Potential Controversies: Causation and the Hodgkin and Huxley Equations

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The import of Hodgkin and Huxley's classic model of the action potential has been hotly debated in recent years, with particular controversy surrounding claims by prominent proponents of mechanistic explanation. For these authors, the Hodgkin-Huxley model is an excellent predictive tool but ultimately lacks causal/explanatory import. What is more, they claim that this is how Hodgkin and Huxley themselves saw the model. I argue that these claims rest on a problematic reading of the work. Hodgkin and Huxley's model is both causal and, in an important sense, explanatory.

1. Introduction. The Hodgkin and Huxley model of the action potential is in many ways the last thing one would expect to be the subject of controversy. It is a mainstay of neuroscience education and stands among the most celebrated achievements in its various histories and retrospectives. One need not look far to see comments like Armstrong and Hille's that "the period from 1939 to 1952 was a heroic time in the study of membrane biophysics" (1998, 371)[1] or Bezanilla's that "the beauty and simplicity of voltage-dependent conductances in the Hodgkin and Huxley (HH) equations goes way beyond explaining the generation and propagation of the action potential" (2008, 457). In recent years, however, the model and its significance have received considerable scrutiny. According to an interpretation defended by well-known proponents of mechanistic explanation (Craver 2007, 2008; Bogen 2008), the model cannot, when taken in historical context, be understood as a genuine causal explanation. What Hodgkin and Huxley provided, they argue,

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1. The reason given, unsurprisingly, is that "during this period, Hodgkin and Huxley explained the propagated action potential" (Armstrong and Hille 1998, 371).

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was a *phenomenal model* able to "describe the electrical behavior of giant squid axon preparations in a mathematically convenient form" (Bogen 2008, 1036) but silent about how it is produced. The HH model, they allege, occupies a space not unlike Ptolemaic astronomy (Craver 2008, 1026).

At the outset, it is important to know the basic model. At its core lies the so-called total current equation:

$$I = C_M dV/dt + g_k n^4(V - V_k) + g_{Na} m^3 h(V - V_{Na}) + g_l(V - V_l). \quad (1)$$

On the left side, we have "total" current; on the right lies the capacitive current and three ionic currents corresponding to potassium, sodium, and leak channels, respectively. The three channel terms have both "g's," representing their maximum conductances, and driving forces, in which each ionic equilibrium voltage is subtracted from the present voltage (the greater the difference, the stronger the force). The middle two terms likewise feature conductance terms, n, m, and h, which were chosen for a mixture of theoretical reasons, simplicity, and goodness of fit. The equation's implications will be explored in greater detail below, but for now it suffices to say that it provides highly accurate predictions about the form of the action potential.

The predictive success is not what is at issue, however. What matters is whether the model offers a causal explanation. For the above-cited authors, it does not. This is because, they argue, causal explanations must make contact with the entities and activities underlying the phenomenon. They need to tell us what sodium and potassium channels do to produce action potentials. The HH model, they allege, is agnostic about such things. Indeed, it would be decades before the relevant physical mechanisms would be even dimly understood. In support of this interpretation, the authors rely on two important claims. The first is that Hodgkin and Huxley do not offer a causal interpretation of the model in their paper. Indeed, they "insist" otherwise (Craver 2008, 1022). Particularly supportive is a passage toward the end of the 1952 paper where the model is proposed. Their predictive success, Hodgkin and Huxley claim, "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. . . . 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" (1952c, 541). Roughly put, if Hodgkin and Huxley did not think of the model in causal terms, we should not either. The second major point concerns the role curve fitting played in the fixation of the conductance terms, n, m, and h. The functional relationship between these terms and the axon membrane potential was, the mechanist critics note, selected by Hodgkin and Huxley according to how well the function fit antecedently gathered data. The problem is that the results of such "curve fitting"

measures carry no force. They may provide a good "data summary" (Craver 2008, 1030), but strictly speaking, the equations will be "neither true nor false, neither explanatory nor descriptive" (Bogen 2008, 1034).

Overall, the mechanists' present a persuasive picture. After reading their papers, it is hard to think of the model as aiming for a causal explanation. Nevertheless, I argue, it does. In what follows I hope to show why. First, I present textual evidence that Hodgkin, Huxley, and their contemporaries interpreted the model (including the controversial conductance terms) causally. Evidence to the contrary, such as the quote above, can be defused without too much trouble. Next, I argue that worries about "curve fitting" are exaggerated. The method by which Hodgkin and Huxley arrived at their conductance terms was theoretically motivated and came with important causal implications. Finally, I consider whether the model "explains" the action potential. I argue that Hodgkin and Huxley explained the action potential as they conceived of it but perhaps not on other potential ways of framing the phenomenon.

