Regularities and causality; generalizations and causal explanations

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Abstract

Machamer, Darden, and Craver argue (Mechanism) that causal explanations explain effects by describing the operations of the mechanisms (systems of entities engaging in productive activities) which produce them. One of the aims of this paper is to take advantage of neglected resources of Mechanism to rethink the traditional idea (Regularism) that actual or counterfactual natural regularities are essential to the distinction between causal and non-causal co-occurrences, and that generalizations describing natural regularities are essential components of causal explanations. I think that causal productivity and regularity are by no means the same thing, and that the Regularists are mistaken about the roles generalizations play in causal explanation.

Humean, logical empiricist, and other Regularist accounts of causal explanation have had the unfortunate effect of distracting philosophers from important non-explanatory scientific uses of laws and lesser generalizations which purport to describe natural regularities. My second aim is to characterize some of these uses, illustrating them with examples from neuroscientific research.

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Wheel, kinetic flow, 
rising and falling water, 
ingots, levers, keys, 
I believe in you, cylinder lock, pulley, lifting tackle and 
Crane . . .
The way things work 
is that eventually 
something catches. (Jorie Graham, 1995, p.3)

1. Introduction

Why do general claims that appear to describe regularities in nature abound in scientific textbook and research report accounts of how effects of interest are produced—even in biology, which many writers have said is not governed by genuine laws as these are traditionally conceived? According to Hume’s and other Regularity accounts of causality, the answer would be that the crucial difference between causal and non-causal sequences of events is that only the former are instances of natural regularities. Some present day Regularists believe causality depends on counterfactual rather than actual regularities (Woodward, 2002; Glennan, 2002). Some settle for local, rather than completely widespread, exceptionless regularities (Mitchell, 2003, pp. 115–160; Schaffner, 1993, pp. 64–168). But all Regularists believe that one thing is not a cause of another unless they instance some sort of regularity. If so, causal explanations would have to include or imply generalizations describing natural regularities.

Machamer, Darden, and Craver (MDC) (2000) claim that effects are produced by mechanisms whose operations consist of ordered sequences of activities engaged in by their parts and that causal explanations answer specific questions about parts of the mechanism that produced the effect of interest, the activities through which they contributed to its production, and environmental factors which influenced the process. MDC’s general description of the way mechanisms operate is congenial

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1 Hume and many later Regularists believed causal explanations can be reduced without residue to non-causal claims about regularities. By contrast Woodward believes causal notions such as intervention and result are indispensable to the explication of causal claims. He and Glennan are Regularists because they include counterfactual descriptions of regularities involving interventions and their results among the truth conditions of causal claims. Woodward emphasized (in correspondence) that he is mainly concerned with epistemic rather than ontological questions about causality. But his view commits him to a strong ontological thesis. If the truth of a causal claim depends upon the obtaining of counterfactual regularities, there is no causality without counterfactual regularity.

2 Complete enumerations of a mechanism’s components, their activities, and the exogenous factors that influence their operation are never required. Which questions a causal explanation must answer, and in how much and what kind of detail varies from context to context with people’s interests and background knowledge, cultural factors, and social settings. By contrast, what parts belong to a mechanism, what they do, how they do it, and how their activities contribute to the production of an effect are matters of fact that neither depend upon nor vary with the contextual factors which determine what should be included in an explanation.
to Regularist accounts of causality. They include regularity of operation in their definition of a mechanism. They say:

Mechanisms are regular in that they work always or for the most part in the same way under the same conditions. (MDC, 2000, p. 3)

Stuart Glennan’s claim that the operations by which mechanisms produce effects ‘can be characterized by invariant, change-relating generalizations’ (Glennan, 2002, p. S344) is congenial to the notion that causal explanations should include general descriptions of natural regularities.

