CHAPTER 5

The Compositional Basis of Resting and Action Potentials

From the opening paragraph of this book, I have referred to Hodgkin and Huxley's reasoning about an experiment to illustrate a set of scientific interpretations that I have been striving to characterize. In this chapter, I locate that experiment, and some of the others I have discussed, in the context of a case study of the role of singular compositional abduction in the development of the Hodgkin–Huxley theory.

Section 5.1 notes that Bernstein's membrane theory represented the received view of the resting and action potentials for much of the first half of the twentieth century. According to this theory, excess intracellular potassium ions generated the resting potential of a neuron, whereas a breakdown of the axonal membrane allowing ions to flow out of the cell generated the action potential. In 1939, Hodgkin and Huxley (HH) used intracellular electrodes to measure an "overshoot" of the action potential, indicating to them that the action potential could not be a mere dissipation of the potassium concentration gradient. This is an instance of abductive disconfirmation. It also reviews the work by Hodgkin, Huxley, Curtis, and Cole (HHC&C) to confirm that the overshoot was a *bona fide* experimental result. This subsequent work illustrates the importance of the data/results distinction from Chapter 3.

Section 5.2 describes how, having satisfied themselves that the overshoot was real, HHC&C looked more closely at quantitative measures of the effects of potassium on axonal function. Here, I pay special attention to HH's work on potassium in Hodgkin and Huxley (1946, 1947), since it very nicely illustrates controlled experiments in which the results are compositional abductively interpreted.

Section 5.3 reviews two key developments in HH's new theory. By 1947, HH had formulated an alternative to Bernstein's membrane theory: a rapid influx of sodium generates the rising phase of the action potential, whereas a delayed efflux of potassium generates the falling phase and the potential reversal. One key development in Hodgkin and Katz (1949a) was the replication of the "Overton experiments," which established a role for sodium in the action potential (see Section 5.3.1). Another key was a series of experiments using "direct methods" of radioactively labeling sodium and potassium to verify their movements during axonal activity.[1] This work provides background information that informed HH's interpretation of the electrophysiological experiments. Further, a philosophical theory of this work needs to recognize a role for the explanation of rates, in this case, rates of radioactive decay and rates of ionic migration (see Section 5.3.2).

Section 5.4 reviews a selection of experiments from HH's 1952 papers. As this discussion focuses on compositional abduction, I have made two significant choices of material to exclude. First, I review the experiments on sodium, but ignore those on potassium. The principal reason for this is that, for technical and theoretical reasons, the determinations of potassium currents involved much more hypothetical reasoning that is inessential to the theory of compositional abductive inference. Second, I exclude from this review any significant discussion of the mathematical Hodgkin–Huxley model from the fifth paper in the series. Although a good case can be made for thinking that this is the most scientifically important work of the series, it is not where singular compositional abduction looms large. Instead, it is concerned with formulating a mathematical model, a topic involving any number of philosophical issues beyond abduction.

Much of the story arc for this chapter will be unsurprising to those who are familiar with the history of mid-twentieth-century physiology and the Hodgkin–Huxley papers of 1952. The novelty in the story is the philosophical account of singular compositional abduction. The story will spell out how the account developed in Chapters 2–4 articulates much of what is implicit in HHC&C's reasoning about axonal activity.

5.1 Bernstein's Membrane Theory and Its Disconfirmation

In 1902, Bernstein proposed that cells exhibit potentials due to selective ion permeability. This membrane theory was predicated on earlier work by Walther Nernst, who showed that electrical potentials could be established by ionic concentration gradients, and the theory of Wilhelm Ostwald, who showed that the voltage across a membrane arises from its selective permeability to specific ions.[2]

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[1] Keynes (1948, 1949), Keynes and Lewis (1951a).

[2] Nernst (1889), Ostwald (1890). For further history, see Lenoir (1986), Seyfarth (2006), and De Palma and Pareti (2011).

The Nernst equation relates a potential across a membrane to the relative concentration of a particular ion, denoted *ion*, inside and outside the membrane.

$$E_{\text{ion}} = \frac{RT}{zF} \ln \frac{[\text{ion}]_i}{[\text{ion}]_o}.$$

In this equation, E is the potential across the membrane for a particular ionic species (e.g., K^+ or Na^+), R is the gas constant, T is temperature in Kelvin, z is the charge of the ion, and F is Faraday's constant. The square brackets signify the ionic concentration with an o subscript for the outside (extracellular) concentration and an i subscript for the inside (intracellular) concentration.[3]

Inserting known values into the equation, Bernstein showed that the Nernst equation captures the relationship between the values on the right of the equation and the membrane potential. Bernstein further reasoned that, if the membrane potential is, in fact, determined in the way indicated by the Nernst equation, then one should find that the membrane potential varies with temperature. And, by measuring the potential at temperatures ranging from -2°C to 36°C, Bernstein confirmed that this relation held.[4]

Consider how this example fits the theory of singular compositional abduction sketched in Chapter 4. An individual membrane potential is a property instance of a neuron. It is ontologically determined by the property instances of the charges on the potassium ions and their relative internal and external concentrations under the conditions specified by R, T, z, and F. For each temperature, Bernstein stimulated the nerve generating a measurable "injury current," which he measured using a "differential rheotome."[5] Here, the injury current results provided evidence of a further result, the membrane potential. For each membrane potential result, there is a distinct set of potassium ions that realizes that membrane potential. Further, taken collectively, the set of estimated potentials for the temperatures from -2°C to 36°C constitutes a controlled experiment. Finally, Bernstein's hypothetical reasoning – if the membrane potential is determined in the way suggested by the Nernst equation, then one should find that the membrane potential varies with temperature – enabled him to provide support for the hypothesis that membrane potentials are determined in the way described by the Nernst equation. Part of the story of this support is compositional abduction.

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[3] Contemporary forms of the Nernst equation have the outside concentration as the numerator and the inside concentration as the denominator. The presentation here follows Bernstein's convention.

[4] See Seyfarth (2006, pp. 5–6).

[5] Seyfarth (2006, pp. 4–5).

Turn now from the resting potential to the action potential. Bernstein proposed that the action potential was simply a breakdown in the membrane that dramatically increased permeability to ions. Theoretically, this would diminish the electrical potential across the membrane, driving it toward zero. Membrane resistance or intracellular anions might prevent the potential from falling entirely to zero, but it should approach zero.[6] Thus, on the membrane theory, the magnitude of the action potential should be roughly equal to that of the resting potential.

Bernstein's membrane theory remained the standard view of resting and action potentials until January 1939. At that time, the 24-year-old Hodgkin had acquired new experimental equipment and "thought it best to begin with a straightforward problem, partly to run-in the new equipment and partly because [he] wanted to leave time for other activities" (Hodgkin, 1994, p. 130). Hodgkin sought to confirm the membrane theory in readily available shore crabs *Carcinus maenas*. Using external electrodes to measure the relative values of resting and action potentials, he found that the latter were significantly larger than the former.[7] If this result were correct, then it indicated that Bernstein's membrane theory was mistaken. He quickly appreciated the significance of the unexpected result:

> [A]s I wrote to my mother on February 6 the result was quite different: 'My experiments have taken on an interesting but rather disconcerting turn. I started off to work out a problem and thought beforehand that one particular result was a foregone conclusion. Now I have found the exact opposite. Of course I may discover a mistake or complication of some kind, but if not, this result means a fairly drastic reorganization of current ideas about nerve'. (Hodgkin, 1994, p. 131)

This autobiographical comment is helpful for two reasons. First, it confirms that Hodgkin quickly saw the significance of the result. By the summer of 1939, HH had devised a system for measuring action potentials in squid giant axons with intracellular electrodes.[8] With this system, they confirmed the overshoot. In their initial brief publication of the result – less than two full columns in *Nature* – HH did not indicate the theoretical significance. However, the autobiographical comment reveals that Hodgkin quickly understood the ramifications. Second, by the time HH could perform the intracellular recording, neither was likely to be surprised

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[6] For Hodgkin's take on the relevance of membrane resistance, see Hodgkin (1994, pp. 130–131).

[7] Hodgkin (1994, pp. 130–135).

[8] Hodgkin (1994, p. 133) credits Huxley with the idea; Huxley (2004, p. 292) credits Hodgkin with the idea.

to find that the action potential exceeded the resting potential. Hodgkin's earlier experiment with external electrodes in crab had prepared them for this result.[9]

The theory of singular compositional abductive disconfirmation provides an account of HH's implicit reasoning in 1939. If the action potential in one of the axons studied in 1939 were due to a breakdown in the membrane permeability to ions, then its action potential should approach zero. The axon's potential does not approach zero; it overshoots zero. Therefore, the action potential is not due to a breakdown in the membrane permeability. This hypothetical reasoning should be interpreted in terms of abductive disconfirmation. It is reasoning about determination relations among things in the world; it is not merely a set of true sentences constituting an instance of modus tollens.

Given the theoretical significance of their result, the next order of business for HH was to verify the qualitative correctness of the overshoot measurements and then develop an accurate quantitative measure of the action potential.[10] In terms of the framework described in Chapter 4, HH, along with Curtis and Cole, were interested in the extent to which their data provided reliable and accurate indications of their data targets. In other words, they were concerned that their data provided reliable results. This concern was a recurring feature of the physiological research of this time, a feature worthy of its own philosophical treatment. I do not mean to provide an exhaustive treatment of these issues here. I do not even try to treat all the issues HHC&C faced in these experiments. My more modest goal is, first, to present enough of the history to indicate that there was an issue and, second, to provide a concrete motivation in the case at hand for the distinction between data and results. For this purpose, I will only touch on two of HHC&C's concerns: potential axonal damage due to the insertion of microelectrodes and junction potentials. These were prominent features of the HHC&C discussions but are also relatively easy to explain. I will set aside factors concerning the electrical features of the experimental apparatus.[11]

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[9] Huxley (2004, p. 292).

