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Opinion

Understanding the Scope of the Contemporary Controversy about the Physical Nature and Modeling of the Action Potential: Insights from History and Philosophy of (Neuro)Science

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Abstract

According to mainstream neuroscience, the action potential (AP) is a purely dissipative electrical phenomenon that should be modeled as such. However, also (essentially) reversible mechanical, thermal, and optical changes in the neuron have been reported to accompany the movement of the AP along the axonal surface. These are not accounted for in the prevailing (bio)-electric theory of neuronal excitability, originally introduced by Hodgkin and Huxley (HH) and mathematically formulated in their famous HH model of the AP. An alternative theory and model of the AP has been developed recently by the membrane biophysicists Heimburg and Jackson (HJ). Based on the laws of macroscopic thermodynamics, in the HJ model, the AP is treated as a compression wave propagating in the axonal surface membrane, similar to the movement of acoustic pulses in a material. Predicting both electrical and non-electrical manifestations of the AP to result from a reversible lipid phase transition in the axonal membrane, the HJ model explains neuronal excitability as an electromechanical process driven by the thermodynamic properties of the lipid membrane. Promising to provide a complete representation of the AP phenomenon, the introduction of the HJ model was heralded by some as a (potential) revolution in neuroscience but was largely dismissed by mainstream neuroscience. Applying Kuhn's well-known philosophical analysis of paradigm shifts in science and Giere's theory of perspectival realism to the case, we here argue that, instead of a competition for truth between the HH and HJ models, chances for further development and evaluation of the thermodynamic theory as a comprehensive explanation of the AP is better served by considering the controversy in terms of an interaction between two incompatible but valid scientific perspectives. In our opinion, doing so will provide a fruitful theoretical basis for experimental efforts to improve the explanatory understanding of the physical nature of neuronal signaling.

Keywords

Neuron; action potential; bioelectricity; paradigm; explanation; axon; thermodynamics; perspectival realism; soliton

A knowledge of the historic and philosophical background gives that kind of independence from prejudices of his generation from which most scientists are suffering. This independence created by philosophical insight is in my opinion the mark of distinction between a mere artisan or specialist and a real seeker after truth.

(Albert Einstein, in a letter to Robert Thornton (1944), as quoted in [1].

1. Introduction: Hodgkin and Huxley's Bioelectric Theory and Model of the Action Potential

It is commonly believed that neurons communicate using binary (all-or-none), stereotyped pulses of electrical activity. According to this view, these pulses, called action potentials (APs), self-propagate along the surface of axons without (significant) change of shape, speed or duration [2]. Described as such, APs, as self-regenerative distinct and conservative waves of electrical activity, are thought not only to represent the essence of neuronal excitability but also to provide a pulse-coded and reliable way of sending information over distance from one neuron to the next. Often treated as a form of received and fully scientifically validated knowledge, nowadays, to most, it appears as unequivocally established that the message contained in and conveyed by the nerve signal is of a purely electrical or, considering synaptic, neurotransmitter-mediated, transmission, electrochemical nature [3]. However, although only scantly acknowledged in recent scientific literature, it is important to note that over the last 150 years this electricity-centered conception of the physical nature of neuronal signaling has been repeatedly challenged (see next paragraph and for more elaborate recent overview see, [4]). In recent decades this critique of the 'electricity-only' theory [3], has focused in particular on the physical underpinnings of the landmark mathematical model of the AP, the so-called Hodgkin and Huxley (HH) model. Careful analysis of the available literature shows that the HH model, introduced in its original form in the early 1950's [5], should be considered the culmination of an intensive effort by a long list of early neurophysiologists from the 1850s onwards to conceptually and physically explain and formally characterize the electrical nature of the pulse-like signal carried by nerve cells [4]. In their highly appraised model, which earned them a shared Nobel prize in Medicine or Physiology in 1963 and attained textbook status thereafter [6], HH loosely linked established laws of physics (i.e., Kirchov's and Ohm's laws of electricity with Nernst's law of the electrochemistry of semipermeable membranes). Based on the outcome of a large set of cleverly designed experiments on squid giant neurons and effective use of the newly introduced voltage-clamp technique, HH then described the neuronal membrane as an electrical circuit where voltage- and time-dependent changes in membrane conductance allow for ion (in particular, Na^+ and K^+) flow along their respective electrochemical gradients [6]. Applying the mathematical formulation of their model, the so-called total current equation [5], HH was able to quantitatively describe the consecutive rise and fall of membrane voltage observed in their experiments. Moreover, with the help of Kelvin's Cable Theory, describing the propagation of charge along an insulated cable, they then successfully extended this "static" picture of the AP into that of a propagating voltage pulse which is carried forward and spreads over long(er) distances by means of both active and passive conduction [5, 6]. The strength of this approach lay in the fact that with the full mathematical formulation of their theory, HH not only provided an explanation for the results of dedicated experiments used to construct their model and fit the model parameters but was also able to fairly accurately predict several characteristics of the traveling electrical signal, including its shape, amplitude, threshold, velocity and refractory period (for more extensive information on the historical background , see e.g. [4] and references therein).

2. Outlining the Battleground

Deservedly treated as a significant scientific breakthrough, it is no wonder that the electrical circuit and conductance-based framework of neuronal excitability outlined in the HH theory and formulated in the HH model was received enthusiastically and accepted quickly in broad areas of neuroscience. This is, for instance, nicely illustrated by the fact that the HH theory and model served as immediate inspiration for the development of simplified electrical circuit models of neural spiking and bursting behavior like the Fitzhugh-Nagumo and Morris-Lecar models. Furthermore, and instrumental in helping the HH model attain near 'paradigm' status in the neurosciences, in corroborating the fundamental idea of Galvani that an intrinsic 'animal electricity' was actively involved in propagating the nerve signal and controlling muscular contraction and other nervous system functions, at the time of its introduction, the HH theory and model appeared to finally prove that the electrical phenomena associated with neuronal excitation are a fundamental component of the nerve signal itself and do not only form "a conveniently recorded sign of the cell's excitation…" [7], representing an "epiphenomenon of an underlying, more essential process" as sometimes argued before [8]. Indeed, using the metaphor of a burning fuse of gunpowder powering its propagation, Hodgkin claimed that with their work HH had demonstrated that "the action potential is not just an electrical sign of the impulse but is the causal agent in propagation" [9]. In fact, in doing so, it appeared as if with their innovative combination of experiment, technology and theory HH, in one broad sweep, had solved all outstanding questions amongst neurophysiologists concerning the physicochemical identity of the nerve signal, its mechanism of propagation and the relationship between neuronal susceptibility to external electrical stimulation and endogenous neuronal activity [10]. This earned the HH model the status of "the model for all seasons" [11], providing the cornerstone for much of later developments in (compartmental) modeling and experimental investigation of neuronal physiology and, more generally, in theorizing about nervous system function. As such, it has played a vital role in cementing the widespread view that the nervous system, including the brain, 'runs on electricity' [3, 4].

