

Physics for neuroscience: the story of Hodgkin and Huxley before any interpretation*

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Abstract: In 1952, A. L. Hodgkin and A. F. Huxley published what was to become known as the model of the action potential. This model would subsequently be considered a cornerstone of electrophysiology and neuroscience, since it concerned the ionic mechanisms involved in the operation of the nerve cell membrane. The story of the Hodgkin–Huxley (HH) model is, on the one hand, a particular example of the use of a scientific experiment and the laws of physics within life sciences. In the case of the HH model, the total current equation is derived from the laws of electricity (Coulomb’s law and Ohm’s law) under specifiable conditions. On the other hand, the HH story has become a key point of reference for the contemporary philosophical debate on the adequacy of scientific models, especially within the new mechanical philosophy. In his pivotal paper on explanatory models, C. Craver interpreted the HH model as a merely instrumentalist one that only “saves the phenomena” via the application of mathematical formulas. Therefore, the aim of this paper is twofold. First, we will reconstruct the story of the HH model and counterargue the claim that the model does not explain the phenomenon in question. Next, our analysis will demonstrate that the problem with Craver’s reading of the HH model stems from the unwarranted assumption that explanations and descriptions should always proceed hand in hand. Finally, we will conclude that although the HH model has proven to be incomplete in various respects, it does not follow that it was simply inaccurate and non-explanatory.

Keywords: Neuroscience, Huxley, Hodgkin, Explanatory models, Phenomenal models, Scientific explanation, Mechanistic explanation

1. Introduction

In 1952, A. L. Hodgkin and A. F. Huxley, two physiologists working at the Physiological Laboratory in Cambridge and the Laboratory of the Marine Biological Association in Plymouth, published the first quantitative description of electrical excitability in nerve cells. The publication of their mathematical model of the action potential is commonly viewed as a cornerstone of electrophysiology and neuroscience. The Hodgkin–Huxley (HH) model, as it was later called, is a particular example of the use of a scientific experiment and the laws of physics within life sciences.

In recent philosophical literature, especially that concerning the new mechanical philosophy, the HH model has become the main point of reference when discussing the role of models in scientific explanation. C. Craver (2006) has interpreted the HH model as an example of a non-explanatory, phenomenal model. In other terms, he has treated it as a merely instrumentalist one that only “saves the phenomena” via the application of mathematical formulas. Therefore, the aim of this paper is twofold. First, I will reconstruct the story of the HH model and counterargue the claim that the model does not explain the phenomenon in question. Next, I will argue that mathematical generalisations describing natural regularities in the case of the action potential have played an essential role in constraining the explanatory import of the HH model. Furthermore, I will demonstrate that although the HH model has

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proven to be incomplete in various respects, it does not follow that it was simply inaccurate and non-explanatory.

2. The story of the HH model before any interpretation

The pore hypothesis became predominant in biology and physiology books in the 1840s, when a number of biophysicists (such as L. Helmholtz and R. DuBois) invoked it in order to explain osmosis. The supposed role of pores was to act as channels, so to say, that pass water and other particles (Hille 1999). Thanks to nineteenth-century physiological investigations (particularly those by S. Ringer, W. Nernst and J. Bernstein), by the late 1930s, scholars had long known that not only was the signalling within neurons electrical in nature, occurring as part of an activity referred to as the action potential, but also that such signalling was stimulated by the flux of ions of potassium and sodium in the vicinity of the neuronal membrane (Hille 2001, pp. 2-5). What was still unknown at the time were the molecular details of the mechanism of the action potential, especially of the proteins known as ion channels. When Hodgkin and Huxley began collaborating on this subject in 1939, new research opportunities arose. In what follows, I will first consider the experimental aspect of their work. Then, I will discuss the main theoretical assumptions of the HH model with a particular emphasis on the application of the physical laws within it.

The new developments with regard to the basic processes underlying the nervous mechanisms began with an experiment conducted by Hodgkin and Huxley in 1939. The two scientists had studied action potentials in the relatively large axons of the squid *Loligo forbesi*, which can grow up to 90 centimetres in mantle length. While most of the nerve fibres were too small to be tested directly, Hodgkin and Huxley succeeded in inserting micro-electrodes into the giant axons and were able to measure electrical changes within the axons, discovering that the membrane potential would momentarily reverse during the action potential (Hodgkin & Huxley 1939).