[10] Hodgkin and Huxley (1945, p. 36) states this explicitly. Note that Hitler's invasion of Poland in 1939 and the call to British military service prevented HH from further experimentation on the matter until after the war.

[11] For a more robust discussion of the issues, see Hodgkin and Huxley (1939), Curtis and Cole (1940, 1942), and especially Hodgkin and Huxley (1945). For further issues with different data and different data targets, see Hodgkin (1938, pp. 89–92), Hodgkin and Huxley (1947, p. 343), Hodgkin and Katz (1949a, pp. 38–42), Hodgkin and Katz (1949b), and Hodgkin et al. (1952).

One of HHC&C's more obvious concerns was that inserting an electrode into an axon damages the axon. Hodgkin and Huxley (1945) report, for example, that the process of dissecting out an axon and inserting a cannula to carry the internal electrode took about 2 h, but that should the microelectrode touch the axonal membrane, the fiber would be "spoilt."[12] To avoid this, HH developed a sophisticated system of mirrors that would better enable them to guide the insertion of the electrode down the middle of the axon.[13] Curtis and Cole (1940, 1942) and Marmont (1949), for their part, developed a cell whose axis would carry the electrode down the center of the axon.

HHC&C relied on two principal checks on possible damage to the axons. First, they relied on comparisons of features of axons before and after the insertion of the microelectrode. So, for example, Curtis and Cole measured impedance before and after insertion and found only a small percentage variation.[14] HH compared the magnitude of the action potential with an external electrode before and after internal microelectrode insertion.[15]

The second check on injury was the constancy of axonal behavior. In their initial report on intracellular electrodes, HH observed that axons survived and transmitted impulses for several hours.[16] Curtis and Cole comment that "some axons remained excitable for as long as 4 hours after impalement. Usually the end which was punctured became inactive very soon and, starting from that point, the rest of the axon would slowly become inactive" (Curtis & Cole, 1940, p. 151).[17] Later, they comment that "Results obtained from axons in which the potentials did not remain constant for at least an hour after impalement were discarded" (Curtis & Cole, 1942, p. 138).

As something of an aside, notice that compositional abduction is at work in so modest a context as developing a sound experimental technique. Consider the explanation-seeking why-question, "Why did the end of the axon that was punctured become inactive very soon and then, starting from that point, the rest of the axon slowly become inactive?" Schematically speaking, HHC&C thought that some activity instances in

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[12] Hodgkin and Huxley (1945, pp. 177–179). See also Hodgkin (1994, p. 132) and Hodgkin (1951, p. 340). Note that HH did not directly measure damage to the axonal membrane caused by a microelectrode. Instead, they hypothesized that touching the membrane caused damage since that would explain the electrical behavior of the axon.

[13] Hodgkin and Katz (1949a, p. 38) describes a different mirror system for the same purpose.

[14] Curtis and Cole (1940, p. 151).

[15] Hodgkin and Huxley (1945, pp. 180, 183).

[16] Hodgkin and Huxley (1939, p. 711). See also, Hodgkin and Huxley (1947, p. 343).

[17] See Curtis and Cole (1942).

some individuals in the membrane ceased. The inactivation of the membrane was implemented by a cessation of certain activity instances in these unspecified individuals of the membrane. What caused the cessation of the activity instances of the parts of the membrane was contact with the microelectrode. When HHC&C proposed that an electrode's touching the membrane damages the membrane, they did not have any direct method to measure what the touching did to the membrane. They simply postulated damage to some parts because that would explain the subsequently measured results in the axon. When Curtis and Cole observed that axonal inactivity advanced from the point of microelectrode insertion, they inferred that the insertion damaged the axon's parts because that would explain the inactivity moving from the insertion point down the axon.

Another of HHC&C's concerns, arising later, focused on junction potentials. This was a potential source of systematic error that had a greater bearing on the quantitative features of the potentials than on the qualitative overshoot of the action potential.[18] Junction potentials arise from the migration of ions at the interface between solutions of different ionic constituents. So, Curtis and Cole (1942) note two junction potentials: one between the KCl of the microelectrode and the seawater and the other between the axoplasm and the KCl of the microelectrode. The former could be accurately calculated from the known ionic constituents, but the latter could not, because of the uncertain ionic concentration of the axoplasm. For the latter, only an estimate was available.[19]

The upshot here is that HHC&C gave reasons to believe that what appeared on their oscilloscopes – their data – provided more or less reliable and more or less accurate indications of resting and action potentials – their data targets or results. Having arrived at this conclusion, they began to work on the ramifications of their results. Hodgkin and Huxley (1945, pp. 189–194) considered four rival hypotheses that might explain the overshoot consistent with the membrane theory. Given how foreign these rivals are to contemporary thinking and how quickly HH abandoned them, I will not digress to review them.

5.2 The Transition to a New Theory: The Examination of Potassium

Proceeding on the assumption that something was amiss with the membrane theory, HHC&C found it natural to take a more quantitative look

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[18] See Hodgkin and Katz (1949a, p. 37).

[19] Curtis and Cole (1942, p. 142).

at the role of potassium ions.[20] Curtis and Cole (1942) measured both resting and action potentials while varying the extracellular concentration of potassium ions. They found that the resting potential changed with KCl concentration as predicted by the Nernst equation (although they did not mention the equation by name).[21]

The Hodgkin and Huxley (1946) investigation of potassium – another brief note in *Nature* – nicely illustrates many of the ideas I have been advancing. Given its brevity, I can review the paper almost line by line. Moreover, conveniently for my discussion, it sets aside the technical details of the experimental apparatus and axon preparation to focus on the experimental results and how HH interpreted them.[22]

Hodgkin and Huxley (1946) was HH's first paper based on postwar experimentation.[23] Rather than pursuing a rival to the membrane theory, HH focused on exploring the consequences of extracellular potassium for action potentials in *Carcinus*. According to the hypothesis, sustained axon activity should release potassium into the extracellular medium. Their goal was to provide "an indirect but very sensitive measure" (Hodgkin & Huxley, 1946, p. 376) of this potassium loss.

To begin with, based on unpublished results, HH believed that if the extracellular KCl content is roughly tripled (from 9.8 to 29.8 mmol/l), then membrane conductance (the inverse of membrane resistance) is roughly tripled. By contrast, trebling extracellular NaCl concentration produces no measurable change in membrane conductance. The NaCl control, thus, eliminates one rival hypothesis concerning the basis for a change in membrane conductance. Therefore, they adopt as a working hypothesis that extracellular KCl increases membrane conductance.

Next, HH proposed, based on optical and electrical measurements, that isolated axons immersed in oil are surrounded by a small volume of seawater adhering to the external surface of the axon.[24] They reasoned hypothetically that, if axonal activity releases KCl into this small space, then sustained tetanic axonal activity should release enough KCl into this space to produce a measurable change in membrane conductance. They then tested this consequence of the KCl-release hypothesis by stimulating

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[20] Hodgkin (1976, p. 13).

[21] Curtis and Cole (1942, pp. 139, 143). Curtis and Cole measured a 50 mV increase in resting potential with a tenfold increase in extracellular potassium. This was close to the "theoretical" value of 58 mV specified by the Nernst equation. See Hodgkin (1994, p. 273) or Brown (2020, p. 24).

[22] These details are, however, discussed in Hodgkin and Huxley (1947).

[23] Hodgkin and Huxley (1945) and Hodgkin and Rushton (1946) were write-ups of prewar work.

[24] For details of HH's calculation of this volume, see Hodgkin and Huxley (1947, pp. 354–355).

an oil-immersed axon for 1 min, and then measuring the conductance. As predicted, the conductance increased. This is an instance of abductive confirmation of the hypothesis that action potentials release intracellular potassium.

HH also reasoned abductively about another result. They noted that, within a few minutes after the tetanic stimulation, the conductance returned to close to its pre-stimulation value. Given this return, HH proposed that the axon rapidly reabsorbs the released potassium. The reabsorption hypothesis would explain the return of the conductance to the neighborhood of its pre-stimulation value.

HH also considered a rival to the potassium reuptake hypothesis: The effects "might equally well have been due to some structural alteration in the membrane which did not depend upon a chemical change in the external medium" (Hodgkin & Huxley, 1946, p. 377). HH performed a control experiment to rule this out. Following the minute of simulation, they immersed the axon in seawater for a few seconds. Their thinking was that this would clear away the extracellular potassium that had accumulated in the extracellular region delimited by the oil. The result was that the axon conductance very quickly returned to the pre-stimulation values. Here we have compositional abductive disconfirmation of the "structural alteration hypothesis."

Having concluded that axonal activity releases potassium, HH then turn to a computation of the amount of potassium released. This is a simple calculation based on the volume of the aqueous solution clinging to the axon and the change in conductance. Based on eleven experimental determinations, they computed an average of 1.7×10^{-12} moles/cm^2 per impulse. Notice that HH were interested in the individual, spatiotemporally localized determinations, since those individual determinations were used to compute the average. This average value can also be checked against values of the membrane capacity. Notice that this computation only supports their conclusion that the axon releases 1.7×10^{-12} moles/cm^2 per impulse on the assumption that action potentials really do release potassium. This is grounds for thinking that HH took the abductive reasoning to lead to a true conclusion, that the abductive reasoning provides confirmation.

HH's experimental results raised the explanation-seeking why-question, "Why did the membrane conductance of the oil-immersed axon increase after prolonged stimulation?" Their explanation is that axonal activity releases potassium into the limited extracellular space and that this increase in extracellular potassium raises the membrane conductance. The compositional hypothesis that potassium efflux implements axonal activity, in part, explains the experimental results. It is HH's interpretation of their experimental results.