But it isn’t obvious that Mechanists need to be Regularists. MDC can agree with Elizabeth Anscombe that:

the core, the common feature, of causality in all its different kinds . . . is that [e]ffects derive from, arise out of, come out, of their causes. (Anscombe, 1981, p. 136)

Since the idea of one thing producing or bringing about another does not include any ideas about natural regularities or generalizations which describe them, why shouldn’t a Mechanist join Miss Anscombe in denying that when A produces B this implies

that every A-like thing comes from some B-like thing or set-up or that every B-like thing or set-up has an A-like thing coming from it, or that given B, A had to come from it, or that given A, there had to be B for it to come from. Any of these may be true, but if any is, that will be an additional fact, not comprised in A ’s coming from B. (Ibid.)

It’s not that causes and their effects never instance natural regularities. It’s just that causality is one thing, and regularity, another.

Many mechanisms operate with impressive reliability, producing the same effects in the same ways frequently and at regular intervals. Although that makes it easier for scientists to study them and apply what they learn to practical tasks, it doesn’t follow that regularity is essential to causality.3 Mechanists can treat such things as pushing, pulling, opening, closing, heating, cooling, attracting, repelling, binding, releasing as causally productive activities, without supposing that their efficacy reduces to actual or counterfactual regularities or thinking our notions of causally productive activities can be analyzed or explicated by appeal to regularities or other non-causal notions (Machamer, forthcoming). If the production of an effect by activities which constitute the operation of a mechanism is what makes the difference between a causal and a non-causal sequence of events, Mechanists need not include regularities and invariant generalizations in their account.

Some causal mechanisms are too unreliable for it to be plausible that their causal efficacy depends on their ‘work[ing] always or for the most part in the same way

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3 Nancy Cartwright (1983), pp. 55 ff., offers a rationale for this which this paper is happy to endorse.
under the same conditions' (MDC, 2000, p. 3) or how well their operations accord with ‘invariant, change-relating generalizations’ (Glennan, 2002, p. S344). The mechanisms which initiate electrical activity in post-synaptic neurons by releasing neurotransmitters are a case in point. They are numerous enough, and each of them has enough chances to release neurotransmitters to support the functions of the nervous system. But each one fails more often than it succeeds, and so far, no one has found differences among background conditions which account for this (Kandel, Schwartz, & Jessel, 2000, p. 261). No one takes the irregularity of their operation as a reason to deny that on the relatively rare occasions when they do operate successfully these mechanisms release neurotransmitters and exert a causal influence on post synaptic neuronal activity.

Regularists may insist that no matter how unreliable a mechanism seems to be it can’t produce effects unless its operation instances natural regularities. Maybe we don’t know how to describe them to a satisfactory approximation. Maybe we don’t even know what they are. But all the same, there must be regularities in there somewhere, and the mechanism must operate in accordance with them. That’s an article of faith. It doesn’t have enough empirical support to rule out the possibility that some causes operate indeterministically and irregularly. As long as there is a non-negligible chance that some causes operate irregularly, philosophical accounts of causality should leave room for them.

If Mechanists don’t have to be Regularists, what contributions should they say generalizations—which seem to describe natural regularities—make to causal explanations? And what should they say about what actual or counterfactual regularities have to do with causality? I will suggest answers to those questions for the case of explanations of the propagation and damping of action potentials. Consisting as they do of descriptions of the parts and activities of causally productive systems, these explanations are unabashedly mechanistic. In this respect they are typical of causal explanations in biology. Here is what I think about them.

4 An anonymous referee pointed out that this is a good thing. Some neurons receive inputs from so many different cells that functionally integrated neuronal activity would be impossible if neurotransmitters were released by every action potential.

5 In most kinds of neurons neurotransmitter release failures are so common that it was news when investigators recently found evidence that rat barrel cortex cells release them to a high degree of probability (Silver et al., 2003).

6 It is a piece of epistemic good fortune that they operate successfully enough overall, and their molecular components occur widely enough in other settings for neuroscientists to learn how these mechanisms work.