However, although nowadays all but forgotten in mainstream neuroscience, and despite all its acclaimed success following its introduction, it was Hodgkin himself who warned against unwarranted (over)confidence in the explanatory validity of the model developed by him and Huxley. Thus, he noted that "In thinking about the physical basis of the action potential perhaps the most important thing to do at the present moment is to consider whether there are any unexplained observations which have been neglected in an attempt to make the experiments fit into a tidy pattern". With this remark Hodgkin referred to what he described as "…perhaps the most puzzling observation is one made by A.V. Hill and his collaborators Abbott et al., (1958)", because. "…Hill and his colleagues found that it" (i.e., the heat release accompanying the moving AP) "was biphasic and that an initial phase of heat liberation was followed by one of heat absorption. A net cooling on open-circuit was totally unexpected and has so far received no satisfactory explanation" [9]. Hodgkin understood that the HH model (and the electric framework it is built on) is unable to do so as it is purely dissipative and, therefore, cannot straightforwardly accommodate reversible, non-electric, physical processes operating simultaneously with the electrical AP. This led Hodgkin to conclude that the inability of the HH model, which predicts continuous dissipation of heat due to charges moving across the ionic channel resistors during AP propagation, to explain the temperature recordings of Hill and others formed an important challenge to the explanatory validity of his model. Of note, some years earlier, the notion of the nerve signal as only a wave of electrical current running along the axonal surface had been put to the test already by researchers noticing that, as an electrical pulse passes through a nerve fiber, the translucent cell interior briefly becomes opaque (for review see, [12]). In other words, it appeared as if the neuronal cytoplasm undergoes a reversible phase transition as the AP passes by. Together, these unaccounted-for observations prompted Ichiji Tasaki, a senior neurophysiologist best known for his (bio)physical characterization of saltatory propagation in myelinated nerves [13], to start an experimental research program investigating more fully these non-electrical manifestations of the nerve signal. In a large set of tests, using multiple physicochemical experimental methods and often tailor-made equipment, Tasaki and coworkers convincingly demonstrated that, besides the production and subsequent absorption of heat, APs are also accompanied by (largely) reversible variations in axonal diameter, intracellular pressure and length (for an overview, see [4] and references therein). As a consequence, as summarized concisely by Fox [14], Tasaki had ample reason to argue that "the transient widening, the rearranging molecules, and the heating and cooling pointed to a startling conclusion: the nerve signal was not just a voltage pulse; it was every bit as much a mechanical pulse. Scientists who listened to nerves with electrodes were missing much of the action". During the last years of his career, in trying to formulate an unifying theory and explain his observations Tasaki, building on the far earlier ideas of Jacques Loeb about the role of ion-exchange chemistry in controlling excitability in living tissues [15], performed a number of dedicated experiments to study the behavior of polymeric cation exchange gels under varying ionic conditions. Based on the outcome of these experiments, Tasaki ultimately proposed a macromolecular physicochemical model in which the electrical as well as the non-electrical manifestations of the nerve signal were treated as the result of a propagating reversible swelling, i.e., a volume phase transition, of submembranous proteinaceous filaments, located directly underneath and running along the axonal surface. These filaments, consisting primarily of actin fibrils, were shown by Tasaki (and others) to be in close contact with the surface membrane, forming a specialized axonal cytoskeleton-membrane structure, which they called the axolemma-ectoplasm complex [16]. However, although Tasaki was well-respected as a neuroscientist and his findings have been largely reproduced (and extended) by others using a variety of neuronal preparations and techniques [17-20], at the time neuroscientific opinion leaders treated them (and have largely continued to do so) as epiphenomena, i.e., "nothing more than side effects of the voltage pulse" [14], As a consequence, the underlying scientific questions were not seriously addressed with the apparent result that "One side got into the textbooks, and the other one didn't" (biophysicist Daniel Parsigian quoted in [14]). These unresolved scientific questions about the mechanical responses observed by Tasaki and others to accompany AP generation and propagation in particular addressed three issues summed up by Terakawa [21]; 1) which cellular component(s) do they arise from?, 2) how are they produced?, and 3) what is their physiological significance? In recent years, scientific answers to these questions have become ever more important with the rising awareness that the current, HH-derived and electricity-centered, (compartmental) models of computational neuroscience, lacking in attention for changes in cytoplasmic ionic concentrations or other (intra)cellular processes, do not allow for integration with the, molecular biological technology-based, (bio)chemistry-centered data sets obtained in systems biology [22]. Whilst accusing the 'HH-framework' of treating neurons as "essentially inanimate objects", i.e., threshold logic devices, in which information processing is considered only in terms of electrical membrane activity and synaptic transmission, ignoring other (intra)neuronal, biological variables, this led anesthesiologist and neuroscientist Stuart Hameroff to argue that, at least for studies into the cellular basis of consciousness and cognition, neuroscience is in need of a new paradigm [23]. This argument follows earlier comments by Mueller and Tyler [24], who, in referring to the apparent failure of the HH model to account for a number of non-electrical biophysical phenomena associated with the nerve signal and the potential consequences thereof, noted in an even more general sense that "To advance our understanding of neuronal function and dysfunction, compartmentalized analyses of electrical, chemical, and mechanical processes need to be reevaluated and integrated into more comprehensive theories." They put forward that only "By considering the collective actions of biophysical forces influencing neuronal activity, our working models can be expanded and new paradigms can be applied to the investigation and characterization of brain function and dysfunction".