Hodgkin and Huxley (1947), sharing the same title as Hodgkin and Huxley (1946), elaborates that earlier work, including details about the apparatus and preparation. It includes another abductive inference based on downstream consequences of axonal activity.[25] HH propose that there should be a linear relationship between the frequency of the tetanic stimulation of the axon and the conductance change, on the assumptions that each action potential releases the same amount of potassium and that conductance is proportional to external potassium concentration. Upon performing the requisite experiment, HH did find a roughly linear relationship. Again, there is support for the hypothesis that action potentials release intracellular potassium since this hypothesis would be part of the explanation of the linear relationship between the frequency of stimulations and the conductance changes.

5.3 The New Theory

In Hodgkin's recounting of the matter, Huxley had assumed that sodium must play a role in the axonal potentials, whereas he was skeptical.[26] What prompted Hodgkin to rethink the matter was receiving a paper from Katz in late 1946 showing that crab axons were inexcitable in salt-free sugar solutions.[27] In January 1947, Hodgkin showed that, in crabs, reducing extracellular sodium reduced the action potential. This prompted Hodgkin to do more sophisticated experiments on squid axons in the summer. After a long delay, the results of these experiments, in time conducted with Katz, made their way into Hodgkin and Katz (1949a).[28] Here, I will not provide an exhaustive review of the lengthy (Hodgkin & Katz, 1949a), but will instead focus on the "Overton experiment," a replication of an experiment performed decades before in plants by Charles Overton.[29] I limit myself to these experiments, as they illustrate singular compositional abduction in controlled experiments. This is perfectly consistent with my proposal that singular compositional abduction plays an important, even if not exclusive, role in Hodgkin and Katz's reasoning.

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[25] For still another related experiment, see Hodgkin and Huxley (1947, pp. 352–353).

[26] Hodgkin (1976, p. 14) and Hodgkin (1994, pp. 269–270).

[27] Katz (1947).

[28] Hodgkin (1994, p. 277).

[29] Overton (1902).

5.3.1 *The "Overton Experiment"*

Chapter 3 proposed that singular compositional abductive inferences implicate explanations of spatiotemporal particulars. Spatiotemporal particulars are especially salient among the first results reported in Hodgkin and Katz (1949a). For one thing, Hodgkin and Katz report that they began their experiments with a series of measurements, which they report in their table 3 (reproduced in part in Table 5.1). Each entry in this table reports a spatiotemporal particular, such as the resting potential of an individual axon at a particular time and place. Based on data collected with a thermometer, silver–silver chloride microelectrodes, oscilloscope, etc., these results are then available for further inferences. Hodgkin and Katz also provide averages of the results, such as the average resting potential of the axons. The individual results, perhaps accompanied by elementary mathematical computations, can serve as the basis of empirical generalizations, such as, "All shore crab axons have a resting potential of 48 mV." The point I emphasize here is that spatiotemporal particulars have a role to play in Hodgkin and Katz's reasoning: they provide the values upon which

Table 5.1 *Electrical properties of axons in seawater*

Temperature	Resting potential	Action potential	Maximum rate rise	Maximum rate fall
(°C)	(mV)	(mV)	(V.sec^{-1})	(V.sec^{-1})
22	46	85	-	-
20	52	93	-	-
21	52	86	490	290
24	51	83	580	380
22	50	86	650	400
22	49	93	770	460
20	40	87	560	330
20	51	98	630	390
–	48	87	520	340
21	46	89	600	360
20	53	99	1,000	530
20	46	85	620	480
19	42	85	490	330
20	45	86	590	360
21	45	82	680	350
Average				
21	48	88	630	380

the averages are computed and they provide the values from which a scientist might draw empirical generalizations.[30]

These points survive the observation that each entry in the table may only be a selection of one of perhaps a handful of measurements Hodgkin and Katz took of each axon. Even if Hodgkin and Katz selected only one of many measurements, they did select one spatiotemporal particular to report. This point also survives the possibility that HH were reporting an average of multiple measurements of a single axon resting potential, for even in that case, each individual measurement would be of a spatiotemporal particular that was used to compute the average for that axon. Finally, these points survive the contention that empirical generalizations are typically more important to scientists than mere mathematical averages.

Hodgkin and Katz's table reveals that they were concerned with spatiotemporal particulars, but there is another spatiotemporal particular that was of great interest to them. They write,

> [W]e have never observed action potentials greater than 100 mV. at 18–23°C., whereas Curtis & Cole describe a spike as large as 168 mV. in a fibre which gave a resting potential of 58 mV. The matter is not one that can be lightly dismissed, because the existence of a fibre capable of giving an overshoot of 110 mV. has far-reaching implications. (Hodgkin & Katz, 1949, p. 43)

Here, Hodgkin and Katz were clearly concerned with a single action potential recorded by Curtis and Cole. It had a spike of 168 mV. Why were they interested? Because they believed that this result was in some sense anomalous. If correct, it would have "far-reaching implications." In the end, Hodgkin and Katz did not explain the anomaly, but that is not the point I need to emphasize. Instead, it is that the consideration of spatiotemporal particulars has some role to play in scientific reasoning. Often, this role is understated as scientists seek to generalize, but they nevertheless have a role to play. The theory of singular compositional abduction is intended to explicate what this role is sometimes like.

Section 3.4 introduced the Overton experiment. Recall that the gist of the experiment was to measure the action potential of a squid axon over time. It began with the axon in a sodium-containing seawater solution,

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[30] Table 3 in Hodgkin and Katz (1949a) also represents spatiotemporal particulars, but does not provide averages. So, that table does not as nicely highlight the differences between particulars, on the one hand, and computations and generalizations from particulars, on the other. Table 2 of Hodgkin and Huxley (1952a, p. 464) provides both individual measurements and averages.

then switching to a sodium-free medium (isotonic dextrose), then switching once again to a sodium-containing seawater solution. In Section 3.4, I reviewed Hodgkin and Katz's interpretation of two principal results of this experiment. First, after the seawater was removed, the peak of the action potential declined, but once the seawater was restored, the peak of the action potential returned to near-normal levels. Second, after the seawater was removed, the rate of rise of the action potential decreased, but once the seawater was restored, the rate of rise of the action potential returned to near-normal levels.

After the core Overton experiment, Hodgkin and Katz explored various controls. These include experiments with reduced-sodium media and sodium-enriched media. For simplicity, the present discussion will focus on the reduced-sodium experiment. In this experiment, Hodgkin and Katz used a sodium, reduced-sodium, sodium protocol with temporal delays (typically about 15 min) between measurements. Hodgkin and Katz assumed that these delays allowed the axons to equilibrate to the changed ionic concentrations. The three reduced-sodium media contained (1) 33% seawater, 67% isotonic dextrose; (2) 50% seawater, 50% isotonic dextrose; and (3) 71% seawater, 39% isotonic dextrose. The experiment showed that the peak of the action potential was reduced with greater reductions in the sodium concentration of the medium. Further, they showed that the effects of the reduced sodium were reversible. Still further, the resting potentials were largely unchanged. The philosophical analysis just given of the first experiment easily carries over to this experiment.

5.3.2 "Direct" Measures of Ion Movements

Although my focus has been, and later will be, on the electrophysiological methods used by Cole, Curtis, Hodgkin, Huxley, and Katz, it is useful to draw attention to other methods that provided background for the electrophysiological work and were important at the time. These are methods that are sometimes omitted in contemporary textbook treatments.

Starting in 1946, Keynes began a series of experiments with a recently introduced technique of radioactive labeling, which enabled him to use radioactive K^+ and Na^+ to trace the movements of these ions in and out of cells. For present purposes, I will focus only on the work on potassium, but essentially the same philosophical account will apply to the experiments on sodium.

Keynes (1948) – a brief communication in the *Proceedings of the Physiological* Society – reported soaking *Carcinus* nerves in a Ringer's solution containing radioactive K^{42} for several hours.[31] Keynes assumed that during this period radioactive potassium would collect within the cell. He then transferred the nerve to a bath that circulated non-radioactive Ringer's solution, thereby carrying away any K^{42} that left the cell. Keynes found that over time the amount of radioactivity in the axon, as measured with a Geiger counter, decreased exponentially. In addition, when the nerve was stimulated at 17 impulses/sec, the level of intracellular radioactivity decreased more rapidly.

Consider what is going on in this simple experiment in light of the theory of Chapter 3. Consider, first, data and results. The Geiger counter generates data that is aimed at counting the number of nuclear decay events per unit time. Each datum on the counter is a spatiotemporal record aimed at another spatiotemporal event, a nuclear decay. Each decay is an activity instance of an individual. It is something that an individual K^{42} atom does just once. Keynes and the other scientists of his day presumed that past research had validated the assumption that the data on the Geiger counter delivers genuine results about decay events.

Next, consider the explanation of rates. Keynes observed that the amount of radioactivity in the axon decreased exponentially over time. He explained this in terms of the number of radioactively labeled potassium ions leaving the axon and being washed away by the circulating Ringer's solution.[32] The exponential decay over time was due to the potassium ions leaving the cell in proportion to their concentration. He further explained the greater decrease in radioactivity during axonal activity in terms of the release of more potassium ions during axonal activity.

Third, consider the explanation of the results of controlled experiments. In Keynes's experiments, the rate of decay under stimulation of the nerve is greater than the rate of decay under resting conditions. One rate is greater than another. This is a comparison that takes place in the context of a controlled experiment. This invites the question, "Why is the rate of decay under stimulation greater than the rate of decay under resting conditions?" Answer: More potassium is released when the nerve is stimulated than when it is in a resting state. This is an explanation in terms of the relative

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[31] See also Keynes (1949), and Keynes and Lewis (1951a, 1951b). Rothenberg (1950) included studies of radioactive sodium.