Moreover, they utilised an innovative experimental technique of the voltage clamp (Schwiening 2012). Since the action potential involves rapid changes in the membrane potential and in the functioning of ion channels, a technique was needed to “freeze” the neuron at particular voltages in order to obtain an understanding of what was taking place. The voltage clamp made it possible to control the desired membrane voltage of the cell by using electrical stimulation and a negative feedback circuit. At this experimental level, the scientists’ calculations were based upon the relation between current intensity, resistance and potential as defined by Ohm’s law. By predetermining the voltage and measuring the current produced in the squid axon, Hodgkin and Huxley calculated the third quantity, namely the resistance of the membrane. The inverse value of the latter was the permeability (conductance) that the experiments were designed to measure.¹ The skills to dissect squid axons acquired by Hodgkin (with K. S. Cole) and the insertion of electrodes using the voltage clamp technique (Cole 1992) were ingenious from an experimental point of view.

The main theoretical contribution of the HH model consists in proving the ionic hypothesis and describing it in a quantitative form. The model shows in an elegant form that depolarisation of the squid axon triggers a rapid inward current carried by Na^+ ions, followed by a slower outward current carried by K^+ ions. Both currents are responsible for generating the action potential. In contrast to these two voltage-dependent channels, there is also a third type of channels described by the HH model, that is, leakage channels. These channels have a low conductance that does not change and are mainly responsible for the resting membrane potential (E_m).

¹ Conductance, that is, the ease of flow of current between two points, is defined by Ohm’s law in the following way: $I = gE$. This means that the current (I) equals the product of conductance (g) and voltage difference (E) across the conductor. The reciprocal of conductance is called resistance (R). Thus, Ohm’s law can also be expressed in a more common way using the following formula: $E = IR$. From these relations, one can easily note that $R = 1/g$.

In essence, the authors described the excitability of the membrane in terms of:

1. fixed parameters:
 - 1.1. membrane capacity C_M ,
 - 1.2. equilibrium electromotive force for Na (E_{Na}),
 - 1.3. equilibrium electromotive force for K (E_K),
 - 1.4. leakage electromotive force for other ions (E_{leak}),
 - 1.5. maximum conductance for sodium (\bar{G}_{Na}),
 - 1.6. maximum conductance for potassium (\bar{G}_K),
 - 1.7. maximum conductance for other ions (\bar{G}_{leak}), and
2. parameters that depend upon the membrane potential:
 - 2.1. the m variable for the activation of the Na gate,
 - 2.2. the h factor for the inactivation of the Na gate,
 - 2.3. the n factor for the activation of the K gate.

To account for the total membrane current, Hodgkin and Huxley divided it into a capacity current and an ionic current:

$$I = C_M \frac{dV}{dt} + I_i \quad (1)$$

In equation (1), the first element of the right-hand side is the capacity current that derives from the property of capacitance. The scholars assumed that cell membranes are capacitors which create a potential difference by means of a separation of charges on the intra- and extra-cellular sides. Qualitatively, the first element says that the current into the membrane is proportional to the size of the capacitance and the rate of change of voltage across it. The second element of the right-hand side of equation (1) is the ionic current that consists of components carried by sodium ions, potassium ions and other ions:

$$I = C_M \frac{dV}{dt} + I_i \quad (2)$$

The individual ionic currents are obtained from the following equations:

$$I_{Na} = G_{Na}(E - E_{Na}); I_K = G_K(E - E_K); I_{leak} = G_{leak}(E - E_{leak}) \quad (3a)$$

In their paper, Hodgkin and Huxley (1952 p. 505) wrote that for a practical application, it is convenient to write the above equations of individual ionic currents in the following form:

$$I_{Na} = G_{Na}(V - V_{Na}); I_K = G_K(V - V_K); I_{leak} = G_{leak}(V - V_{leak}) \quad (3b)$$

It can be noted that equations (3b) derive from Ohm's law. The current is defined by the latter as $I = gE$, which means that the current (I) equals the product of conductance (g) and voltage difference (E) across the conductor. The V , V_{Na} , V_K and V_{leak} values were measured by Hodgkin and Huxley directly as displacements from the equilibrium potential due to the following relations:

$$V = E - E_{eq}; V_{Na} = E_{Na} - E_{eq}; V_K = E_K - E_{eq}; V_{leak} = E_{leak} - E_{eq} \quad (4)$$

Set (4) of equations shows that Hodgkin and Huxley introduced the modification to Ohm's law in the form of the factor $E - E_{eq}$. The latter is the so-called driving force on the ion, that is, a measure of how far the membrane potential is from the equilibrium potential in question. The formula for finding the equilibrium potential of the ions in question (E_{eq}) is given by the Nernst equation, which states that ionic equilibrium potential varies linearly with the temperature and logarithmically with the ion concentration ratio (Hille 1992, pp. 13-18).

