernstein, his family background, and his academic career. I will then describe two of his discoveries for which he is best known, i.e., the first description of the action potential in nerve and muscle (in 1868), and his Membrane Theory of 1902. Finally, I will mention some of his other achievements and what became of them.

2 Family background, education, and academic career

Bernstein was born in Berlin in 1839 – nine years before the German Revolution of 1848 – into a very progressive and liberal environment. His father was Aaron Bernstein (1812–1884), a political writer, journalist, and publisher, who was one of the founders of the "Berliner Jüdische Reformgemeinde" [Berlin Congregation of Reform Judaism] in 1845. Eduard Bernstein (1850–1932), a well-known politician, writer, and theoretician of the Social Democratic Party, was

Sommersemester 1882.

1) Publice: Medicinische Physik, Montag von 9–10 Uhr.

2) Privatim: Physiologie des Menschen, die animalen Functionen, Dienstag bis Sonnabend von 9–10 Uhr.

3) Privatim: Physiologische Übungen im Laboratorium, 2 mal wöchentlich von 4–6 Uhr.

4) Privatissime u. gratis: Untersuchungen im physiologischen Institut, für Geübtere, täglich von 8–1 Uhr

Anfang Donnerstag d. 27 April.

J. Bernstein.

Halle a/S
22. April. 82.

Physiologisches Institut

Fig. 1 J. Bernstein as Professor and Chair of Physiology at the University of Halle. *Left* Portrait taken ca. 1875 (Archiv, Humboldt-Universität Berlin). *Right* Bernstein's announcement of his public lectures and private lab courses, summer semester of 1882. Note that the lecture listed under [*1)*] is entitled "Medical Physics" (Universitätsbibliothek Heidelberg: Heid. Hs. 2649,64)

Table 1 Brief chronology of Julius Bernstein's academic career

Year	Position
1858–1860	Medical studies at Universität Breslau (Silesia); Bernstein's mentor was the physiologist Rudolf Heidenhain (1834–1897).
1860	Return to Berlin; training in electrophysiology in Emil du Bois-Reymond's laboratory.
1862	Doctoral dissertation on muscle physiology of invertebrates.
1864	Postdoctoral position ("Assistant") with Hermann von Helmholtz in Heidelberg; development of differential rheotome.
1865	University Lecturer ("Habilitation", Dozent).
1869	"Ausserordentlicher Professor", Universität Heidelberg.
1871	Interim Head of Physiology Department, Heidelberg, after von Helmholtz assumed position as Chair of Physics in Berlin.
1873–1911	Chair of Physiology at Martin-Luther-Universität, Halle a.d. Saale, succeeding the renowned neurophysiologist Friedrich Leopold Goltz (1834–1902).
1890/1891	Rector Magnificus, Universität Halle.

Julius Bernstein's cousin. In his biography of Aaron Bernstein, Schoeps (1992) provides an excellent introduction to the intellectual and political history of mid-19th century Berlin.

Aaron Bernstein supported his son's interest in the natural sciences. In fact, when still a young student at the Gymnasium, Julius often visited the laboratories of the Physiological Institute at the University of Berlin – which was then directed by du Bois-Reymond (1818–1896). After medical studies at the University of Breslau (Silesia) he returned to Berlin and earned a doctorate in medicine for work done on invertebrate muscle physiology in du Bois's laboratory. He then spent seven formative years as an assistant to the renowned physiologist and physicist Hermann von Helmholtz (1821–1894) in Heidelberg.