2. Interpreting HH Causally. I begin with the most general arguments against a causal reading. Although both mechanists make the claim, I will focus on Craver's argument, as he spends more time on the issue. The noncausal reading is supported by at least two historical claims, one negative and the other positive. On the negative side, he argues that there is insufficient evidence in the quantitative paper and subsequent work to indicate that the authors saw the model as anything more than a mere formalism. We can choose to interpret it causally, but Hodgkin and Huxley give us no reason to (truthfully, they actively oppose it). In the positive part, Craver makes the additional claim that the state of knowledge at the time renders a causal/explanatory interpretation anachronistic. Our reading, Craver alleges, is tinted by factors "difficult for those who know much more than Hodgkin and Huxley did about the mechanism of the action potential to forget" (2008, 1028). If we were to strip away this implicit background knowledge, it would become clear that the authors did not have enough knowledge to meaningfully interpret the model (and the conductance terms in particular) causally.

Both claims draw on a conceptual distinction between mathematical structure of the kind seen in the HH model (that conductance is a function of voltage, say) and causal relations (that voltage causes conductance change). The two are easily equivocated, but they involve very different commitments. In and of itself, Craver argues, the mathematical model does not separate causal relations from mere correlations. More powerfully still, its deductive consequences will be the same "whatever one's interpretation of the causal structure" (Craver 2008, 1030). We can manipulate the model however we like. He is not arguing the "absurd" position that causal explanations cannot be given in mathematical language, but if the math is meant to embody causal claims, this must be made clear: "the equations must be supplemented by a causal

interpretation: one might, for example, agree by convention that the effect variable is represented on the left, and the cause variables are represented on the right, or one might add 'these are not mere mathematical relationships among variables but descriptions of causal relationships in which this variable is a cause and this other is an effect'" (1027). From here, the argument moves to the historical contention that Hodgkin and Huxley provide no such interpretation. This premise may be supported by the supposed absence of an interpretation in their writing, quotes where Hodgkin and Huxley seem to rebuff causal readings, and the aforementioned claim that details needed to provide a proper causal interpretation were not available at the time. To be clear, there is no denial that the authors had some relevant causal knowledge of the system, it is that they did not have enough and that what they did have they generally did not "include explicitly in the model" (1027).

First, let us assess the claim that they do not give the model a causal reading. It is true that they do not state "these are not mere mathematical relationships," but this is far from damning. Such statements do not occur in most scientific papers. More commonly, context specifies whether a mathematical dependency (or an arrow in a picture or the phrase "depends on" in a sentence) is causal. Hodgkin and Huxley's case is no different. When one examines the experiments discussed and the way they talk about the model, there is more than enough material to unambiguously indicate a causal reading. To start with, they use a lot of causal terms (a fact noted by Weber 2008), even when discussing the conductance terms (challenging Weber's [2008, 1000] conductance-excluding view; see below). One finds passages like: "an *effect* of this kind is to be expected on our formulation, since the entry of $Na+$ which *causes* the rising phase, and the loss of $K+$ which *causes* the falling phase, are *consequent on* increases in the conductance of the membrane to currents carried by these ions" (Hodgkin and Huxley 1952c, 529, emphasis mine). Likewise, in his Nobel speech, Huxley describes the calculations much as one would discuss concrete experimental preparations, writing that "we . . . calculated the responses of our mathematical representations of the nerve membrane to the equivalent of an electrical stimulus" and "calculating the effect of a stimulus [to the model] . . . one would see the forces of accommodation-inactivation of the sodium channel, and the delayed rise of potassium permeability—creeping up and reducing the excitatory effect of the rapid rise of sodium permeability" (1972, 61; again, it seems like conductance is included, as the "forces of . . . inactivation" likely refers to the h conductance term). None of these quotes suggests the authors saw the model or "formulation" as causally uncommitted.