Coming back to the fixed parameters 1.1 through 1.7, while 1.1 is provided by the experimental measurements, 1.2 through 1.4 are derived from the Nernst equation for potentials. What about G_{Na} or G_K ? Hodgkin and Huxley explained that when specific ion channels are open, such as the whole population of potassium or sodium channels, then the actual conductance (G_K or G_{Na}) will be obtained by using the statistical approach to generate predictions for the probability of channels being open. This probability in the case of K -channels was assumed to be n^4 . The actual conductance of potassium is then part of the maximum possible K conductance (\bar{G}_K), i.e., $G_K = \bar{G}_K n^4$. The scientists applied similar reasoning to the actual conductance of G_{Na} , the difference being that apart from rapidly-responding activation gates (the m -gates), each Na channel contains a slower-responding inactivation gate (the h -gate). A combination of these two types of gates explains the increase in Na conductivity that results from membrane depolarisation. The HH model proposed that the probability of a whole Na channel being open was m^3h , and that $G_{Na} = \bar{G}_{Na} m^3h$. Since the variables n , m , h represented the portion of potassium, sodium and inactivation particles in certain regions, respectively, these variables were voltage- and time-dependent.

Having collected the aforementioned main theoretical assumptions, the scientists expressed them in an equation representing the total current as a function of time and voltage:

$$I = C_M \frac{dV}{dt} + \bar{G}_K n^4 (V - V_K) + \bar{G}_{Na} m^3 h (V - V_{Na}) + \bar{G}_{leak} (V - V_{leak}) \quad (5)$$

3. The HH model and the role of empirical laws

The HH model links the microscopic level of ion channels in an elegant way to the macroscopic level of action potentials and currents. It does so thanks to the vast amount of experimental data collected by Hodgkin and Huxley via the use of the voltage clamp technique applied to squid axons. At the same time, the model relies heavily on the application of the simple laws of physics to the study of ion channels, namely Ohm's law and the equilibrium potential as expressed by the Nernst equation.

What is the role of these laws in the HH model? Firstly, they play a crucial role in ensuring that the quantities present in the equation can be measured. In other words, mathematically formulated scientific laws are part of the definition of the HH model and make it effective in predicting and explaining a certain class of phenomena. Secondly, the HH model assumes at least two idealisations. In the case of Ohm's law, it can be noted that it refers to ion channels and other neuronal structures as if they were Ohmic conductors, that is, as if the difference in potential varied uniformly with the current flowing through the ions and with their conductance or resistance. Moreover, Hodgkin and Huxley are explicit that "the membrane capacity was assumed to behave as a 'perfect' condenser" (1952, p. 542). Thirdly, the cell membranes are treated as capacitors that store opposite charges on the intra- and extra-cellular sides. Since the HH model describes the physical model of the opening and closing of gates within a channel, it is entirely reasonable to apply equations describing the movement of charged particles in an electric field. Fourthly, two types of equations seem to be present in the HH model: 1) those essentially empirical but based upon equations that describe the movement of a charged particle in an electric field (which is the case with the equations describing the voltage dependency of transition rate constants with

the use of the factors α and β (Hodgkin & Huxley 1952, pp. 507-518)); and 2) those directly based on Ohm's law and the Nernst equation (e.g. (3a), (3b) and (4)).

While it is beyond the aim of this paper to discuss the metaphysical status of scientific laws (Psillos 2002, pp. 139-214), a more general philosophical perspective on such laws is needed for the purpose of our further discussion. Scientific laws are usually expressed in equations that represent relations between measurable properties. The formulation of such laws is of crucial importance, since it enables scientists to learn some of the invariant rules, dependencies and relations according to which natural phenomena take place (Dorato 2012). An efficient way to characterise these laws is to say that the laws are intended to express "how things are" or "that something is the case". Laws formulated in a theoretical language are propositions that assert relations established by observation or by experiment. On the contrary, theories or hypotheses essentially attempt to answer the question "why something is the case" (Agazzi 2014, p. 358). With regard to the interpretation of laws within the HH model, the issue stems from the different interpretations of equations embedded in scientific laws. Essentially, there are two ways to read equations: as explanatory equations or as merely descriptive ones. For instance, Snell's law is considered to be a descriptive equation, whereas Newton's law of universal gravitation is considered to be an explanatory equation. Then, there is also the issue of how certain an equation is: there can be certain explanatory equations or uncertain explanatory equations; certain descriptive equations or uncertain descriptive equations. Since the influential contribution by K. Popper, there has been some confusion when it comes to interpreting the role of laws (Agazzi 2014, pp. 353-358). Popper's move to reject any positive certainty from science, including that which is traditionally ascribed to laws, consisted in qualifying laws as being hypothetical ones, that is, as being uncertain. As a consequence, laws are treated as conjectures, considered to be more or less certain, and their role is to state "that is the case". In consequence, they are expected to provide accurate descriptions rather than illuminating explanations. In other words, explanations rely primarily upon hypotheses and only secondarily on laws. For the above reasons, in his comments on the HH model, J. Bogen states that "[the current equation] does not explain; it describes" (2005, p. 403).