It is within the latter context, that in the next paragraph we will deal with and discuss the most prominent features of the latest and most extensively covered 'competitor' of the HH model of the AP, the so-called soliton model of Heimburg and Jackson (HJ; [25]). Following this, we will address the current status of this model and investigate if and how far it has progressed to becoming a "threat" for the current 'animal electricity' paradigm, as represented by the HH model. For comparison and analysis, we will use relevant elements of the popular philosophical framework for the study of progress in the sciences and, more in particular, the role of shifts in scientific paradigms therein, originally introduced by Thomas Kuhn in the early 1960s and updated thereafter by him [26]. Whilst recognizing that terms like paradigm shift and revolution have become scientific cliches, frequently reserved in the (neuro)sciences for attracting attention to newly developed techniques or tools (see for instance [27]), we chose to do so because we believe that Kuhn's groundbreaking approach and theory contains (many) concepts who are not only familiar to many neurobiologists but can also provide them with valuable insights to grasp the broader scope of the discussion and potential impact of the controversy about the physics of the AP beyond that of a 'simple' scientific argument about the validity of competing theories. We will demonstrate that (much) of the dynamics of the controversy (or apparent lack thereof), including reported positions taken in the debate by representatives of mainstream neuroscience, should be understood according to terms and concepts introduced by Kuhn in his historical analysis of the path to scientific progress through paradigm shift and scientific revolutions. Doing so will, however, also lead us to conclude that, at least so far, introduction of the HJ model has not led to a Kuhnian crisis in the reigning paradigm and that its opportunities for further development to become a generally acknowledged and innovative physical theory of neuronal excitability are not served well by continuing to consider the case as a competition between an aspiring new paradigm (i.e., the thermodynamic framework of the HJ model) and the current paradigm (i.e., the bioelectric framework of the HH model) of neuronal excitability. As such, the present study should be considered complementary to our previous paper by Holland et al. [28]. in which we investigated the prospects for the development of a general unifying model of the nerve impulse along the lines suggested by Mueller and Tyler [24]. For a more extensive overview and discussion of the physics involved and scientific arguments against or in favor of the HJ model compared to the HH model, we refer to some recent publications by us and others [29-31]. Moreover, in Table 1 the arguably most informative biophysical characteristics of the HH and HJ models are summarized in a qualitative comparison.

Table 1 Comparison of the major (different) physical features of the Hodgkin-Huxley and Heimburg-Jackson models of the action potential (AP).

	Hodgkin-Huxley model	**Heimburg-Jackson model**
The model is based on…	voltage-controlled flow of ionic (primarily Na^+ and K^+) currents through resistors (i.e., channel proteins) in the axonal membrane. Therefore, it is dissipative in nature and heat generation is predicted.	macroscopic thermodynamics, thus, predicts a role for all thermodynamic variables. The propagating voltage pulse (i.e., the AP) is an inseparable part of a more generic signal that implies changes in all these variables, like temperature, lateral pressure, area and length.
The AP is considered as…	the consequence of voltage- and time-dependent changes in the conductance of Na^+ and K^+.	a single electromechanical pressure wave (i.e., a soliton) coupled to lipid phase transitions in the axonal membrane.
The AP is consistent with…	quantized ionic currents attributed to the opening and closure of specific voltage-dependent channel proteins.	non-linearity of the elastic constants is close to the melting transition of the lipid axonal membrane and of dispersion.
The propagation of the AP…	is driven by the dissipative flow of ions. The AP is considered as a segment of charged membrane capacitor.	does not generate heat because it is driven by an adiabatic process.
The model does not predict…	changes in (other) thermodynamic variable,	an explicit role for ion-channel proteins. The model does account

	besides (changes in) charge and electric potential. The propagating voltage pulse is the sole signal.	for channel-like pore formation in lipid membranes which cannot be distinguished from ion-channel protein conductance measurements.
The model accounts for a refractory period and hyperpolarization as a consequence of…	the complex time-dependence of ion-channel conduction.	mass conservation.