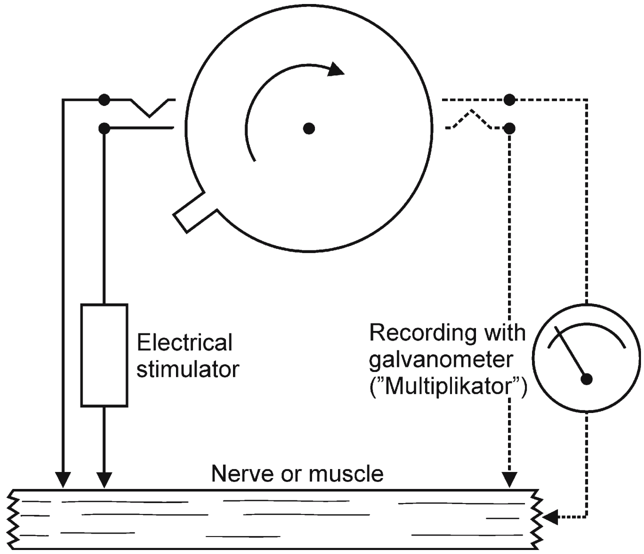


Fig. 2 Differential rheotome ("time slicer"), principle of operation. The cam on a turntable briefly closes a circuit for electrical stimulation and subsequently a second circuit, in which a galvanometer records the nerve or muscle activity ("negative variation"). The delay time between stimulus and recording interval is set by adjusting the angle between the two switches. The speed of the spinning wheel and the width of the cam are set so that the galvanometer is connected to the recording electrodes for only a fraction of a millisecond (adapted from Schuetze 1983)

Following another brief interlude in Berlin, Bernstein (at the age of 34) was appointed Chair of Physiology and Director of the Physiological Institute at the University of Halle. The portrait shown in Fig. 1 was taken at about this time. In 1881 he moved into a new institute building that had been constructed and equipped according to his specific requirements and wishes. He lectured on "Medical Physics" and taught courses in physiology (Fig. 1, right). Bernstein worked in Halle until his retirement in 1911. Table 1