4. The HH model and its instrumentalist interpretation

The story of the HH model has become a key point of reference for the contemporary philosophical debate on the adequacy of scientific models, especially within the new mechanical philosophy. In his discussion of this model, C. Craver (2006) interpreted it as being merely instrumentalist. According to him, the HH model was only able to make predictions, to summarize experimental data. It was not an explanatory model on account of being incapable of going beyond the mere description of the action potential by offering a causal interpretation of the underlying molecular mechanism of the *explanandum*. Craver is convinced that his claims about the phenomenal character of the HH model are well justified by what Hodgkin and Huxley stated themselves in their pivotal paper. In fact, there is a long passage in the third part of that paper, in the last section entitled "Discussion", which seems to suggest such an interpretation:

The agreement [between the model and collected data] must not be taken as evidence that our equations are anything more than an empirical description of the time-course of the changes in permeability to sodium and potassium. An equally satisfactory description of the voltage clamp data could no doubt have been achieved with equations of very different form, which would probably have been equally successful in predicting the electrical behaviour of the membrane. It was pointed out in Part II of this paper that certain features of our equations were capable of a physical interpretation, but the success of the equations is no evidence in favour of the mechanism of permeability change that we tentatively had in mind when formulating them (1952, p. 541).

Hodgkin and Huxley in fact insisted that they had “no evidence” in favour of the mechanism of permeability. At the beginning of their paper, they discussed various models of such a mechanism. They invalidated the hypothesis that the charged particles acted as carriers for sodium and instead opted for the hypothesis that the particles allowed sodium and potassium to pass through the membrane when they occupied particular sites in the membrane (1952, p. 502). The point is that, on the one hand, Hodgkin and Huxley were well aware that changes in the membrane potential were to be explained in terms of permeability changes. For instance, they wrote that “one of the most striking properties of the membrane is the extreme steepness of the relation between ionic conductance and membrane potential” (1952, p. 503). On the other hand, they clearly stated that sodium movement depended on the presence of charged molecules:

Details of the mechanism will probably not be settled for some time, but it seems difficult to escape the conclusion that the changes in ionic permeability depend on the movement of some component of the membrane which behaves as though it had a large charge or dipole moment (1952, p. 504).

One may ask: if they had “no evidence” in favour of the precise mechanism of permeability, why did they, at the same time, claim that it was “difficult to escape the conclusion” that ionic permeability depended on the movement of some components of the membrane? Hodgkin and Huxley struggled with the characterisation of the effects produced by the unknown molecular mechanism, but they nevertheless described relations among electrical quantities in a way that was sufficient to offer an explanation of a wide range of phenomena (including the refractory period, subthreshold, threshold, action potential and speed of propagation). In the background of their model, there was the fundamental idea of the charged particles moving in the electric field. The general agreement between predictions derived from the HH model and experimentally established values of the relevant quantities was a strong confirmation that the model was working correctly and that the details of the assumed mechanism of ion flux across the membrane was still to be determined.

Although the HH model incorporated equations that did not constitute an explanation of the underlying molecular processes, the scientists put essential temporal and spatial constraints in place to guide any further consideration of the possible mechanism. While working on the quantitative representation of the changes in conductance as a function of time and voltage, Hodgkin and Huxley found a certain shortcoming in their equations. It was the case that “the equations governing the potassium conductance do not give as much delay in the conductance rise on depolarization (e.g., to the sodium potential) as was observed in voltage clamps” (1952, p. 542). Trying to resolve this “discrepancy puzzle”, they explained that it was the fourth power of the potassium variable (n^4) and the third power of the sodium variable (m^3) that provided a better fit of the theoretical solutions of the equations to the voltage clamp data. Their intuition of the underlying mechanism of the movement of some components of the membrane was much more than simply having found accurately simple equations fitting the experimental data.

5. Conclusions

The HH model should be distinguished from phenomenal models by virtue of the fact that it correctly guided further investigation on the underlying structures of the action potential thanks to its representational and interpretational capabilities. In fact, the HH model was able to identify the most relevant components in the action potential mechanism; it correctly represented their spatial and temporal organisation and provided a sufficiently quantitatively accurate description of the interaction and activities of the components. Although both actual references and unknown molecular elements were part of the model, the model’s interpretation gave cues on the modes of interaction between causal

factors which were still poorly understood. Therefore, an interpretation of the more or less successful explanatory role of the HH model requires keeping its descriptive and explanatory roles distinct rather than conflated while recognising that they work together. The struggle to unravel the underlying mechanism of the action potential can be characterised as an articulated process through which the iterative relations between the *explanans* and the *explanandum* were present.

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