3.Competition from Thermodynamics: The Soliton Model of Heimburg and Jackson

All but buried in mainstream neuroscience, but inspired by the decades of work of Tasaki, the search for the physical basis of the apparent overlap between electrical and non-electrical phenomena accompanying the nerve signal was revived in the early years of the 21th century in a small research program initiated by a group of membrane (bio)physicists in Denmark led by Thomas Heimburg and joined shortly afterwards by Matthias Schneider and coworkers in Germany. Besides criticizing the HH model for its focus on explaining the AP as an exclusively electrical signal that appears to obey general laws of physics but ignores changes in any other (biological) variables than charge and electrical potential, Heimburg and his coworker Andrew Jackson, in addition, noted that the HH formalism also ignores changes in membrane capacitance resulting from variation in membrane thickness as the membrane potential changes [28, 32, 33]. This latter issue has been taken up specifically in recent studies that have incorporated non-linear changes in membrane capacitance into the HH model to help explain AP dynamics [34, 35]. These modeling efforts, however, await experimental confirmation. Altogether, as usual in physics, with its supposed preference for deductive reasoning, unification and application of laws of nature rather than the search for mechanisms, as favored in biology (discussed more fully in, [29]), in order to overcome these perceived shortcomings of the HH model the theoretical and experimental work of Heimburg and Schneider focused on reconciling all of the established physical manifestations of the propagating AP in one, macroscopic thermodynamics-based, physicochemical framework. Doing so, they followed in the footsteps of famous 19th-century predecessors, like von Helmholtz and du Bois Reymond, who pledged to discover the fundamental physical principles guiding biological phenomena [36]. For building their thermodynamic framework, the groups of Heimburg and Schneider relied heavily on earlier work by theoretical physicist Konrad Kaufmann on the macroscopic thermodynamics of lipid membranes and the propagation of acoustic pulses in membrane interfaces [37]. Different from Tasaki, however, who relied heavily on experimental observations, Heimburg and Jackson started with deriving a wave equation for single electromechanical pulses in lipid membranes (a soliton) and proposed that the quantized, all-or-none, conduction events coupled with reversible mechanical (e.g., thickness, swelling, pressure) as well as thermal changes observed during AP propagation can be explained by considering the nerve impulse as an “acoustic pulse along the membrane” in which the movement of a single adiabatic wave (a soliton) through the lipid bilayer is responsible for axonal conduction of the pulse [25]. Fundamental to understanding the HJ model is the underlying idea that, as the solitonic pulse moves along, the axonal membrane is “partially moved through a phase transition from a liquid-disordered membrane state to a solid-ordered state" [38]. As discussed by us more extensively elsewhere [3, 29], this lipid phase transition, during which the membrane shifts between the fluid and liquid-crystal phases resulting in a sort of localized "freezing" event, would be accompanied by a density change which, as the direct consequence of increased membrane tension, inevitably results in a change in membrane area and thickness, changes in membrane charge density and, therefore, membrane potential. Because of the (at least partly) reversible nature of the structural changes in the membrane (i.e., a reversible sol-gel lipid phase transition), as the pulse starts moving, the self-sustaining and localized density pulse will present itself also as a voltage pulse, identified as the propagating AP in the electric HH theory. Most importantly, following this line of reasoning, in this thermodynamics-based framework developed by HJ, the movement of the AP relies on the same fundamental physical principles that cause the propagation of sound waves in a material and not on the flow of ions or current as per the HH model [29]. Instead, HJ boldly claimed that the complete electro-mechanical phenomenology of the nerve signal emerges naturally from the collective, physicochemical, properties of the axonal membrane interface in which a compression wave (the soliton modeled as a sound wave) propagates. To underscore the validity of the assumptions underlying their model, HJ noted that indeed "the associated changes in the thickness of the membrane, the length of the axon and the reversible release of the latent heat have all been found experimentally" [38]. Moreover, the theory outlined by HJ is in line with experimentally verified predictions from thermodynamics that changes in transmembrane voltage will modulate membrane tension and cause membrane movement [39, 40], a phenomenon recently found to be associated with alterations in neuronal viscoelasticity [41]. However, perhaps the most important contribution to filling in the gap between HJ theory and experimental proof has come from the work of Matthias Schneider and coworkers. Primarily using artificial lipid membranes and some simple *in vitro* biological model systems they observed that a mechanical wave could be triggered in the lipid layer by exposure to a voltage pulse. Interestingly, this mechanical wave moved at a speed comparable to APs measured in nervous tissue. Additional work by Schneider's group confirmed these mechanical and electrical pulses to be part of the same membrane wave. More surprising, but highly similar to neurons, which only fire an AP when stimulated by an electrical pulse sufficiently strong to overcome a threshold potential (i.e., the all-or-nothing phenomenon), Schneider et al. found that the electromechanical waves elicited in their model systems were also all-or-nothing. In other words, the stimulus must overcome a membrane threshold. Subsequent experiments demonstrated that this happens if stimulus strength is strong enough to induce a lipid phase transition in which the membrane momentarily switches from a soluble, liquid-disordered state to a solid, ordered state, in line with the original predictions of HJ (for overview, see [31] and references therein). Built on first principles, i.e., starting directly at the level of established science (i.e., the laws of thermodynamics) without making assumptions in the form of empirical models and parameter fitting, and supported by an increasing number of experimental data, the macroscopic thermodynamic framework introduced by HJ in their soliton model to (more) fully predict, explain and understand the multi-physical manifestations of the nerve signal as the result of one, integrated, sound-like wave phenomenon propagating in the axonal surface membrane promised to become a serious competitor to the current standard, as represented by the electric framework formalized by HH in their famous model. Indeed, considering the pivotal role of the HH model in: 1) firmly establishing the apparent overall validity of the 'animal electricity' paradigm developed by neurophysiologists over a period of approximately 150 years, and 2) its maintained status as the foundation for broad areas of modern neuroscientific research from molecular to circuit level [42], where it forms the "crown jewel" of the subject [43], which is used to illustrate the success of innovative, good and clever science in virtually every contemporary textbook in scientific disciplines like (electro)physiology, (computational) neuroscience, or biomedical engineering, the challenge posed by the HJ model, if successful, would herald the start of a Kuhnian shift of paradigm and scientific revolution in (cellular) neuroscience with enormous (potential) impact for broad areas of neuroscientific research [44].

4. What Lies Hidden Beneath the Barricade(s): A New Paradigm or False Alarm?

It seems fair to conclude that, contrary to early enthusiasm and expectation(s) (e.g., see [14, 45]), once attracting scrutiny from the established (neuro)scientific community the HJ model was met with increasing skepticism [46, 47], if not outright enmity (see for instance remarks of Catherine Morris quoted in [14]), by representatives of the majority view in (mainstream) neuroscience. Even attempts to integrate the soliton model into the prevailing electrical framework of the AP by joint efforts of physiologists and computational scientists were not taken seriously and readily dismissed [48, 49]. As a consequence, the paradigm shift and 'scientific revolution' in (cellular) neuroscience, anticipated at the time of the introduction of the macroscopic thermodynamics and acoustic physics-based HJ model of the nerve signal has, at least thus far, failed to live up to expectations.