[32] Another factor in the decrease would have been a small decrease in the radioactivity of the K^{42}. It would have been small, since the half-life of K^{42} is about 12.5 h and the experiment ran for over 3 h. Keynes (1948) does not discuss this.

numbers of activity instances of individuals. Keynes did not spell all of this out in his paper, since it was evident to the physiologists at the time.

Mid-century physiologists perceived a difference between the HHC&C electrophysiological methods and Keynes' radioactive tracer methods. They conceptualized this difference in terms of "direct" and "indirect" methods.[33] Hodgkin (1951) offers these comments on the differences between electrophysiological methods and chemical methods:

> [T]he introduction of radioactive tracers and the development of sensitive chemical methods have enabled ionic movements to be followed experimentally. These methods are direct, in the sense that they leave no doubt about the identity of the ion under observation, but they suffer from the disadvantage that their time-resolving power is very poor. They can, for example, be used to prove that potassium ions leak out of a nerve when it is active, but they do not show whether this is a sudden event which forms an essential link in the process of conduction or whether it is a relatively slow affair connected with the recovery process. The resolving power of electrical instruments is now much better than anything that physiologists are likely to require, but the results are indirect, in that they give no certain information about the identity of the ions which carry the electric current. (Hodgkin, 1951, p. 339)[34]

Hodgkin notes that the radioactive tracer experiments show that sodium and potassium cross the membrane, but they do not show the precise time course. The way to read Hodgkin's comment about "no certain information" is as a recognition that the identity of the ions carrying the current is hypothetical. It is given by compositional abduction.

5.4 Hodgkin and Huxley 1952

As mentioned in the introduction of this chapter, my treatment of the 1952 Hodgkin–Huxley papers will be selective.[35] To describe matters informally, the Hodgkin–Huxley papers offer three "stories." First, there is a driving force story, which is an account of the potential and

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[33] See, for example, Keynes and Lewis (1951a).

[34] Just to be clear, Hodgkin (1951), being a lengthy review article, contains a lot of information that informed Hodgkin, Huxley, and Katz's thinking. But, as a review article, rather than an experimental article, it does not fall within the scope of my case for singular compositional abduction.

[35] Brown (2020) and Raman and Ferster (2022) provide extensive exposition and commentary on the entire series of papers. Aidley (1998, pp. 58–65) provides a helpful complement to the present account. It is a more compact textbook presentation, albeit sometimes anachronistic, that captures the course of HH's experimentation as described here. Hodgkin (1994, pp. 288–296) also provides a concise exposition of the course of the experimentation described here.

concentration gradients that generate forces that can move ions across an axonal membrane. Second, there is a permeability story. A simple lipid bilayer membrane is largely impermeable to ions. Yet, at rest, the membrane is apparently selectively permeable to some ions and, during an action potential, this permeability rapidly and selectively changes. Finally, there is a propagation story. This is a story about how local changes at one point along an axon induce changes in adjacent regions of the axon so as to propagate the action potential into those adjacent regions.

From the experimental work in 1947, along with the radioactive tracer work, HH had by 1949 embraced the sodium–potassium understanding of the action potential. This substantiated part of the driving force story. In the fall of 1947, HH heard from Cole about two experimental techniques. The first provided for feedback control which enabled an experimenter to hold the current constant or the potential across the membrane at a desired command potential. The voltage clamp enabled the study of another part of the driving force story. The second involved using long electrodes that could maintain a constant voltage along a substantial length of the axon. The space clamp eliminated complications that arise with the generative feedback underlying the propagation of the action potential, thereby enabling HH to develop the driving force and permeability stories apart from the propagation story. In March of 1948, Hodgkin spent several days meeting with Cole and George Marmont, learning in person about these techniques.[36] One of the central conclusions Hodgkin took away was that by using feedback to maintain a constant voltage, one observes that a 50 mV depolarization is followed by a brief surge of what he interpreted as a capacity current, then a short phase of inward current, and then finally an outward current.

After spending more than a year refining their experimental technique, Hodgkin, Huxley, and Katz spent much of the summer of 1949 performing the experiments that, after various delays, formed the basis for the five classic papers of 1952. Of these papers, the second, third, and fourth papers, that is, Hodgkin and Huxley (1952a, 1952b, 1952c) will be most relevant. The first paper – Hodgkin et al. (1952), the "voltage-clamp paper" – focuses on the description and validation of the experimental procedures, whereas the fifth paper – Hodgkin and Huxley (1952d), the "modeling paper" – works the experimental results into a quantitative description.

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[36] Hodgkin (1976, p. 17) and Hodgkin (1994, p. 282).

5.4.1 "Currents Carried by Sodium and Potassium"

HH distinguish three theoretical goals for Hodgkin and Huxley (1952a), the "Currents Carried" paper. They are: (1) the study of the role of sodium concentration in the external medium, (2) the resolution of ionic currents (a hypothetical contributor to the total current) into sodium and potassium currents, and (3) the expression of membrane permeability in terms of units of ionic conductance.[37] These three goals form the basis for the following three subsections.

The effects of sodium concentration. As I have repeatedly referred to the first experiment of Hodgkin and Huxley (1952a) as illustrating one or another feature of abductive inference, there is no need to review that again here. Section 3.3 above introduced HH's second experiment highlighting the role of the potential across the membrane. Recall from Section 3.3 that, in this second experiment, HH retained the sodium-containing, sodium-free, sodium-containing protocol, thereby retaining experimental control over the sodium in the external medium. In addition, the experiment varies the potential at which the axon is clamped, thereby expanding the number of variables under experimental control. Assuming the reliability of the oscilloscope, an oscilloscope trace (a datum) in one run of this experiment provides evidence for an initial inward current in axon no. 21 (a result). Further, it could be shown that these currents are slowly reduced and eventually replaced by an initial outward current, as the voltage clamp potential is decreased. Each trace corresponds to a numerically and qualitatively distinct current in axon no. 21 and each current may be given a singular compositional explanation in terms of ion fluxes. This family of singular compositional explanations supports the hypothesis that the current flowing across the membrane is the resultant of two opposing forces, a chemical gradient and a potential gradient.

The following comment from HH is one piece of textual evidence supporting a role for abduction in the interpretation of the first two experiments:

> When the axon is placed in a sodium-free medium, such as the 'choline sea water', there can be no inward flux of sodium, and the sodium current must always be outward. This will account for the early hump on the outward current which is seen at all but the lowest strength of depolarization in the centre column of Fig. 2. (Hodgkin & Huxley, 1952a, p. 452)

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[37] Hodgkin et al. (1952, p. 425).

The first sentence draws attention to the sodium concentration gradient. It was noted earlier that there is sodium inside the axon, so that in a sodium-free medium, the concentration gradient would run from higher in the axon to lower in the extracellular medium. Physiologists also knew that sodium would flow down this concentration gradient, unless this gradient was offset by a counteracting potential gradient. So, supposing that "account for" is synonymous with "explain," HH are proposing that the "early hump" in the outward current is an explanandum that is compositionally explained by the sodium concentration gradient.

Later sections of Hodgkin and Huxley (1952a) indicate that HH understand their abductive inferences to confirm the sodium hypothesis. At an early point in their discussion section, HH comment, "We have shown in the earlier parts of this paper that there is good reason for believing that the component of membrane current that we refer to as I_{Na} is carried by sodium ions" (Hodgkin & Huxley, 1952a, pp. 465–466). This is connected to confirmation by assuming that if something provides good reason for P, then it provides confirmation for P. A second comment, in the final summary section, adds another piece of textual evidence in support of the view that HH think abduction provides confirmation. HH review the first two experiments and then comment, "These results support the view that depolarization leads to a rapid increase in permeability which allows sodium ions to move in either direction through the membrane" (Hodgkin & Huxley, 1952a, p. 471). Supposing that "support" is synonymous with "confirm," the idea is that the sodium gradient's explanation of the early hump confirms the sodium hypothesis. Contrast what HH write with what they do not write. They do not write that, "In the earlier parts of this paper we have introduced the hypothesis that the component of membrane current that we refer to as I_{Na} is carried by sodium ions." They do not write that, "In the earlier parts of this paper we have proposed that the hypothesis that the component of membrane current that we refer to as I_{Na} is carried by sodium ions is pursuit-worthy." So, in adopting the sodium hypothesis because it is compositionally explanatory, HH do not intend merely to introduce the sodium hypothesis as worthy of further investigation. They intend to confirm it, to provide good reasons to believe it, or to support it. So, while the abductive interpretation of HH's work is, obviously, an interpretation, there are textual grounds for it. It bears emphasizing that HH's comments on their work complement the direct examination of their work.

As part of their interpretation of their second experiment, HH note that, "These results are in *qualitative* agreement with the hypothesis that the inward current is carried by sodium ions" (Hodgkin & Huxley, 1952a, p. 450, italics added). Further, HH note that, in the case of the medium containing sodium, there is a "critical value" – the sodium potential, E_{Na} – at which the inward driving force of the sodium concentration gradient equals the outward driving force of the membrane potential. Further, the sodium potential should be determined according to the Nernst equation. These two comments about the qualitative agreement and the Nernst equation foreshadow things to come in their third experiment, an experiment that provides what they take to be quantitative confirmation of the Nernst equation specification of the sodium potential.

HH's third experiment is a variation on their second, wherein the sodium-free solution is replaced by a sodium-diluted solution. This is a successor to the "reduced-sodium experiments" of Hodgkin and Katz (1949a). One sodium-diluted solution contains 10% of the sodium of seawater; the other 30%. Further, the sodium-containing, sodium-free, sodium-containing protocol is slightly modified in favor of a reduced-sodium-containing, sodium-containing, reduced-sodium-containing protocol.