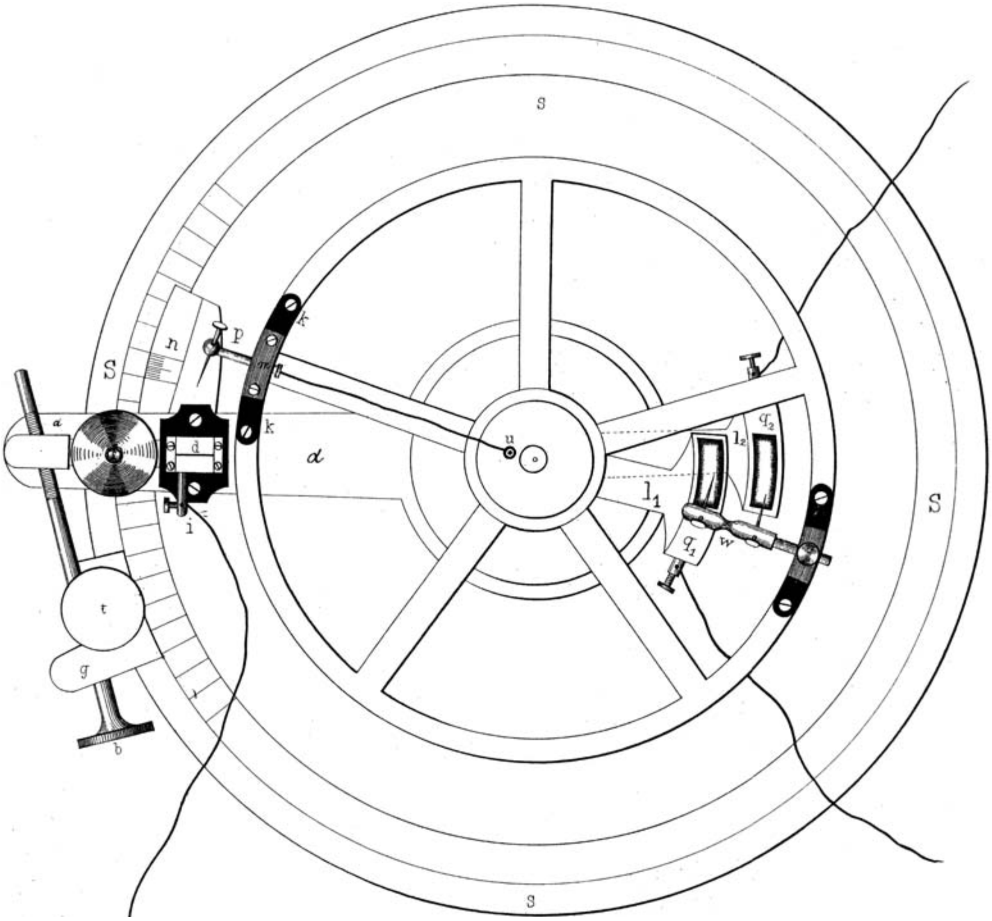


Fig. 3 Bernstein's differential rheotome; top view of instrument (reproduced from Bernstein 1868). A fine pin (p) on the rotating wheel briefly touches a thin copper wire (d) to close the stimulus circuit (*left*). The recording circuit (*right*) is closed when a pair of pins lightly brushes across mercury contacts contained in q_1 and q_2. The closing time (= sampling interval) is set by adjusting the relative positions of the mercury contacts. The delay between stimulus and recording is fine-adjusted by screw b. The whole device is less than 20 cm in diameter

summarizes the major positions of his training and academic career. Additional biographical details are provided by Zett (1983).

3 The differential rheotome: first description of action potential (1868)

Bernstein's time in Heidelberg under Helmholtz proved to be very productive. Four years after he moved there, he published a paper in Pflügers Archiv, vol. 1, that made his name well-known among physiologists. In modern terms, Bernstein's report was the first quantitative description of the "action potential".

To appreciate the importance of Bernstein's first major achievement, some brief historical background information is required: Around 1840 – in experiments on cross-sectioned, resting frog muscle – the Italian physicist Carlo Matteucci (1811–1868) had observed an outward current flow from the area of the axial cut (i.e., from inside) to the undamaged surface (the outside) of a muscle preparation. This was called "injury current" or "demarcation current" in *resting* nerve and muscle.

A few years later, using electrical stimuli to activate the nerve or muscle, du Bois-Remond discovered a temporary decrease in the injury current that he termed "negative variation". At about the same time, in 1850, Helmholtz found that the conduction speed of the "excitatory process" in nerve-muscle preparations was about 30 m/s ["*Fortpflanzungsgeschwindigkeit der Nervenreizung*"]. But it remained controversial whether Helmholtz's "excitatory process" and du-Bois' "negative variation" were conducted at the same speed. Were they possibly identical? The response time of du Bois' instrument was simply too slow to answer the question [see, e.g., the article by Piccolino (1998), for a detailed discussion of these historical controversies].

Bernstein solved the problem. He designed a new instrument, a differential rheotome or "current slicer", that allowed him to resolve the time course of electrical activity in nerve and in muscle. The principle design and operation of the new instrument are shown in Fig. 2. Essentially it is a "ballistic galvanometer" with a timing and sampling device: The center piece is a turntable with a small cam that closes and opens two circuits: one for electrical stimulation of a piece of nerve or muscle, the other for recording – or actually sampling – du Bois' "negative variation" with a conventional galvanometer. Specifically, the device connected the galvanometer to the recording electrodes for only a fraction of a millisecond (= angle subtended by the cam divided by the angular velocity of the wheel; usually 0.3 ms), and only after a delay following the brief stimulus (= angle between stimulus and recording switches, again divided by the angular velocity of the wheel). The delay was variable and could be set with submillisecond precision. Bernstein used repetitive stimuli and added (that is, he essentially averaged) the recordings. Figure 3 is a drawing of the actual instrument as shown in Bernstein's original description of 1868. The history of electromechanical devices leading up to Bernstein's rheotome are reviewed in a detailed article by Hoff and Geddes (1957).

Figure 4 shows Bernstein's reconstructions of the time course (top) and the spatial distribution (lower panel) of the "negative variation" in frog nerve as sampled with the differential rheotome. These diagrams, published in 1868, are considered the first accurate description of the action potential in nerve (Schuetze 1983).