However, taking Kuhn's approach, it seems that this is what was to be expected. Kuhn noted that, contrary to the cherished image proffered by many scientists, science, in general, is rather conservative in nature. Therefore, change and the accompanying shift in professional commitments are not taken lightly and, as a consequence, resisted strongly by the established community of scientists. As part of this process, according to Kuhn and illustrated very pointedly by Parker [44], taking the case of adult neurogenesis as a recent example of a controversy from neurobiological practice, dissenting opinions and anomalies in theory and/or interpretation of experimental results, often contributed by the input of outsiders and/or young(er) colleagues arguing against the established view in the discipline or field of study are taken as an insult to authority and brushed aside by so-called opinion leaders or left as problems for future investigation [50]. Thus, unexpected findings, like non-electrical manifestations of the nerve impulse, will be treated as epiphenomena, "nothing more than side effects". This description fits rather well with what happened to Tasaki in reaction to his opposition to the theory and model of HH. It is also exemplary of the welcome given to the HJ theory and model by (cellular) neurophysiologists and other neurobiological scientists. Summarizing the reaction of one expressive critic of the HJ model, Fox writes that he was told that "the whole line of work reeks of superiority from a physicist who thinks he can simply march into a different field and set people straight" [14]. Referring to the apparent, but misunderstood (for discussion see, [29] and arguments below), denial of a role for ion channel proteins in the HJ theory and the work of Schneider, Fox then proceeds with quoting this same neuroscientist as saying "They just blithely ignore vast amounts of biology" [14]. This reaction is remarkably similar to that of another neurobiology opinion leader referred to by Parker, who at the time of the controversy about adult neurogenesis is described as having noted that accepting adult neurogenesis as a fact "would be like removing a page from a book" [44]. Thus, as a first point of observation, to become successful in drawing serious attention, patience, and endurance are warranted because scientific revolutions and paradigm shifts, like any other major change in worldview, take time to develop and gain support from opinion leaders in the relevant scientific community. Where this is concerned it is, therefore, important to acknowledge that, in comparison to the current 'paradigm', i.e., the HH model, which does provide a quantitative account of both AP generation and propagation, in its original form the HJ model, although able to explain a number of aspects of neuronal excitability not covered by the HH model, did so only in a qualitative sense. As such, at least from a modeling and explanatory perspective, the HJ model was lacking at the time of its introduction compared to the HH model and clearly required further work [3, 29]. Within this context, the importance of such additional work to further develop a competing theory over time is nicely illustrated by the discussion about the apparent inability of the HJ model to capture the so-called annihilation phenomenon, which occurs when two APs, moving along the same neuronal axon from opposite direction, run into each other. Failing to recognize its original status as the "simplest" description and first attempt that tries (and to a certain extent succeeds) to predict and describe the essential features of an adiabatically propagating phase transition in a membrane [29], it is this issue which was eagerly taken up by representatives of mainstream neuroscience to strongly contest the scientific validity of the HJ model as such, and the thermodynamic foundations it is built on, more in general (see for instance [46, 51]). This fierce criticism, however, has been met by showing that incorporation of higher order terms into the soliton model, in fact, allows for the annihilation of colliding APs both mathematically [52], as well as experimentally [53, 54], thus strengthening the explanatory validity of the thermodynamic framework.

For his analysis of the path to paradigm shifts and scientific revolutions, Kuhn studied a number of groundbreaking episodes in the history of physics, including the Copernican, Newtonian and Einsteinian revolutions. His work led Kuhn to believe that such revolutions are relatively rare and that science and scientific knowledge progress along two distinct paths, which he called normal science and revolutionary science, respectively [26]. According to Kuhn, normal science, which overall is the prevailing mode of scientific practice, is characterized particularly by a relatively long period of time during which knowledge accumulates slowly and in a linear fashion whilst research is "firmly based upon one or more past scientific achievements, achievements that some particular scientific community acknowledges for a time as supplying the foundation for its further practice" [26]. Thus, at least as described by Kuhn, normal science steadily follows its path amidst a general agreement within a scientific community, in the form of a conceptual framework, about what problems need to be solved and how efforts to do so should look and be evaluated [55]. Within this context, Kuhn stressed the vital importance of recognizing this general agreement to be a sort of by-product of the acceptance by a specific scientific community of certain "past scientific achievements" as *exemplars* of good scientific work. These exemplars Kuhn called paradigms [55].

In answer to serious and well-founded criticism of his definition and use of the term paradigm in his original publication [56], in later accounts, Kuhn redefined the notion of the *exemplar* as paradigm to become "the concrete problem-solutions that students encounter from the start of their scientific education" which "show them by example how their job is to be done" [26]. This would include gaining experience and understanding from 'classical' experiments during laboratory practicals and preparation for examination by studying dedicated textbook chapters describing typical (successful) examples of the scientific discipline under study. As a consequence, exemplars are transmitted and inculcated by the training of (young) scientists which allows them to "see the world in a certain way that enables them to solve scientific problems in ways analogous to those in the exemplars" and, most importantly, in agreement with the current views held by normal science [57].

In addition, and to further narrow down and pinpoint the notion of the term paradigm in his theory, Kuhn also introduced the term disciplinary matrix to comprehensively describe another meaning of the paradigm concept which, according to Kuhn, is the "entire constellation of beliefs, values, techniques" as well as generalizations and models that are shared by a community of scientists [55], Accordingly, in Kuhn's view, a paradigm defined as a disciplinary matrix is the complete theoretical, methodological and evaluative framework within which a scientific discipline conducts its research. This framework also constitutes the basic assumptions of the scientists active within the discipline about how research should be conducted and what is expected from a valid scientific explanation [57]. Kuhn urges that the stability of a paradigm in both senses, which he proposes, is necessary to sustain normal science.