Before beginning to interpret their results, HH note that the figures they provide do not represent the total current. Instead, they represent a hypothetical ionic current. HH postulated that the total current is the sum of a capacity current and an ionic current, that is, $I_{total} = I_c + I_i$. HH hypothesize that the potential change associated with voltage clamping gives rise to a very brief capacity current. This current can be measured for a single case, then scaled appropriately for different potential changes, and then subtracted from the measured total currents to yield a hypothetical ionic current. Recall a point from Chapter 2 regarding derivative compositional explanations. Here is a case in which HH were able to provide more than a mere derivative compositional explanation of the total current, they were able to provide a compositional explanation of the capacity current, which is a contributor to the total current.

Notice, in addition, that HH's comment about the capacity current reveals implicit compositional abductive reasoning. They measured a brief spike in total current lasting about a microsecond. It is the time course of this spike just after the onset of the voltage clamp that led HH to this hypothesis. They had no experimental means of directly detecting the congregation of charges on either side of the axonal membrane, as was hypothesized in a capacity current. By contrast, a capacity current would explain the brief time course of this spike following the onset of the voltage clamp, thereby giving HH reason to believe that a component of the total current is due to a capacity current. HH's fellow physiologists would surely comprehend this reasoning, albeit not necessarily described in terms of abductive reasoning.

HH report that the results of their third experiment are in keeping with what one would expect from the second experiment.

> Inward current is present, but only over a range of membrane potentials which decreases with the sodium concentration, and within that range, the strength of the current is reduced. A definite sodium potential still exists beyond which the early hump of ionic current is outward, but the strength of depolarization required to reach it decreases with the sodium concentration. (Hodgkin & Huxley, 1952a, p. 452)

The more significant aspect of this experiment, however, is presented in a separate section, "The external sodium concentration and the 'sodium potential'." This section begins with the claim, "Estimation of the 'sodium potential' in solutions with different sodium concentrations is of particular importance because it leads to a quantitative test of our hypothesis" (Hodgkin & Huxley, 1952a, pp. 452–454). This "quantitative test" is an instance of extended hypothetical reasoning.

HH note that, just as the Nernst equation determines the sodium potential in seawater, so it determines corresponding sodium potentials, E'_{Na}, in the two reduced sodium media:

$$E'_{Na} = \frac{RT}{F} \log_e \frac{[Na]_i}{[Na]'_o}.$$

They next note that the difference between these two sodium potentials – a sodium potential shift – is given by

$$E'_{Na} - E_{Na} = \frac{RT}{F} \left\{ \log_e \frac{[Na]_i}{[Na]'_o} - \log_e \frac{[Na]_i}{[Na]_o} \right\} = \frac{RT}{F} \log_e \frac{[Na]_o}{[Na]'_o}. \quad (1)$$

E_{Na} and E'_{Na} yield displacement membrane potentials given by $V_{Na} = E_{Na} - E_r$ and $V'_{Na} = E'_{Na} - E'_r$, where E_r is the resting potential in seawater and E'_r is the resting potential in a reduced-sodium medium. Rearrangement and substitution of these last equations yields

$$\left(V'_{Na} - V_{Na}\right) + \left(E'_r - E_r\right) = \frac{RT}{F} \log_e \frac{[Na]_o}{[Na]'_o}. \quad (2)$$

(2) yields an "observed shift" specified by

$$E'_{Na} - E_{Na} = \left(V'_{Na} - V_{Na}\right) + \left(E'_r - E_r\right) \quad (3A),$$

Table 5.2 *Observed and theoretical change in sodium potential when the extracellular medium is changed from seawater to a low sodium medium*

Axon no.	Temp. (°C)	$\frac{[Na]'_o}{[Na]_o}$	V_{Na} (mV)	V'_{Na} (mV)	(E'r - Er) (mV)	Observed (mV)	Theoretical (mV)
20	6.3	0.3	-105	-78	+3	+30	+28.9
20	6.3	0.1	-96	-45	+4	+55	+55.3
21	8.5	0.1	-100	-48	+4	+56	+55.6
21	8.5	0.1	-95	-45	+4	+54	+55.6

and a "theoretical shift" specified by

$$E'_{Na} - E_{Na} = \frac{RT}{F} \log_e \frac{[Na]_o}{[Na]'_o} \qquad (3B).$$

All terms in these last two equations can be measured, thereby enabling HH to compare the theoretical shift with the observed shift.[38] This comparison appears in Table 5.2, reproduced from HH's table 1. Commenting on this comparison, HH write,

> It will be seen that there is good agreement, providing strong evidence that the early rise or fall in the recorded ionic current is carried by sodium ions, moving under the influence of their concentration difference and of the electric potential difference across the membrane. (Hodgkin & Huxley, 1952a, p. 454)

HH's two brief paragraphs invite two philosophical observations. First, historians and philosophers of science should step back from this relatively complicated computation to consider a point that HH do not make, but that would have been evident to mid-twentieth-century physiologists. In point of logic, one might have tested the application of the Nernst equation by substituting values into the right-hand side and comparing the results with the measured results. Although this test was logically possible, it was practically impossible for HH. To accurately measure $[Na]_i$ using the methods available at that time would have damaged the cells under study. Here is Jane Cronin's commentary on HH's "indirect procedure" based on the third experiment:

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[38] Strictly speaking, the V_{Na} was not measured, but interpolated as spelled out in Hodgkin and Huxley (1952a, pp. 454–455).

> [To test the sodium potential hypothesis], the reasonable procedure would seem to be to compute E_{Na} by using the Nernst formula and to compare the observed experimental value (close to 79 mV) just described. The difficulty in such a direct procedure is that the value of $[Na]_i$ is needed, but $[Na]_i$ is not known with any accuracy for the axon being studied experimentally. (Indeed, to measure $[Na]_i$ would require the destruction of the axon.) Consequentially, . . . the more indirect procedure is used. (Cronin, 1987, p. 28)[39]

Cronin's commentary draws attention to what would have been well-known to physiologists at the time. Moreover, it explains why HH used the relatively complicated experimental method they used in their third experiment. The methodological moral for historians and philosophers of science: limiting one's philosophical account to what scientists make explicit may omit important details. One needs to be aware of relevant background information.

The second philosophical point to note is HH's use of hypothetical reasoning. The hypothesis was that the Nernst equation specifies the relationship between the internal and external sodium concentration and the sodium potential. Because of the technological limitations on measuring the value of $[Na]_i$, HH had to resort to a more complicated experimental procedure, one that required more reasoning than many other examples. In practice, HH had to engage in a more complicated form of hypothetical reasoning. In this reasoning, (3A) gives a hypothesis that is tested against "observations" generated by (3B).

For decades, historians and philosophers of science looking at HH's hypothetical reasoning would have been tempted to interpret it as an instance of hypothetico-deductive confirmation. HH logically deduced an "observable" consequence of their hypothesis, and then noted that this consequence obtained. An abductive theory of confirmation, however, offers a different interpretation of HH's reasoning. What HH's reasoning shows is that the expression in (3B) represents the way in which the values of two concentrations of external sodium ions, etc., will determine two distinct sodium potentials, that is, a sodium potential shift. (3B) represents an ontological dependence relation among things in the world. (3A) reveals another ontological dependence, one that, in combination with measurements of V_{Na}, V'_{Na}, and $(E'_{Na} - E'_r)$, allows a measurement of the sodium potential shift. What is crucial for the abductive approach is that what is

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[39] Aidley (1998, p. 59) and Raman and Ferster (2022, p. 79) make the same point.

represented in (3B) explains the sodium potential shift, so that HH believe they have "strong evidence" of what is represented in (3B).

All of this is a more complicated version of the idea broached in Chapter 4. Recall that Chapter 4 included a review of a compact one-paragraph argument from Curtis and Cole (1940). This was the argument that a measured potential change was due entirely to the passage of an action potential. It was an argument that, on its face, serves as a perfect illustration of HD confirmation in action. The reasoning was laid out as an instance of affirming the consequent. Chapter 4 proposed that the theory of HD confirmation provides one philosophical interpretation of Curtis and Cole's reasoning, but that the theory of abductive confirmation provides another. Those who believe that scientists are interested in what is going on in the world, rather than in logical relations among sentences, might incline to the abductive approach. Further support for the abductive approach is that it provides a diagnosis of the tacking problems that have beset HD confirmation for decades. There is, therefore, reason to adopt an abductive interpretation. The hypothetical reasoning of Hodgkin and Huxley (1952a, pp. 452–454) is like Curtis and Cole's, only more complicated.

One final wrinkle. Note that the explanandum in this experiment is the shift in the sodium potential. This is a difference between two sodium potentials, one in seawater and another in a reduced-sodium medium. Each of the two potentials is compositionally explained by way of the Nernst equation and each of these explanations is involved in the explanation of the difference. So, strictly speaking, the proposal here is not that HH's hypothetical reasoning is an instance of compositional abduction. It is more complicated than that, the complication lying in the explanation of a shift. *Prima facie*, this is just an instance of explaining the results of a controlled experiment wherein the results are potentials.

The resolution of ionic currents. Recall that when HH voltage-clamped an axon, they could only measure the total current. They hypothesized, however, that the total current at any given time was the sum of a capacity current and an ionic current. In Hodgkin and Huxley (1952a), they used the time course of the capacity current and its temporal relation to the change in membrane potential to support the capacity current hypothesis.[40] This allowed them to subtract the capacity current from the total current leaving

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[40] In Hodgkin and Huxley (1952b), they used a slightly different method involving depolarization and hyperpolarization. This method invoked the symmetry of the resulting currents as a basis for compositionally abductively inferring that there exists a capacity current.

the ionic current, a current that is maintained for much longer than the capacity current. Their next theoretical step was to decompose the remaining ionic current into the currents of different ionic species. For simplicity, I focus on the separation of the hypothetical ionic current into sodium and potassium currents.[41] The arc of their argument involves hypothetical reasoning.