Three years later, Bernstein summarized his observations in a monograph with 240 pages and numerous illustrations (Bernstein 1871). He dedicated the book to his prominent mentors, du Bois-Reymond in Berlin and Helmholtz in Heidelberg. The main results and conclusions from his measurements are: (i) The "negative variation" is transient; it lasts about 1 ms, and its time course is not dependent on stimulus strength. (ii) With strong stimuli, the amplitude exceeds that of the injury current ("overshoot"). Hence the negative variation is more than the simple breakdown of a resting state. Bernstein did not reliably observe an "overshoot" in recordings from muscle, only from nerve, and chose to ignore this finding in later work (see the discussion of his "Membrane Theory" below). (iii) The average rate of propagation is 28.7 m/s, i.e., similar to Helmholtz's result of 1850. Hence "excitatory process" and "negative variation" are presumably identical. (iv) In muscle, the negative variation has almost run its course *before* the onset of contraction. This seemed to indicate that the negative variation is a molecular process, and that it prepares the contraction.

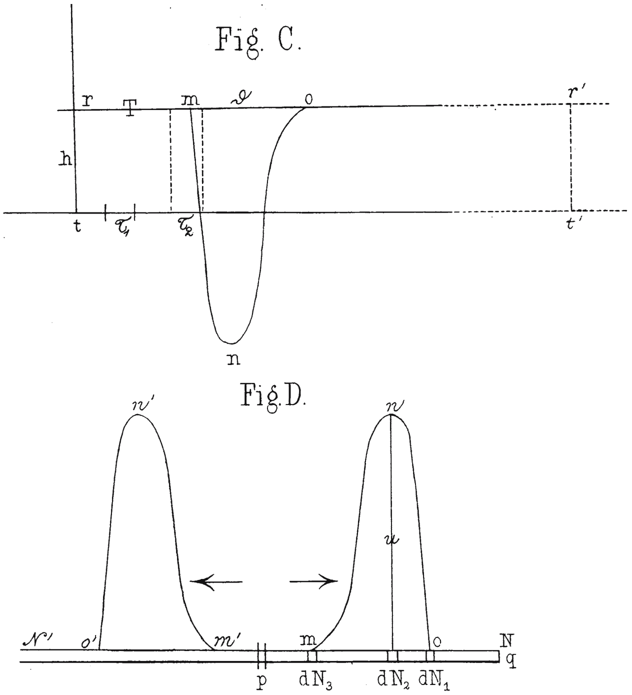


Fig. 4 "Negative variation" (action potential) in frog nerve as sampled by Bernstein with differential rheotome. *Top* Bernstein's reconstruction of the sampled (and averaged) signal along time axis $t - t'$ corresponding to one rotation cycle of the rheotome. T_1, T_2 sampling interval; r–m latent period; m–o duration of negative variation n. Note that the "negative variation" greatly exceeds the amplitude of the "injury current", h. *Bottom* Spatial distribution of "negative variation" along nerve fiber at one given moment. Bernstein plotted two waves resulting from a stimulus delivered at point p and moving in opposite directions (*arrows*). The distance o–m corresponds to the spatial distribution of "negative variation" mno with the peak amplitude u; dN_1, dN_2, dN_3 represent sampling intervals (reproduced from Bernstein 1868, Tafel III)

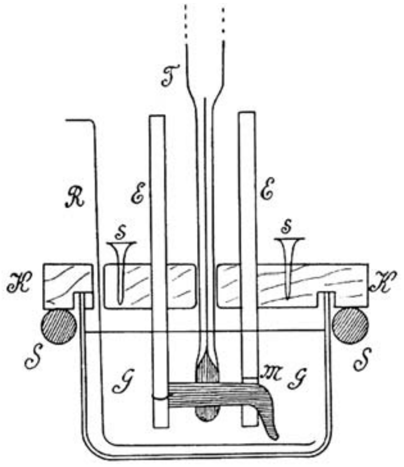
4 Membrane theory (1902)

Bernstein's second major achievement was his Membrane Theory, first published in 1902 when he was 64 years old. This theory provided the first plausible, physico-chemical explanation of bioelectric events. It was based on two assumptions that he tested with relatively simple experiments and calculations (Fig. 5).