The major hurdle to the causal reading is, of course, the lengthy quote claiming that predictive success "must not be taken as evidence that our equations are anything more than an empirical description" (Hodgkin and Huxley 1952c, 541). It is easy to see this as offering a phenomenal interpretation of

the model, even if the quotes above speak against this view. If one considers the full quote and its context, however, another interpretation emerges: they are merely expressing a transient underdetermination claim. They faced a modeling choice between first-order and higher-order kinetics for conductance (see below). The available evidence did not favor either, although they did imply different underlying mechanisms and causal relations (512). Knowing this, the "must not be taken as evidence" probably refers to the fact that the likelihood of their model given the evidence was no greater than the likelihood of the alternative higher-order model. This gains support from the fact that the immediately following sentence refers to an "equally satisfactory alternative." If so, the causal reading of the equations would be insulated. No one is defending the thesis that causal claims cannot be underdetermined at the time of their introduction (i.e., that causal models can compete with one another). Indeed, if Hodgkin and Huxley are discussing comparative evidence, it would seem to presuppose a causal view. The hallmark of a phenomenal model is that it is not intended to make claims about underlying causes. If it tracks the observable data, that is enough.

What about the claim that Hodgkin and Huxley did not have enough information for a legitimate causal interpretation? One of the main contentions, recall, is that explanatory readings inadvertently import background knowledge unavailable before the 1970s or 1980s. Weber in particular is taken to task for the "historically inaccurate" suggestion that they "had any knowledge of voltage-gated channels" (Craver 2008, 1031). Even if the previous paragraph is correct in its argument, this claim could still pose a problem. A model can be presumed to capture causal regularities without its creators actually knowing enough to make sense of its workings. That is, one could grant that they read the model causally and still think that they only had sufficient background to meaningfully interpret half of it.

To assess the issue more clearly, we first need a sense of what a causal interpretation demands. Obviously, if the only thing sufficient to provide an interpretation is molecular detail, then Hodgkin and Huxley did not have enough information. It is doubtful that the mechanists are making such a demand, though. Although molecular details may be emphasized (Craver 2008, 1029), other writings suggest a less firmly reductionist stance. Craver (2007), for example, states that nothing on his view implies "a privileged level at which all causes act or at which all relevant causes are located" (104), noting that causal variables could be as broad as socioeconomic status. In any event, the fact is that we still do not know all the central molecular details. When it comes to sodium channels, for example, the term "conformational change" plays a role not unlike "inactivation" once did. Hodgkin and Huxley could not have explained the action potential because we have not. Rather than molecular detail, then, I follow Craver (2007) in adopting a broadly interventionist stance on causation (Pearl 2000; Woodward 2003). The model will have a

causal interpretation if its features map onto (potentially "ideal") interventions on the system. To avoid anachronisms, I require that these interventions be recognized by the authors or their near contemporaries. It is not enough that we can interpret parts of the model as transmembrane integral proteins if nobody near the time would have.

The issue, then, is whether the equations embody interventions recognized by Hodgkin, Huxley, and their peers. I claim they do. The model contains a particular set of mathematical dependencies (Craver 2008). Total current (I) is a function of four subcurrents. These are then functions of still further variables, and so on, until we arrive at a set of exogenous variables that are left as is. The relationships are a bit easier to see if, following conventions from the causal modeling literature, they are represented as a directed graph (fig. 1).