HH propose to separate the sodium and potassium currents using the results of the experiments on currents in seawater and in reduced-sodium media, given certain assumptions.[42] These assumptions – these hypotheses – are the following:

> (1) The time course of the potassium current is the same in both cases.
>
> (2) The time course of the sodium current is similar in the two cases, the amplitude and sometimes the direction being changed, but not the time scale or the form of the time course.
>
> (3) $dI_K/dt = 0$ initially for a period about one-third of that taken by I_{Na} to reach its maximum.
>
> (Hodgkin & Huxley, 1952a, p. 457)

In more detail, (1) is the assumption that differences in the external sodium concentration do not change the potassium current; (2) involves several points we might separate. It says that the external sodium concentration affects the driving force on sodium, which changes the amplitude of the sodium current. Further, with sufficiently large changes in the external sodium concentration, the driving force can be changed from driving sodium into the axon to sometimes driving it out. These changes in the driving force, however, do not change how long the currents flow, that is, the time scale of the current. Nor do these changes in the driving force change the initial rise in inward current or the subsequent decline in the inward current, that is, the time course of the current. Assumption (3) reflects the putative delay in the rise of the potassium current. More specifically, the potassium current is unchanged for the first third of the time it takes for the sodium current to reach its peak.

The procedure for separating the currents began with currents measured using the sodium, low-sodium, sodium protocol and then plotted on a graph. Capacity currents, corrected for the different sodium

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[41] To follow up on HH's treatment of other ionic species, one may begin with the single paragraph on Hodgkin and Huxley (1952a, p. 461).

[42] Cronin (1987, pp. 29–34) provides a complementary, more mathematical exposition, of HH's reasoning.

concentrations, were then subtracted from the total current curves. The currents from the first and third curves were then averaged to allow for the deterioration of the axons over the course of the experiment. A further correction was added for the difference in resting potential in the sodium and low-sodium media. They next let I_i, I_{Na}, and I_K represent the ionic current, sodium current, and potassium current in the sodium medium and I'_i, I'_{Na}, and I'_K represent the ionic current, sodium current, and potassium current in the reduced-sodium medium. This permits some simple calculations.

Although not listed among the three assumptions, HH's working hypothesis is that $I_i = I_{Na} + I_K$ and that $I'_i = I'_{Na} + I'_K$. So,

$$I_i - I'_i = (I_{Na} + I_K) - (I'_{Na} + I'_K) = (I_{Na} - I'_{Na}) + (I_K - I'_K). \qquad (4)$$

Given assumption (1) that $I_K = I'_K$, it follows from (3) that

$$I_i - I'_i = I_{Na} - I'_{Na} \qquad (5)$$

Given assumption (2), that the time course of I_{Na} and I'_{Na} are the same, we have it that $k = I'_{Na}/I_{Na}$, for a constant k. So, $I'_{Na} = kI_{Na}$, so

$$I_i - I'_i = I_{Na} - I'_{Na} = I_{Na} - kI_{Na} = (1 - k)\, I_{Na}. \qquad (6)$$

Hence

$$I_{Na} = (I_i - I'_i)/(1 - k) \qquad (7)$$

$$I'_{Na} = k(I_i - I'_i)/(1 - k) \qquad (8)$$

$$I_K = I'_K = I_i - I_{Na} = (I'_i - kI_i)/(1 - k). \qquad (9)$$

(7), (8), and (9) allow plots of I_{Na}, I'_{Na}, I_K, and I'_k in terms of the known quantities I_i and I'_i. These plots are shown in Figure 5.1, redrawn from Hodgkin and Huxley (1952a, p. 459, figure 5).

Were Hempel to review this case, he might interpret HH's reasoning here as another illustration of HD confirmation. He might suggest that HH introduced hypotheses, then derived some consequences from them and then checked those consequences against "observations." Yet, the very nature of the experimental situation precludes comparing the derived sodium and potassium curves from Figure 5.1 with "observed" sodium and potassium curves. The very nature of the experimental situation is that HH could only measure the total current under a voltage clamp, not the isolated sodium and potassium currents. They could not measure the sodium and potassium curves that the HD method prescribes. Consider, now, how this influenced HH's reasoning.

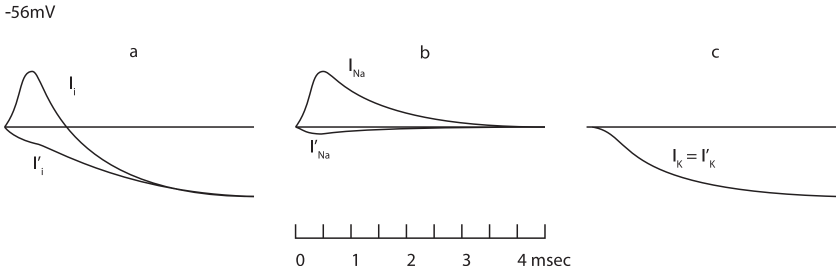

Figure 5.1 "Curves illustrating separation of ionic current into I_{Na} and I_K. a, ionic currents: I_i axon in sea water, membrane potential lowered by 56 mV; I'_i axon in 10% sodium sea water. b, sodium currents: I_{Na} sodium current in sea water; I'_{Na} sodium current in 10% sodium sea water. c, potassium current, same in both solutions." Redrawn from Hodgkin and Huxley (1952a, p. 459, figure 5).

Having introduced their three assumptions, HH immediately provide the following methodological commentary on them:

> The first two of these assumptions are the simplest that can be made, and do not conflict with any of the results we have described, while the third is strongly suggested by the form of records near the sodium potential … These points are sufficient reason for trying this set of assumptions first, but their justification can only come from the consistency of the results to which they lead. (Hodgkin & Huxley, 1952a, p. 457).

Notice that HH introduce the first two assumptions as "pursuit-worthy" because they are simple and because they do not conflict with any of the results they have to date. They do not introduce them because they are explanatory.[43] Also, notice that HH offer some set of hypotheses and refer to "results to which they lead." Given the presuppositions of HD confirmation, one would expect HH to claim that the justification for the hypotheses can only come from their consistency with measurements – with observations. But, of course, given the nature of the experimental situation described in the last paragraph, they cannot check that consistency. They did not have independent access to the sodium and potassium currents; they only had indirect access to the ionic current by abductive reasoning. Moreover, they fully understood this. This is why HH made the slightly different claim that the justification for the hypotheses "can only come from the consistency of the results to which they lead." This interpretation is supported by HH's subsequent reasoning about

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[43] These observations do not square with the Peircean line of thought about the introduction of hypotheses.

reconciling the consequences of their hypothetical reasoning with the experimental results. What I will now try to do is show how HH's commentary really does capture what they did.

Having presented the results of their derivation in one figure, HH added another figure presenting the proposed potassium current curves for different depolarizations (see Figure 5.2, redrawn from Hodgkin & Huxley (1952a, p. 459, figure 6)). With these figures on the table, HH begin to make their case for the justification or validity of the sodium and potassium current curves in Figure 5.1:

> A satisfactory feature of these curves, which is to some extent a check on the validity of the assumptions, is that the general shape is the same at all strengths. If the time courses of I_{Na} and I'_{Na} had not been of similar form, Equation [9] would not have removed sodium current correctly. It would then have been unlikely that the curve of potassium current at a potential away from the sodium potential would have been similar to that at the sodium potential, where the sodium current is zero and Equation [9] reduces to $I_K = I_i$ because $k = \infty$. (Hodgkin & Huxley, 1952a, p. 458)

In this passage, HH refer to the potassium curves of Figure 5.2, which all have the same general shape at all strengths. This would not happen if the second assumption, that is, $I'_{Na} = kI_{Na}$, were false. Why? Compare the potassium current with a depolarization to the sodium potential with the potassium current with a depolarization to a potential other than the sodium potential. On the hypothesis that $I_i = I_{Na} + I_K$, (capacity current having been subtracted out), at the sodium potential, the sodium current I_{Na} should be zero, because the driving force is zero, so the $I_i = I_K$. Further, given the proportionality of $I'_{Na} = kI_{Na}$, the other curves should have a shape similar to this. This indicates that HH really did link the justification of their assumptions to the consistency of the results to which they lead.

An abductive interpretation of HH's hypothetical reasoning proposed that the reasoning is a matter of drawing out the ontological consequences of assumptions (1)–(3). The idea is that were things in the world laid out as specified in these assumptions, then the ontological consequences are such that the potassium current curves near the sodium potential should be similar to the potassium current curves far from the sodium potential. Further, those similarities are found to hold. This provides abductive confirmation of the hypothesis, but not textbook HD confirmation.