Taken together, this description very nicely fits the commonly held notion by historians of neuroscience and active neuroscientists alike that, after Galvani, neurophysiological investigation of the function, characteristics and physical foundations of neuronal excitability, in general, and the AP, in particular, successfully proceeded under normal (neuro)science within the boundaries of the disciplinary matrix provided by the animal electricity paradigm which cuts across all of neuroscience [44]. It is also widely agreed that in this area of investigation, the HH model serves as one of the most important, if not its most impressive and enduring exemplars. In the decades following its introduction, this position of the HH model as the "most important model in all of the physiological literature" [58], was strengthened even further with the help of spectacular new techniques from cellular electrophysiology and molecular biochemistry. In this context we refer, in particular, to the introduction of the patch-clamp technique, a modification of the voltage-clamp technique, which allowed for a detailed study of the electrical characteristics of single ion channels [59], and the unraveling of the molecular structure of voltage-dependent ion channel proteins as separate entities by the use of combinations of gene-cloning and X-ray crystallography [60]. In line with Kuhn's ideas, this contribution from technology was of special importance as it helped to solve an unsettled question in the electronic circuit theory of HH. This riddle regarded elucidation of the mechanism(s) underlying the experimentally established flow of ions across the membrane during AP generation and propagation. In fact, in its original formulation the HH model had only offered a macroscopic phenomenological description of the AP phenomenon and suggested a plausible explanation for the voltage- and time-dependent movement of ions over the membrane [61]. However, it had failed to provide a full mechanistic account in terms of 'real' molecular entities and their interactions, as highly appreciated by (neuro)biologists [62, 63]. Thus, although driven by revolutions in molecular technology rather than by progress in theory, and encouraged by the contemporary rise in popularity of the so-called 'molecular gaze' in established neuroscience [64], by the end of the 20th century a significant upgrade in the explanatory status of the HH model seemed to have taken place. As a consequence, at least from the perspective of the mainstream neuroscience community, the validity and stability of animal electricity had been reconfirmed, and alternative conceptual frameworks for the study of the nerve impulse could be ignored. More in general, the contribution from technology, enabled by the coinciding revolution in molecular (neuro)biology, also serves to substantiate earlier observations by Maslow, who put forward that, besides theoretical considerations, the process towards acceptance of a new stance is also strongly driven by the means, i.e., the tools and techniques, at the time being developed and/or available and familiar to the scientists involved [65]. Recently, Bickle further prioritized Maslow's claim by arguing that revolutions in neuroscience have turned on the development of new experimental tools and techniques [27]. Relevant to neurophysiological investigation of the physical basis of neuronal excitability, this, in fact, follows far earlier observations by the Nobel laureate and famous neurophysiologist Edgar Adrian who, in discussing the role of electrical technique in the study of signaling by neurons, emphasized that "The signals which they transmit can only be detected as changes of electrical potential and these changes are very small and of very brief duration. It is little wonder therefore that progress in this branch of physiology has always been governed by the progress of physical technique" [66]. It should, therefore, come as no surprise that consideration by mainstream neuroscience of the HJ model, and the thermodynamic framework it stands for, as a comprehensive and (potentially) superior approach to prediction and explanation of all, i.e., electrical as well as non-electrical, physical facets of neuronal excitability, as deemed desirable by Mueller and Tyler [24], lags behind the HH model not only because of theoretical considerations referred to above, but also because of a dearth in dedicated experimental tools sensitive enough to test its claims and minimal experience with the few available in regular neuroscience laboratory settings. Only recently, with technological advances in the tools used to study changes in the biomechanical characteristics of nervous tissue, this situation has slowly started to change [67].

Directly linked to this, and perhaps even more important, as pointedly noted by Tasaki [13, 68], the path to recognition and serious consideration of an alternative view will also depend on the familiarity of adherents of the established view with the principles and practices (theory and experiment) underlying the scientific approach(es) of their colleagues. If limited in its extent and low in its appreciation, this will seriously impair both the willingness and ability of this community of older and younger scientists representing the 'authorities' in the field to critically judge the suggestions and achievements of the 'new kids on the block' or even discuss them on an even footing. As such, the HJ model is not helped by the fact that most modern-day neurobiologists and other biomedical scientists and students consider thermodynamics, let alone acoustic physics, as outside their area of expertise, often rather abstract in nature and very difficult to understand [69, 70]. The discussion between the two groups of scientists, i.e., mostly cellular neurophysiologists and computational neuroscientists familiar with terms and techniques from electronic engineering, computing, and/or cellular and molecular biology vs membrane (bio)physicists knowledgeable in the laws of nature and focused on the material properties of membrane interfaces and the role of phase transitions in pulse propagation, therefore, if taking place at all tends to be restricted to expression of well-known positions along the lines of the respective disciplines with little attention for, interest in or understanding of arguments from the other side. In our opinion, therefore, as an important consequence of this big divide in scientific background and lack of meaningful interaction it is generally overlooked by those involved that the misunderstandings and other tensions which complicate the debate between the adherents of the HH and HJ models, respectively, are better off being treated as (unrecognized) differences in what is considered to be explanatorily relevant between the two groups of scientists rather than a competition for truth between the two models [71]. Whereas, for instance, individual molecular entities like ion channel proteins may not be necessary to account for membrane ionic permeability changes during AP generation and propagation according to the macroscopic thermodynamic framework, which, for explanation, draws from the collective material properties of the membrane interface as a whole, as discussed above, the bioelectric framework in its current form relies on them to explain neuronal excitability.

Thus, albeit misguided, it is easy to understand that from the perspective of mainstream neurobiology, the HJ model is accused of failing to account for what it considers "established" features of the nerve impulse. Conversely, in the HJ model emphasis is put on the inability of the HH model to explain non-electrical manifestations of the propagating AP which, in the thermodynamic perspective, are considered to be explanatorily relevant features of neuronal pulse transmission.

This leads us to the discussion of the concept of anomaly in Kuhn's theory and its importance in the path to revolutionary science. According to Kuhn, a phase of revolutionary science is expected in every area of scientific investigation because no paradigm is sufficiently stable to serve as the basis for solutions to all of its problems within its paradigmatic constraints [55]. Such a problem, which resists solution within the confines of the ruling paradigm, Kuhn called an anomaly. Persistent failure to adequately address such anomalies will result in a paradigm crisis and attempts by the community of interested scientists to find solutions for the problems outside the constraints of the current paradigm. Thus, scientific revolutions begin, at least in the view of Kuhn [26].