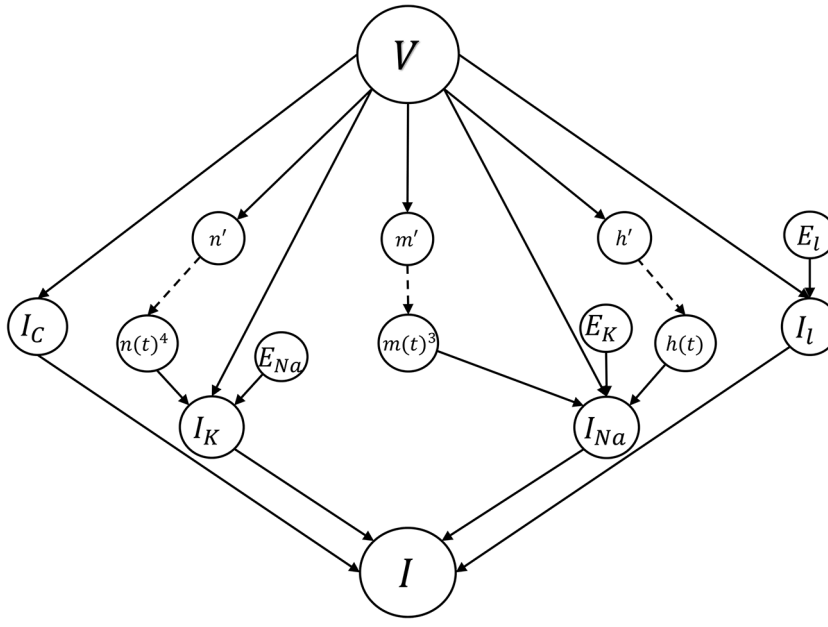

Figure 1. Functional relationships in the HH equations. Arrows reflect causal and constitutive relations between variables: V represents voltage; I's represent the total, capacitive, and ionic currents; and E's represent equilibrium voltages. Primed variables reflect the rate of change of the conductance terms m, n, and h. Terms not shown, such as the αs and βs for sodium and potassium, are treated as parameters. Following Iwasaki and Simon (1994) and Voortman, Dash, and Druzdzel (2012), integration over time is represented with dashed lines. Consistent with their experimental practice, voltage is treated as an exogenous, experimenter-controlled variable. In simulating the action potential and related phenomena, however, V is no longer regarded as exogenous and is instead determined by integrating ionic currents (Hodgkin and Huxley's [1952c] discussion of simulation procedures covers pp. 522–40).

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Are the mathematical dependencies in the system something Hodgkin and Huxley could have given sufficient interpretation? I claim that they are. There is obviously quite a lot here, and there is neither space nor reason to discuss every dependency. We can, however, cover some of the more salient features. Each of the following statements relates to some experiment, physical basis, or otherwise cause- or intervention-implying language (parentheses contain Hodgkin and Huxley [1952c] page numbers unless otherwise stated):

a) Independence of potassium, sodium, and leak equilibrium potentials (the "Es") (505)
b) Independence of potassium, leak, and sodium permeability, contingent on voltage (V) (503)
c) Dependence of both sodium and potassium channel conductance on the "effect of the electric field on the distribution or orientation of molecules" that allow/prevent ionic passage (501, 507, 512)
d) A distinct inactivating agent for the sodium (h) but not potassium channels (503, 512)
e) Myriad facts about how modulating temperature and ionic concentrations will affect neurons (525–26; Huxley 1972, 64–67).

Many of these had been tested by Hodgkin and Huxley themselves. Point *a*, for example, implies that one may change the various ions' equilibrium potentials individually, selectively altering the ionic currents associated with each (Hodgkin and Huxley 1952b), while *b* implies the dissociability of the channels (suggested in Hodgkin and Huxley [1952a] and shown by later blockage experiments). Not every part had a prior experiment, of course. This is certainly true of the much maligned conductance terms. Yet it is worth noting that even in this uncertain element of the model we find discussions in concrete terms. Potential interventions are obvious. The presence of an inactivating agent for sodium channels implies the dissociability of sodium inactivation from sodium conductance, for example. This ideal intervention became a real one when Armstrong, Bezanilla, and Rojas (1973) (who explicitly discuss the HH model) found they could selectively eliminate sodium inactivation using intercellular enzymes. Finally, although *a*–*e* are all dependencies that panned out, there is one important instance when the model got it wrong. Sodium is inactivated by a distinct "particle," but it is not voltage dependent as implied. This might seem detrimental to my case, but the fact is that this was/is regarded as a shortcoming in the model (Aldrich 2001). Thus, on this issue, Armstrong et al. indicate that their results implied an inactivation mechanism "not entirely consistent with the Hodgkin and Huxley equations" (1973, 388). If the equations can get interventions wrong, however, it clearly cannot be the case that they make no causal commitments (Craver 2008, 1026) or are "neither true nor false" (Bogen 2008, 1034).

3. What about Curve Fitting? Despite the arguments listed above, there's likely some residual uneasiness about the methods used to determine the conductance terms. The precise form each took and the values of the α and β functions associated with them were determined largely as a matter of convenience and agreement with experimentally derived curves. Bogen, for instance, labels the n, m, and h terms "uninterpreted weighting constants" (2008, 1042). Even Weber (2008), who I have otherwise found much reason to agree with, grants that "the conductance model was purely a result of curve fitting to which Hodgkin and Huxley tried to give a physical rationale later" (1001), arguing that the explanatory work is done by the rest of the model.