To conclude this subsection, I remind the reader of a proposal from Chapter 2, that part of Hodgkin and Huxley's achievement was to provide compositional explanations of the capacity current, the sodium current, the potassium current, and the leak current. Further, they showed how

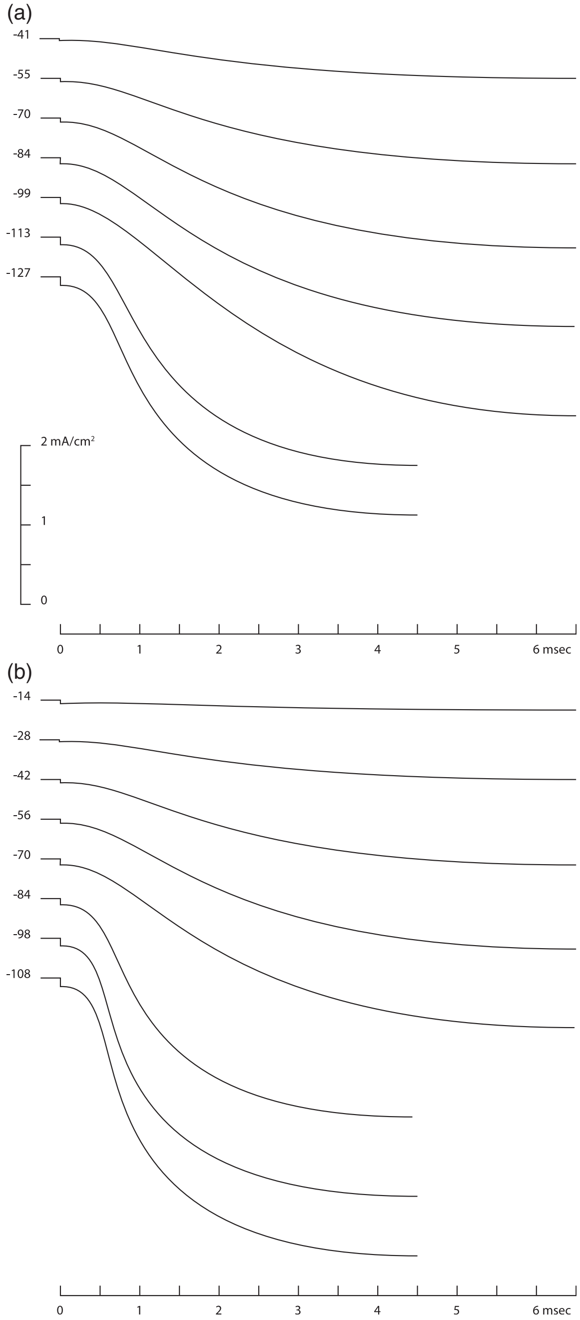

Figure 5.2 Curves of potassium current against time for various strengths of depolarization. Displacement of membrane potential when axon is in seawater is indicated for each curve, in millivolts. a, derived from voltage clamps with axon in 30% sodium seawater, seawater and 30% sodium seawater. Axon no. 20; temperature 6.3°C. b, derived from voltage clamps with axon in 10% sodium seawater, seawater and 10% sodium seawater. Axon no. 21; temperature 8.5°C. Redrawn from Hodgkin and Huxley (1952a, p. 459, figure 6).

each of these currents contributes to the total current. This achievement contrasts with any number of cases in psychology wherein psychologists are unable to separate the contributions to behavior.

Conductances. To this point in the chapter and to this point in Hodgkin and Huxley (1952a), I have focused on the "driving force story." Now, I follow HH in taking up the subject of the membrane permeabilities. The gist of the permeability problem for HH was that they knew that depolarization somehow changes something in the membrane to allow sodium to enter the axon early and for a limited time and potassium to exit the axon following a brief delay. Moreover, this something must somehow enable charged particles to cross a high-resistance lipid bilayer. The core challenge for HH was that, whereas much was known about sodium and potassium ions, very little was known about the contents of the membrane.

HH hypothesized that an ionic current, I_{Na} or I_K, is determined by the driving force – which is the difference between the membrane potential and the ion potentials, E_{Na} or E_K – and the membrane permeability. This is a relation among physical quantities in the world that might be represented mathematically by the equations

$$I_{Na} = g_{Na}(E - E_{Na})$$
$$I_K = g_K(E - E_K),$$

where g_{Na} and g_K represent the sodium and potassium conductances and where $E - E_{Na}$ and $E - E_K$ represent the driving forces on sodium and potassium. HH, however, do not begin with these equations. Instead, they "defined" conductances in terms of the currents, membrane potentials, and ionic potentials:[44]

$$g_{Na} = I_{Na}/(E - E_{Na})$$
$$g_K = I_K/(E - E_K).$$

Based on the results of the third experiment, HH had determined E_{Na} in the way described above. Further, borrowing from their next paper, Hodgkin and Huxley (1952b), they had values of E_K. Finally, given the resolution of the sodium and potassium currents, I_{Na} and I_K, HH could get an empirical handle on g_{Na} and g_K. They could plot the time course for both sodium and potassium conductances (see Hodgkin & Huxley, 1952b, p. 462, figure 8). Further, they were able to determine the rates of rise of conductances against the strength of depolarization.

These equations require both philosophical and scientific commentary. Having introduced the conductance equations, HH comment "the usefulness

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[44] See also, Hodgkin and Huxley (1952b, p. 477).

of the definitions, and the degree to which they measure real properties of the membrane, will clearly be much increased if each of these relations is a direct proportionality, so that g_{Na} and g_K are independent of the strength of the driving force under which they are measured. It will be shown in the next paper (Hodgkin & Huxley, 1952[b]) that this is the case" (Hodgkin & Huxley, 1952a, p. 462). Logical empiricists who embrace DN explanation and HD confirmation will likely latch on to HH's use of the word "definitions." Yet, HH do not mean by this term what some philosophers might mean, namely, some stipulation about how they will use notation. Instead, HH are advancing an empirical hypothesis about the relations among "real properties" of the membrane. More specifically, they have in mind the hypothesis that these quantities are linearly related. Although it does not appear in Hodgkin and Huxley (1952a), their idea is that the quantities are related as specified by a rearrangement of Ohm's law, $V = IR$, where the voltage is given by $E – E_{Na}$ and g is the inverse of R. This would have been obvious to HH's fellow physiologists but was only explicitly mentioned in the later papers. The idea that they are advancing an empirical hypothesis, rather than a stipulative definition, is important insofar as it helps philosophers of science resist the empiricist interpretations of HH's work.

On the scientific front, one can foresee in these equations their general strategy for getting an experimental handle on conductances. E is the voltage set by the voltage clamp. Following their results of the third experiment in Hodgkin and Huxley (1952a), they had shown how to calculate E_{Na} and E_K. Finally, given their resolution of the ionic current into sodium and potassium currents, they could measure the time course of I_{Na} and I_K. Thus, an important part of the work following the first three experiments was to show how voltage clamp results could provide for an indirect means of ascertaining the conductances. This was a significant theoretical and empirical step forward that was explored in the third and fourth papers of the 1952 series. Roughly speaking, the third paper concerns the "activation" of membrane permeability, whereas the fourth paper concerns the "inactivation."[45]

Why was this empirically and theoretically important? Recall that, in explaining the action potential, Bernstein's membrane hypothesis posited changes in membrane permeability. Bernstein, however, had no means of isolating changes in membrane permeability from changes in the potential. Having established that sodium permeability rises and falls in the early phase of the action potential and that potassium permeability rises with a delay and remains stable, HH have apparently made the scientific problem

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[45] For this terminology, see Hodgkin and Huxley (1952c, p. 497).

more difficult. There is not merely ionic permeability to consider. There are two ion permeabilities with their distinct time courses to consider. How can a scientist get an empirical handle on these permeability changes? By postulating a relationship between the time course of conductances and the time courses of ion currents, membrane potentials, and ionic potentials. Such features of conductances began to pave the way for a compositional explanation of instances of the conductance of the membrane in terms of activity instances of individuals in the membrane.

It is worth emphasizing this theoretical strategy since little in HH's discussion draws attention to its significance. Their paper has no historical contextualizing. There is only a minor section break. Moreover, philosophers of science who have written about the Hodgkin–Huxley model have often noted that HH could not provide a compositional explanation of the changes in membrane permeability.[46] While this last point is true, it understates the importance of HH's experimental and theoretical advance. Further, it ignores just how early in the course of scientific research it would have been had HH come up with the correct account of the "physical basis" of membrane permeability.

5.4.2 "The Components of Membrane Conductance"

Although there is much of philosophical importance in Hodgkin and Huxley (1952b, 1952c), the present account will be limited to some of the first experiments on sodium conductance in "The Components of Membrane Conductance." These experiments bear out the role of compositional abduction in HH's interpretation of their experimental results. The overarching experimental method was to voltage clamp axons at different potentials, recording the currents at the times of change. In effect, the different potentials immediately changed the driving force for the current, but the changes in membrane permeability followed with some delay. As HH put it, there was a discontinuity in the currents, but continuity in the conductances. This temporal difference allowed HH to infer the time course of conductance changes.

In Figure 5.3, the left column represents the time course of command voltages, whereas the right column represents the time course of currents. In the top row, a single depolarization of 41 mV (represented in a on the left) gives rise to the usual initial rise in inward current eventually declining and giving way to an outward current (represented in A on the right). HH assume without comment that there is an initial capacity current at $t = 0$.

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[46] See, for example, Craver (2008) and Levy (2014).

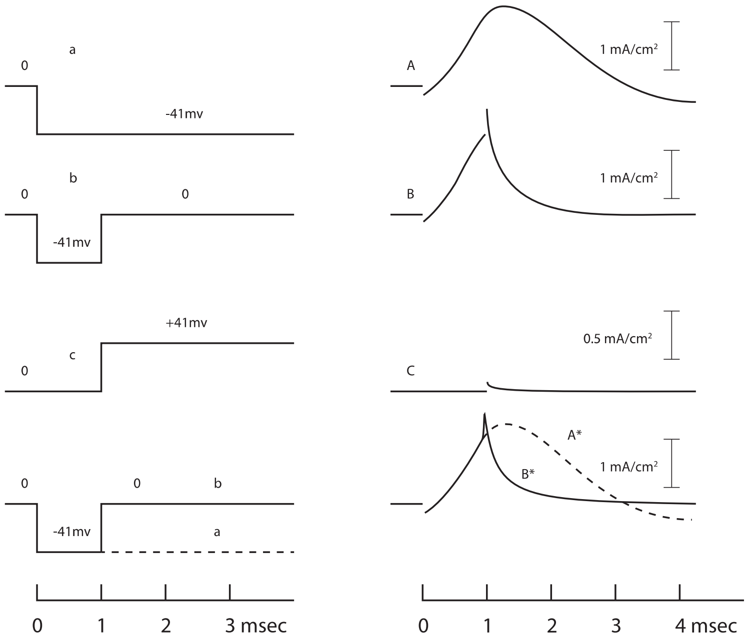

Figure 5.3 Left-hand column: a, b, c, time course of potential difference between external and internal electrode. Right-hand column: A, B, C, records of membrane current associated with changes in membrane potential shown in left-hand column. (The amplification in C was 90% greater than that in A and B.) A*, B*, time course of ionic currents obtained by subtracting capacity current in C from A and B. Axon 25; temperature 5°C. Redrawn from Hodgkin and Huxley (1952b, p. 474, figure 1).