Are there Kuhnian anomalies in the current paradigm and, if so, how are they dealt with in mainstream neuroscience? From the thermodynamic perspective, as discussed, the failure of the HH model, and the bioelectric framework as such, to predict or adequately explain the non-electrical features of the AP should be considered as a crucial anomaly in the animal electricity paradigm. In this argument, special attention is devoted to the unaccounted-for reversible heat release accompanying the propagation of the nerve signal. Besides scientific considerations coming from thermodynamics [72], this emphasis on the thermal profile of the propagating AP should come as no surprise, because this (potential) 'soft spot' in the bioelectric theory and HH model was already acknowledged by Hodgkin decades ago (see above) [9], but never taken up and investigated seriously by other representatives of 'normal' neuroscience afterward. Most neuroscientists might not know this apparent anomaly in their paradigmatic model or understand its physical underpinnings. Therefore, they will fail to recognize its potential impact or refuse to address it. As a result, at present the issue remains undecided. If, however, recognized as an anomaly, according to Kuhn, representatives of the mainstream view will usually face such a situation by devising various articulations or introducing ad hoc modifications of their favored theory and/or model(s). They do this to eliminate any apparent conflict and, to this end, isolate and describe the perceived anomaly more precisely and give it structure. Eventually, this should help to accommodate the anomaly within the constraints of the existing paradigm and, thereby, avert a crisis. Only if seen as more than just another, to be uncovered, piece in the puzzle of normal science will a crisis erupt [73].

This approach to dealing with unavoidable anomalies in the prevailing theory is nicely illustrated, for instance, by the way in which representatives of mainstream neuroscience have framed mechanical phenomena, like axonal swelling and movement, which accompany AP generation and propagation. Thus, in discussing the much-needed improvement in our understanding of the role of voltage-gated ion channel proteins in neuronal information processing, in an article in the popular scientific monthly Scientific American about the HJ model and its potential ramifications, the science journalist Douglas Fox quotes well-known neuroscientist Simon Laughlin as saying that "The existence of these mechanical effects is not in doubt". However, according to Laughlin, "The question is whether neurons actually use them to do something useful" [14]. With this, Laughlin essentially reiterates the earlier questions formulated by Terakawa ([21]; see above), about the origin and physiological significance of the mechanical changes observed by Tasaki and coworkers to accompany the nerve impulse. Although largely ignored at the time, from the perspective of mainstream neuroscience these questions have become highly relevant because of the recent and ongoing identification and characterization of mechanosensitive ion channel proteins in the surface membrane of many cell types, including neurons, and various microorganisms [74-76]. This has also led to an upsurge in interest in the role of membrane lipids and/or cytoskeletal elements in the gating of voltage-sensitive ion channels [77, 78]. The renewed interest in the function of constituents of the axolemma-ectoplasm complex should be understood against the background that biophysical forces raised by membrane lipids and/or membrane-associated cytoskeletal fibrils during neuronal excitation may exert control over the exact timing of the opening and closure of these "notoriously noisy and jittery" membrane pores by using their mechanosensitive properties. If proven correct, such a model might, at least in theory, allow for a molecular-level mechanism to ensure reliable transmission of the information contained in the AP, thereby helping to solve an old mystery that has continued to puzzle neuroscientists over the decades [79]. In fact, some experimental evidence has been obtained suggesting that at high neuronal firing rates a mechanical membrane wave elicited by the electric current may assist groups of voltage-sensitive ion channel proteins to open in unison over some distance, instead of one by one as per the HH theory and model [80]. This would allow for reliable timing and fast transmission of information contained in the electrical AP along neurons and neuronal networks, an alleged prerequisite for effective neuronal computation and, perhaps, cognition, in a manner not accounted for by the current exemplar. More important here, however, without compromising the primacy of the electrical phenomenology as the explanatory core of the AP in terms of the voltage- and time-dependent opening and closure of membrane ion channel proteins, mechanical manifestations are seemingly, i.e., thus far only in a qualitative sense, accommodated as part of the AP phenomenon. In effect, by doing so and acceptable to mainstream neuroscience, the nerve impulse stays an essentially electrical signal but with an important, yet secondary, mechanical component [81]. Thus, in line with Kuhn's expectation, the apparent anomaly is explained away within the limits of the current paradigm albeit with some, relatively minor, adjustments. In this manner, the paradigm is stabilized, a crisis is prevented and a paradigm shift becomes unwarranted and unnecessary. Indeed, in recent years, increasing recognition of the dual electromechanical character of the nerve impulse has led to the formulation of a few alternatives to the HH model, which are best considered as extensions of the HH model (for review, see [4, 82]). So far, these have attracted only minor attention. Nevertheless, and important to note, like the HH model and assuming the different manifestations of the nerve impulse to be the result of separate but electricity-initiated and/or driven physical processes, these models are incompatible with the HJ model which claims that all manifestations of the nerve impulse are features of the same physical process and should be modeled as such [28]. Thus, using Kuhn's terminology, the controversy has entered a stage of incommensurability between two incompatible and incomparable theories on the physical basis of the nerve impulse phenomenon, in which both sides use completely different, but scientifically justified criteria, i.e., standards of adequacy, to evaluate what counts as a good representation of the AP [26]. As a result, lacking a common measure, at this moment in time it is impossible for scientists to objectively determine which of the two competing models in general offers the better solution to allow complete and accurate understanding of neuronal signaling. Concerning the HJ model as the competitor, this also means that far more work is needed before it can be established that the thermodynamic theory can provide an explanation of the AP that is overall more satisfactory than the explanation offered by the current bio-electric paradigm. In light of these considerations, in the absence of marked theoretical and/or experimental progress or clear directions about the best route to take, it may be questioned whether the aim of comparing the explanatory validity of the thermodynamic framework with the bio-electric framework is best served by the continuation of the discussion in terms of competition for truth between two fundamentally different theories (Figure 1).