(i) Following the suggestions of Walter Nernst (1889) about diffusion potentials of chemical solutions at different concentrations and temperatures, Bernstein treated muscles and nerves as chains of concentration circuits. The concentration values of inorganic substances inside and outside of nerves were well known at the time. Bernstein applied the equations first developed by Nernst to predict the electrical potentials from concentration gradients and compared these with the "injury or resting current" that he measured in nerve and muscle.

(ii) Almost at the same time as Nernst published his equations, the chemical physicist Wilhelm Ostwald (1853–1932) suggested that the electrical potential across artificial semipermeable membranes was due to their selective permeability to ions. Bernstein applied these concepts to muscle and nerve fibers, and treated the non-conducting fiber shell as a semipermeable membrane.

The simple experimental setup used by Bernstein for his measurements is shown in Fig. 5. He kept an isolated preparation of frog muscle (or nerve) in oil in a glass jar. Clay recording electrodes (non-polarizable, soaked in saline) and a sensitive thermometer were attached to the muscle. The jar was put in a water bath, the temperature was varied between −2 °C and +36 °C, and the "resting/injury current" was measured carefully. Bernstein found that the current (here representing the "electromotive force") increased linearly with absolute temperature, both in muscle and in nerve. Hence



Nernst equation:

$$E = \frac{RT}{F} \ln \frac{\left[K^+\right]_{out}}{\left[K^+\right]_{in}}$$

E: equilibrium potential of potassium

T: absolute temperature

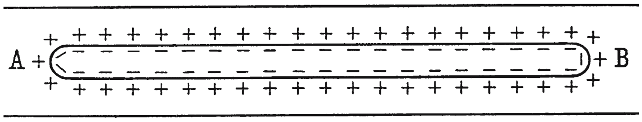
R: gas constant

F: Faraday (electr. charge/mole)

$[K^+]$: potassium concentration (activity)

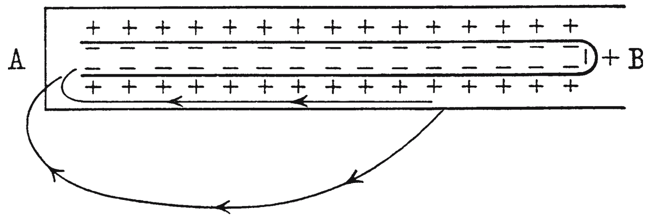
Fig. 5 Membrane theory of 1902. *Left* Experimental setup used by Bernstein to measure the effect of temperature on "resting/injury current" of muscle or nerve (reproduced from Bernstein 1902). The muscle preparation (M) is kept in oil in a glass jar (G); clay electrodes (E) are attached to the cross section (*left*) and the surface of the muscle (*right*) to measure the "injury current". A thermometer (T) monitors the temperature of the muscle surface. A cork-lid (K), held by rubber bands tied around pins (s) and a support (S), tightly closes the setup. The jar is put in a water-bath for gentle heating. A stirrer (R) serves to keep the temperature even in the oil surrounding the preparation. *Right* Nernst equation for potassium as found in modern textbooks. See further discussion in text

Fig. 32a.



Unverletzte Faser mit elektrischer Doppelschicht, stromlos.

Fig. 32b.



Verletzte Faser mit elektrischer Doppelschicht,
Längsquerschnittsstrom.