Such negative assessments are unwarranted, I argue, not only because Hodgkin and Huxley thought of the conductances in causal terms (see above) but because their methods have been unfairly criticized. In particular, previous commenters have not distinguished between two relevantly different modeling practices. The first, which I simply call curve fitting, involves fitting a stock function to some data set. The prototypical case is something like linear regression, where the parameters have no theoretical basis and involve no causal commitments. A relevantly different process, sometimes called model fitting, is carried out to estimate the value of parameters in an antecedently hypothesized system.[2] The fundamental causal model (what connects to what) stays the same; one simply pins down the precise amounts, rates, and so on, involved. Hodgkin and Huxley's practice is better seen as the latter.

The path Hodgkin and Huxley took ran roughly as follows. First, each conductance term was taken, for theoretical reasons, to be a dimensionless variable sensitive to voltage and time (rather than, say, current; Hodgkin and Huxley 1952c, 501, 507). From here, they had to choose whether the variables would obey higher-order differential equations or first-order equations. The evidence did not favor either, but first-order kinetics were simpler. Each conductance term was modeled in terms of shifting "particles" obeying the equation:

$$\frac{dx}{dt} = \alpha_x(1 - x) - \beta_x x, \tag{2}$$

where x stands for n, m, or h depending on the context and α and β stand for the rates (i.e., frequencies) at which particles transition between allowing and preventing ions to pass through the membrane. The rates at which these particles transitioned were taken to be voltage dependent, and functions mapping voltage to each were selected on the basis of fit.

Despite earlier (Weber 2008) claims that Hodgkin and Huxley developed their physical model of the channel as an afterthought, there is evidence to sug-

2. See also Pearl (2000, 38–39) on the distinction between "causal" and "statistical" parameters and assumptions.

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gest that the decision to model the system as they did was theoretically motivated. Circumstantially, it is a bit easier to see a preexisting "gating" picture leading to equation (2) than it is to see (2) emerging first and leading to the theory later on. Moreover, if Weber is correct in thinking that Hodgkin and Huxley's comment that "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*" (541, italics mine) refers to the conductance terms, then it would imply that the interpretation came first. Finally, we have Huxley's (2002) retrospective assertion that their final voltage-clamp results were interpreted "on the assumption that the ions crossed through channels that were opened or closed by alterations in the membrane potential" (557). This strongly suggests that the channel idea occurred to them on the heels of the experiments and was developed simultaneously with or before the formal 1952 model.

If we grant this theoretical background, though, it is hard to see the process as particularly suspect. The causal picture is in place. The only thing left over are a few parameters, each playing a clear role in the system. The power to which the terms are raised, for instance, is taken by Hodgkin and Huxley to reflect the number of "particles." Values were estimated and, while not perfect, were not bad (sodium channels, m, have four rather than three subunits). One could double down on this shortcoming, but it would be splitting hairs, especially given that the estimates were as close as they were. If I claim that an object thrown at x miles per hour broke a window, my account is not devastated if it happens that the object was actually going $y > x$ miles per hour (note Hodgkin and Huxley's [1952c] discussion on p. 509). The α and β terms seem more complex on the surface, but the same basic point holds. They are rate constants given theoretically motivated dimensions and functional roles by Hodgkin and Huxley. At base, they amount to a claim about the probability that (or "frequency" with which) a "particle" switches between states. One might claim that estimating the probabilities is not enough, that the reason why the probabilities take their values must be given, but this would clearly demand too much. It would amount to disputing probabilistic causality, as the rate constants simply represent the claim that modulating voltage will increase or decrease the frequency of a given kind of particle state transition. What is more, we still do not build these terms "from the bottom up," as the objection would demand; rather, there is a mix of macroscopic modeling techniques, with Hodgkin and Huxley's remaining popular (Carbonell-Pascual et al. 2016). If the inability to unpack these fundamental probabilities undermines Hodgkin and Huxley, it undermines us too.