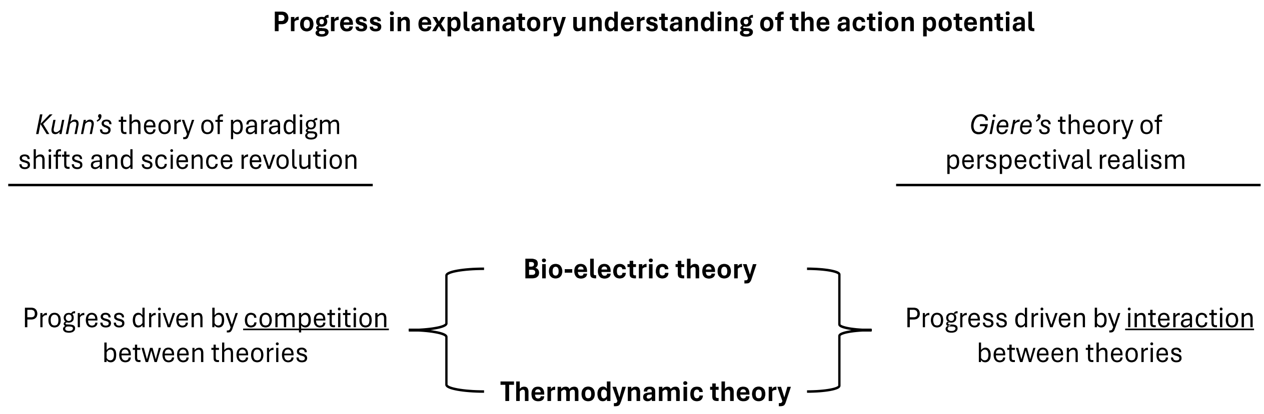

Figure 1 Two philosophical approaches to the controversy about the physical basis of the action potential (see text for further details).

5. Conclusions: Perspectival Realism Instead of Scientific Revolution as the Philosophical Way Forward?

Instead of defining science as an enterprise of finding truth, in the philosophy of science, an alternative line of thought has been developed that looks at science as an activity that aims at constructing, inevitably, inexact models of reality. Accordingly, models are always simplifications with different models suitable for different explanatory and/or practical objectives. Whether a model provides a useful representation of a phenomenon of interest depends on the purpose for which the model is used by scientists. For instance, the electrical circuit model of HH provides a useful representation of the axonal membrane if used to study the electrical manifestations of the nerve impulse. However, it is unsuitable for studying other non-electrical manifestations of the same phenomenon (for an overview, see [28] and references therein). Thus, different models may be required to study different aspects of the same phenomenon depending on the interests and formulated goals of the scientists using them. This emphasizes that a model as such cannot represent a phenomenon simpliciter but that a scientist (or other user) is needed who uses the model as a representation of the phenomenon for a specific purpose s/he wants to achieve. Extending this notion to scientific theories in general, the philosopher of science Ronald Giere argued that in formulating theories scientists in effect "create perspectives within which to conceive of aspects of the world" [83]. Accordingly, the fit between models and 'the world' may be better described in terms of similarity than truth since a perfect fit is not expected.

Over the past twenty years this so-called idea of scientific perspectivism, also known as perspectival realism, has been developed into an acknowledged philosophical theory for the study of processes underlying progress in scientific knowledge and understanding [83, 84]. Crucially, modern perspectivism posits that science, as the result of human effort, is historically and culturally situated and, thereby, always practiced from a particular perspective or vantage point. Perspectives may not only change over time but are also likely to vary between different communities of scientists. Moreover, important in light of the above discussion, according to perspectival realism there is no way to establish that one perspective is true while others are false. Different, even contradictory, perspectives may all be valid and valuable, depending on their explanatory aim(s). Somewhat similar to the concept and function of the Kuhnian paradigm, a scientific perspective may be broadly defined as the set of claims considered central to explaining the phenomena that are studied by a community of scientists that is historically- and intellectually situated. Different, however, from Kuhn's theory, which emphasizes the importance for progress in science of competition for truth between models, the value of a perspectivist analysis does not so much rely on its regard for questions concerning the truth of the theories and models formulated in the different perspectives, but rather on its interest in answering questions concerning the way(s) in which the different perspectives involved stimulate progress in the explanatory understanding of the phenomena under study. For evaluation, according to a recent interpretation of perspectivist theory [85], explanatory understanding, interpreted as an ability rather than knowledge, has increased when scientists can answer more so-called what-if-things-had-been-different questions about a phenomenon. Thus, the added value of having different perspectives on the same phenomenon is realized by the ability to provide answers to more and/or different what-if questions about a phenomenon or making the existing explanations more cognitively salient for scientists due to the use of different models in different perspectives. Undoubtedly, considering the history of neurophysiology after the introduction of the HH model, the bio-electric perspective on the physics of the AP has allowed for answering of more what-if questions (e.g., the molecular characterization of ion channel proteins) about this phenomenon, thereby increasing explanatory understanding of neuronal signaling. However, taking the HH model and the voltage clamp as its fundament, the bio-electric perspective has not been able to shed light on the relationship between the electrical and non-electrical manifestations of the nerve impulse. For pragmatic reasons, scientists developing the bio-electric perspective of neuronal signaling, therefore, chose to ignore this question. In contrast, emphasizing the importance of reasoning from thermodynamic principles to deduce the expected behavior of the nerve signal, this is not acceptable to the scientists developing the thermodynamic perspective. In their theory of the nerve impulse, both electrical and non-electrical manifestations follow from the laws of thermodynamics. As a consequence, there is no possible justification for choosing to explain one without considering the other. To overcome this perceived flaw in the HH theory and model, the thermodynamic theory and the HJ model were developed, and experiments were devised to validate its predictions. In this manner, scientists pursuing the thermodynamic perspective of neuronal signaling, on their part, have contributed to increasing explanatory understanding by answering more and different what-if questions about this phenomenon than those addressed in the bio-electric perspective. Moreover, as exemplified for instance by the models of El Hady and Machta [86] and Rvachev [87] and the ideas of Johnson and Winlow [47, 48], the work of Tasaki and co-workers and the groups of Heimburg and Schneider has also served to stimulate interest from scientists active in the bio-electric perspective for incorporation of non-electrical manifestations as integral and functional parts of the nerve impulse phenomenon no longer considering these as mere epiphenomena. Thus, from a perspectivist viewpoint the controversy about the physics of the nerve impulse is best dealt with as a (potentially) fruitful interaction between two scientifically valid but incompatible perspectives both of which, in their way and for their ultimate purpose(s), may help neuroscientists to fathom better and characterize the (multi)physical nature of the nerve impulse (Figure 1). As such, further development of the thermodynamic perspective alongside the bio-electric perspective, in our view, is strongly recommended.

Author Contributions

Both authors contributed equally to the conception, discussion, writing and revision of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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