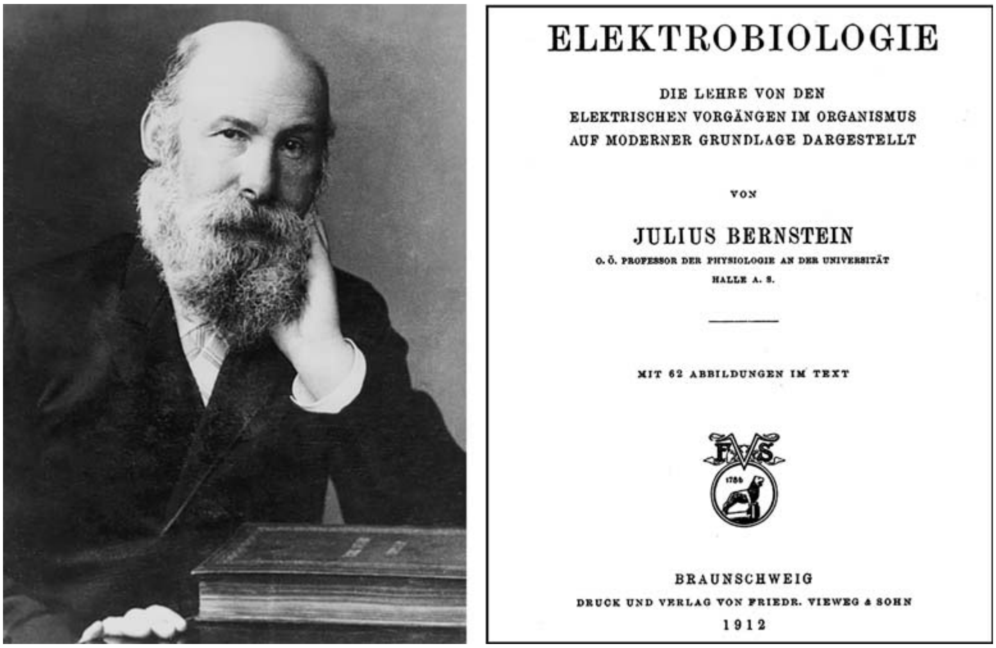
Fig. 6 Schematized drawing of the "electrical double layer" at the surface of a muscle fiber (AB) that was used by Bernstein to discuss the essential features of his "Membrane Theory" of 1902. *Top (Fig. 32a)* intact fiber, in which no current flow was measurable. *Bottom (Fig. 32b)* fiber injured on the left (i.e., cross-sectioned at *A*); now the "negative charges towards the inside and the positive charges towards the outside (...) become apparent" (reproduced from Bernstein 1912)

his experimental results matched his predictions based on the Nernst equation (Fig. 5, right). This was good evidence to assume "*that the electrical potential of the lesioned muscle is caused by the electrolytes, in particular by inorganic salts such as* K_2HPO_4*, already contained in the undamaged muscle fiber*" (Bernstein 1902).

Bernstein used the illustration shown in Fig. 6 to compare the situation in intact versus injured fibers, and he wrote (Bernstein 1902) – referring to the injured fiber (Fig. 6, lower panel):

"*Let us imagine that these electrolytes diffuse unhindered from the axial cross section of the fibrils into the surrounding fluid, while they are prevented from diffusing through the longitudinal section by an intact plasmalemma which is impermeable to one kind of ion such as the anion* (PO_4^- *etc.) to a greater or lesser degree. Then an electrical double layer would emerge at the surface of the fibril, with negative charges towards the inside and positive charges towards the outside. Indeed, this electrical double layer must also exist in the undamaged fiber, but would become apparent only in response to lesion or stimulation (negative variation). This assumption would imply a theory of pre-existence. As the semipermeable membrane plays an essential role in this theory, I will succinctly call it 'Membrane Theory'*." [My translations from the original German text].

The main results and conclusions from Bernstein's (1902) study are: (i) Living cells are composed of an electrolytic interior surrounded by a thin membrane that is selectively permeable to ions. (ii) *At rest*, there is a pre-existing electrical difference of potential across this membrane that only becomes apparent upon injury. It increases linearly with absolute temperature and does not depend on metabolic processes. This potential corresponds exactly to the "resting or injury current", hence confirming the predictions made by the Nernst equation. (iii) During *activity*, the ion permeability of the membrane increases (primarily for potassium) in such a way as to reduce this potential to a comparatively low value – thus causing the "negative variation". (iv) Curiously, Bernstein (1868) limited his considerations to potassium as the decisive cation and did not trust his previous result of the "overshoot", i.e., the reversal in potential. It was not until the 1940s and



ELEKTROBIOLOGIE

DIE LEHRE VON DEN
ELEKTRISCHEN VORGÄNGEN IM ORGANISMUS
AUF MODERNER GRUNDLAGE DARGESTELLT

VON

JULIUS BERNSTEIN
O. Ö. PROFESSOR DER PHYSIOLOGIE AN DER UNIVERSITÄT
HALLE A. S.