In the second row, a pulse of depolarization by 41 mV is followed by a restoration of the potential to the resting potential after 1 msec (represented in b on the left). The current initially rises just as before for the first msec, but there is a jump in the value of the inward current immediately after the restoration of the resting potential (represented in B on the right). HH assumed that two things happen at $t = 1$ msec. First, there is a jump or discontinuity in inward current, because of the jump or discontinuity in the driving force on sodium ions and that there is an inward capacity current. The experiment depicted in the third row explores this. In c, there is a single hyperpolarization step that induces a current spike shown in C which HH abductively infer is a capacity current. What would explain this short-lived current in the direction of the potential change? A capacity current. They then subtract this capacity current from A and B to get the reconstructed curves in A* and B* in the fourth row.

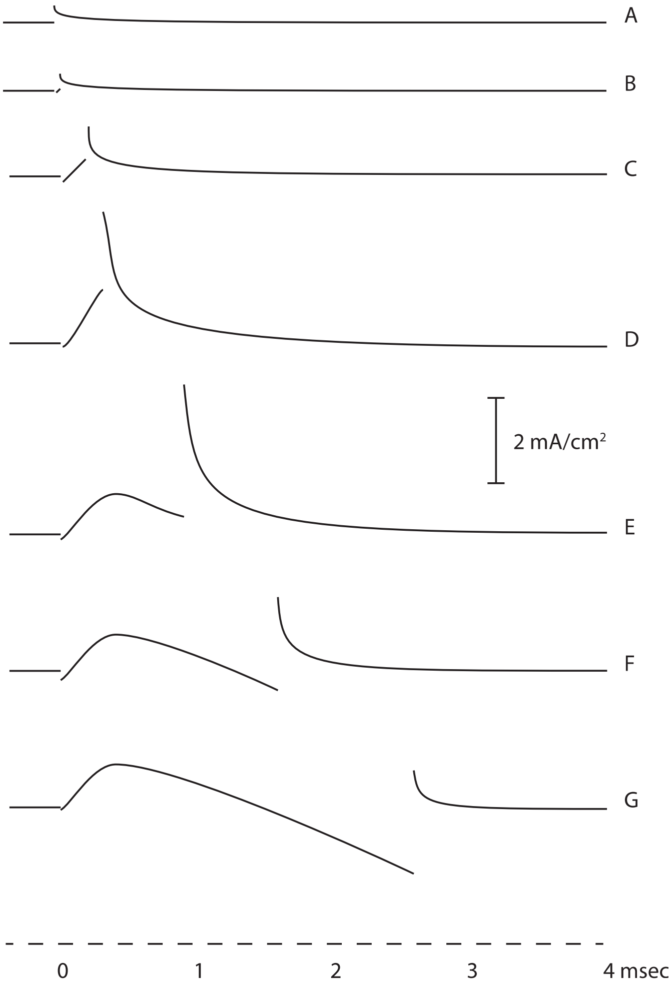

Figure 5.4 Records of membrane current associated with depolarization of 97.5 mV lasting, 0.05 (A), 0.08 (B), 0.19 (C), 0.32 (D), 0.91 (E), 1.6 (F) and 2.6 (G) msec. Redrawn from Hodgkin and Huxley (1952b, p. 475. figure 2).

In a second experiment designed to reveal the discontinuity in the inward current, HH set the initial pulse to a value close to the sodium potential. In this case, the driving force during the pulse, hence the current during the pulse, would be near zero. This follows from the assumption that $I_{Na} = g_{Na}(E - E_{Na})$. HH then varied the duration of the pulse. In curves A–D of Figure 5.4 above, the discontinuity grows. Why? HH

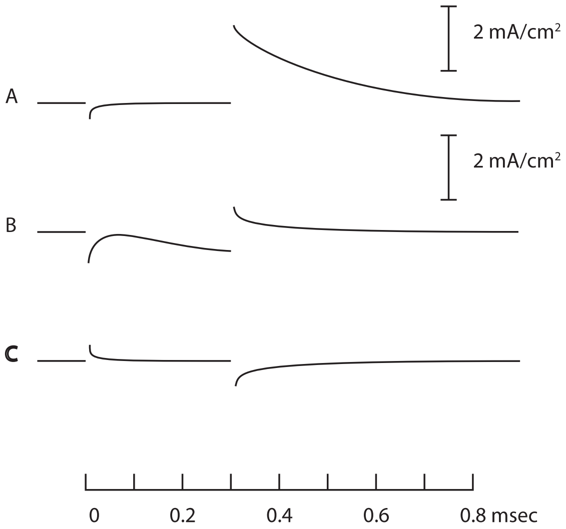

Figure 5.5 A, membrane current associated with depolarization of 110 mV lasting 0.28 msec; nerve in seawater. B, same, but with nerve in choline seawater. C, membrane currents associated with an increase of 110 mV in membrane potential; nerve in choline seawater. Axon 25; temperature 5°C. Redrawn from (Hodgkin & Huxley, 1952b, p. 476. figure 3).

reason that the depolarization triggers increasing membrane permeability that peaks at about 0.5 msec. Because the membrane permeability increases, the current increases. In E–G, however, the inward current declines as potassium permeability increases and potassium ions begin to leave the axon.

In a third experiment designed to nail down the role of sodium, HH began with a short 0.3 msec pulse depolarizing the cell to the sodium potential, then restoring the resting potential (see Figure 5.5). The pulse produced a capacity current but no ionic current. This was expected as there was no driving force on the sodium, because the cell was depolarized to the sodium potential. After the pulse, however, the rest potential gave rise to an inward driving force. This result is shown in A. In the next condition, the axon was placed in choline seawater. Here, the results are shown in B. During the pulse, some of the intracellular sodium flowed down the concentration gradient generating an outward current. Upon restoration of the resting potential, there was no extracellular sodium to flow into the axon, hence no inward current. Finally, in C, HH show the results of an increase in polarization of 110 mV, followed by a restoration of the rest potential in a sodium-containing medium. This generated only an outward capacity current during the pulse, and then an inward capacity current upon restoration of the resting potential.

Each of these experiments validated the picture of sodium as responsible for the initial inward current. To confirm that conductances satisfied Ohm's law, HH then used two pulses, the first for a duration of 1.53 msec (to maximize conductance) at -29 mV, and the second for a range of different potentials -60 mV to +30 mV. Plotting the sodium conductances for these short times revealed the linear relation anticipated in Hodgkin and Huxley (1952a). Recall that, in order to get this sodium conductance curve, HH had to determine the sodium potential, then isolate the sodium current from the capacity current and the potassium current, then experimentally separate the sodium current from the sodium conductance. And there was a parallel development of the potassium conductance curve. The thread of this argumentation can be hard to follow through the many careful comments that HH insert along the way. Moreover, it is easy to lose sight of the idea that the ultimate confirmation for all of this apparatus is that it enables HH to explain the multiple sets of experimental results they obtained along the way.

HH's development of the sodium and potassium conductance curves was an important experimental achievement. It set the stage for the advancement of a compositional explanation of the conductances. In point of logic, over the course of Hodgkin and Huxley (1952a, 1952b, 1952c), HH might have been able to determine enough features of the sodium and potassium conductances to enable them to abductively confirm some hypothesis regarding the individuals in the membrane whose activity instances might explain one or another experimental result.[47] Their work might have done the equivalent of measuring enough features regarding rat maze navigation to enable the psychologist to infer that the rat was navigating using a cognitive map, rather than a local response strategy. In the end, however, the best HH could do was to disconfirm a membrane permeability hypothesis they had entertained when they first conceived their experiments.[48] On this rejected view, negatively charged "carrier" molecules shuttle the positively charged ions across the membrane in response to depolarization. The fatal flaw in this model was that it predicts an initial *outward* negative current that was not detected. In other words, the hypothesis led to a conclusion about

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[47] Hodgkin and Huxley (1952b, pp. 495–496) and Hodgkin and Huxley (1952c, pp. 505–506) provide concise summaries of potential explananda.

[48] Hodgkin and Huxley (1952d, pp. 502–504). See also Hodgkin (1976, p. 15).

something that was not detected, something that should be interpreted as an instance of compositional abductive disconfirmation.

5.5 Summary

The principal aim of the present chapter has been to illustrate how the philosophical account of singular compositional abduction developed in Chapters 2–4 characterizes some of Hodgkin, Huxley, Curtis, and Cole's reasoning about their experimental results. It is meant to illustrate how the account of singular compositional abduction makes explicit so much of what is merely implicit in this body of mid-twentieth-century physiological research.

As scientifically important as the HH theory is and as familiar as it is in the context of the New Mechanism, historians and philosophers of science have not even scratched the surface of the complexity of this work. Few of HH's papers are even cited in the philosophical literature. Unfortunately, the present chapter does not go far in rectifying the situation. Far from being a complete or even thorough examination of the mid-twentieth-century work on the action potential, it even ignores large parts of HH's 1952 papers. There is simply too much ground to cover the subtleties of the experiments and the theoretical background to them. This chapter only touches on one aspect of the mid-twentieth-century neuron physiology, namely, some instances of the use of singular compositional abduction.