4. Concluding Remarks on Explanation. The previous two sections argue that a causal reading of the HH model, conductance terms included, is most consistent with its authors' scientific practice and published statements. This still leaves open the issue of explanation, though. It may be argued that,

while causal, the model is still only a mechanism sketch, an explanation that leaves critical features unexplored (Craver 2008, 1027). In response to this, I may point to the interventions enumerated above or to still others left unmentioned. I could cite earlier authors who have argued forcefully that the features left out of the model do not matter for the relevant explanatory purposes (Weber 2008; Levy 2014). Ultimately, though, there is a sense in which the sketch claim is correct. In his Nobel speech, Huxley plainly states that he and Hodgkin took the model as "a first approximation . . . for the actual mechanism of the permeability changes on the molecular scale" (1972, 69). This is not something that I think is sufficiently captured in either Weber's or Levy's discussions. Weber pins all nonexplanatory talk on the conductance terms, but the quote above is directed at "these equations" generally, rather than the conductance terms specifically. Levy grants that the model is not a sufficient molecular-level explanation but contends that it is "implausible" to regard the HH model as aiming toward such explanatory goals (2014, 482) and that, even if Hodgkin and Huxley started with this aim, their interests had shifted by the writing of the quantitative paper (487 n. 9). Here again, though, Huxley does seem to think of the model as addressing, in a tentative way, some molecular concerns.

I take it, then, that we ought not to deny that the authors sought a molecular explanation and successfully produced a "sketch" of one. Nevertheless, it cannot fairly be claimed that "if Hodgkin and Huxley are right, one needs to know [complex mechanistic details] to explain the action potential" (Craver 2008, 1025) or that explanatory claims stem from illusions about the state of molecular neuroscience at the time (1030). When Hodgkin and Huxley speak of having a "sufficient explanation" of the relevant phenomena or when contemporaries like Bezanilla claim that the model "goes way beyond explaining" the action potential, we cannot simply sweep it under the rug.

What I would like to suggest in the brief space remaining is that Hodgkin and Huxley did explain the action potential as they understood it (1952c, 500, 541) but not as it might be interpreted by all parties involved. In other words, we are dealing with different explananda. The action potential could be understood in a "thin" way that refers only to the voltage spike familiar to physiologists going back to the nineteenth century. So understood, the action potential would be tied to a specific set of results, including things like anode breaks, voltage "overshoot," and refractory periods (to list the phenomena cited by Hodgkin and Huxley 1952c; Huxley 1972, 2002). The action potential of an author like Craver (2008), by contrast, may be better described as a complex thing-in-the-world (cf. Craver 2014)—the kind of object molecular processes could be said to "make up" (1025). It involves a "thick" or open-ended notion more akin to Huxley's "actual mechanism . . . on the molecular scale" (1972, 69). One is an object of classical electrophysiology, the other of biochemistry.

In wondering whether Hodgkin and Huxley "explained the action potential," then, one could be asking at least two different questions. If the goal is to account for voltage and current dynamics and to chart how they behave under interventions like the shifting of ionic concentrations or the elimination of specific channels, then the model appears sufficient. A few elements proved inaccurate (e.g., the voltage dependence of sodium inactivation), but the model captures sufficiently many causal relations and experimental phenomena to be called an "explanation," at least as the term is usually understood. However, if the aim is to characterize the biochemical mechanisms at play—to know about the structure, composition, or operation of ion channels (cf. Bogen 2008, 1043)—then Hodgkin and Huxley's charged "particles" provide only the roughest of approximations. The causal picture from the previous sections may provide leads for investigating these matters, such as the existence of distinct agents of sodium inactivation, but they are highly general. The term "sketch" does not seem inappropriate.

Thus, depending on one's interest, it may still be possible to side with Craver and Bogen in believing that the model does not "explain the action potential." One's reasons for doing so will need to differ from theirs, however. It cannot rightly be claimed that Hodgkin and Huxley make no causal commitments. As we have seen, the model is rich with implications, and many of them were followed up on by Hodgkin, Huxley, and their peers. Nor is it reasonable to criticize the model because of the role "curve fitting" played in its development. Doing so would catch perfectly legitimate causal modeling procedures in the cross fire. Finally, it would not be fair to claim that the popular history of the model is anachronistic or that Hodgkin and Huxley themselves claimed not to have explained the "action potential." This would mean interpreting the term quite differently from the authors or subsequent researchers in the same tradition. Bezanilla, Armstrong, and Hille, who did so much to discover the form and composition of ion channels, are not simply confused about how much Hodgkin and Huxley knew about these mechanisms. In the end, one parts little from the received view. The model provides a causal account of neuronal voltage dynamics and a very limited guide to molecular mechanisms. In other words, Hodgkin and Huxley explained the action potential to the extent that is generally recognized, but no more.

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