MIT 62 ABBILDUNGEN IM TEXT

BRAUNSCHWEIG
DRUCK UND VERLAG VON FRIEDR. VIEWEG & SOHN
1912

Fig. 7 *Left* Julius Bernstein as Rector of the University of Halle; portrait taken ca. 1890 (Universitätsarchiv Halle, Repro 40, BI 18). *Right* Title page of Bernstein's seminal treatise "Elektrobiologie" of 1912. It remained the definitive text on the topic for the next 25 years and is still cited in textbooks

the development of intracellular recording techniques that the overshoot was "re-discovered" and Hodgkin and Katz (1949) formulated their "sodium hypothesis", which explained the transient reversal in resting potential by an influx of Na^+ (see also the discussion by Grundfest 1965).

In 1912, shortly after his retirement, Bernstein published a detailed summary of his electrophysiological work and his theoretical concepts under the title "Elektrobiologie" (Fig. 7, right panel). The book contains numerous illustrations and drawings from his own hand. On the very last page (p. 212) Bernstein suggests using the cathode-ray oscilloscope to record rapid (and spontaneous) nerve signals. His treatise amounts to the first quantitative theory of nerve- and muscle action based on solid experiments, exact measurements, and biophysical models that finally led to a paradigm shift in the understanding and further investigation of bioelectrical processes.

5 Concluding remarks

Here I have only briefly touched upon two of Bernstein's major accomplishments. Although his name is now primarily associated with his Membrane Theory, Bernstein was definitely a hands-on experimental physiologist. In fact, he pursued an intense and long-range program of experimental research that kept him and his associates busy for several decades. He developed several novel techniques and invented new apparatus for his measurements, among them various electromechanical stimulators and intricate timing devices. His differential rheotome of 1868 has been called "in a real sense the first instrument of electrophysiology" (Hoff and Geddes 1957); its electromechanical design and physiological application remain landmarks in the development of biomedical engineering techniques. In most of his work Bernstein achieved a new level of refinement and precision, thus providing new insights and a firm basis for future studies [see the article by Lenoir (1987) for a detailed discussion of the transition in physiology from merely descriptive work to analytical studies]. His publication list contains well over 100 titles, including 5 monographs. His textbook "Lehrbuch der Physiologie" [General Physiology for Medical Students] (Bernstein 1894) acquainted several generations of medical students with modern (i.e., contemporary) physico-chemical concepts of physiology; it went through three updated editions and included an Appendix on basic concepts of chemistry and physics. Bernstein trained several medical scientists who later became well known in their own fields such as the Hungarian gerontologist Fritz Verzár (1886–1979) and the pharmacologist Ernst Laqueur (1880–1947).

In 1890, Julius Bernstein was elected Rector of his university (Fig. 7, left panel). As a title for his rectorial address he chose "The Mechanistic Theory of Life – its Foundations and Successes", a theme very much in the tradition of the Berlin school of "organic physics". Bernstein was the first Jewish rector of a German university. Despite the wide-spread anti-Semitism that pervaded German society at that time, I found no signs of overt discrimination against him.[1]

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[1] The situation drastically changed in 1933 after the rise to power of the Nazis. They immediately dismissed Bernstein's two sons who held academic positions at the University of Göttingen (Felix Bernstein, 1878–1956) and the University of Halle (Robert Bernstein, 1880–1971). Both were forced into exile with their families.

Julius Bernstein died in Halle in 1917 – six years after his retirement. He was highly regarded by his friends and colleagues – as scientist, university teacher, and mentor. His former student and collaborator Armin von Tschermak (1919) called him "a true paragon of a German scholar".

Acknowledgements This paper is based on an invited lecture that I gave at the inauguration of the *Bernstein Centers for Computational Neuroscience* in Berlin on October 14, 2004. I thank Leo Peichl, Andrew S. French, and Gerrit Isenberg for helpful information and advice. Archives at the universities of Halle, Berlin and Heidelberg provided the photographs and other source material.

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