7 For an unintentional parody of this view see Davidson (1980).

8 Most people acknowledge indeterminism for quantum mechanical phenomena. Neuronal activity and evolution feature processes that appear to be indeterministic independently of their quantum mechanical underpinnings. For more examples see Suppes’s heroic (1984). Even though some indeterministic causes produce their effects with unvarying probabilities, that does not mean they produce them always, or that they produce them at regular intervals.
a. Generalizations purporting to describe natural regularities are often used in investigations aimed at discovering causes, and developing, evaluating, modifying, and applying causal explanations. So employed, the work the generalizations do is epistemic rather than explanatory. Instead of explaining how effects are caused, they are used to:

- describe facts to be explained,
- suggest and sharpen questions about causal mechanisms,
- suggest constraints on acceptable explanations,
- measure or calculate crucial quantities, and
- support inductive inferences without which mechanisms could not be successfully studied, and the results of their study could not be applied to new instances of causal productivity.

To do these epistemic jobs satisfactorily generalizations must (as Sandra D. Mitchell puts it) provide ‘expectations of the occurrence of events and patterns of properties’ which are reliable enough to further the scientist’s predictive, explanatory, and practical endeavors (Mitchell, 2003, p. 124). Typically this does not require them to be necessary or exceptionless, or to meet other normative standards traditionally invoked to distinguish laws from lesser generalizations (ibid). In many cases they are not even approximately true.

b. General claims which I’ll call ‘generalities’ are often used to indicate how one or more instances of an effect were actually produced. If the explanation is satisfactory, the effect must have been produced pretty much as the generalizations say, but only for the case or cases they are used to explain. Contrary to the Regularists, the goodness of the explanation of one or more instances does not depend on whether the generalizations are true (even approximately) of further instances. In some cases they hold for further interests, but it is not by virtue of this that any of the happenings they describe are instances of causal productivity.

c. An explanation of one or more items of kind E may say explicitly that instances of E are caused by items of kind C. It is trivial that the explanation is acceptable only if the generalization is true; if the generalization were false, C items would not be causes of E items. That doesn’t tell us anything interesting about what distinguishes causal from non-causal sequences of events.

d. There are only two ways in which regularities are necessary for the causal productivity of the mechanisms I’ll consider. One of the them is trivial. The other is substantive, but of no particular philosophical interest (see Section 5 below). Neither supports the idea that regularity is what makes causal processes different from non-causal sequences of events.

e. Although investigators may appeal to counterfactual generalizations for epistemic purposes, causality is not grounded in counterfactual regularities as Woodward, Glennan, and other Counterfactual Regularists suppose.
2. Action potentials and the Hodgkin–Huxley equations

An action potential is a brief pulse of electricity which travels rapidly down the axon toward the synapse at constant velocity and amplitude. At the synapse it can initiate a process that influences the probability of a functionally significant change in the post-synaptic cell’s electrochemical activity. Ordered sequences of action potentials are essential to neuronal signaling.

Axons are hollow tubes filled with, and bathed in, aqueous solutions containing charged ions. An axon is at rest when the electrical activity inside the tube is too weak or disorganized to produce an action potential. The membrane of a resting neuron is polarized: charged ions are distributed in such a way that the charge on its inner surface is negative relative to the charge on its outer surface. The membrane potential \( E_m \) is the difference between the charges (Hille, 2001, p. 27). Under certain conditions one or more segments of the membrane depolarize: the charge on the inner surface becomes more positive relative to the charge on the outer surface. Under other conditions, the membrane repolarizes: its potential moves back toward its negative resting value.

Since the 1940s it has been generally agreed that action potentials are propagated down the axon by a mechanism that allows positive ions (mainly \( Na^+ \)) from the fluid outside the membrane to flow inward (ibid., p. 26). Their propagation is stopped by another mechanism, which allows positive ions (mainly \( K^+ \)) to flow outwards to initiate repolarization. Positive ions flowing inward through one bit of membrane set up a local current which moves downstream to depolarize the next bit of axon membrane. There, additional positive ions cross the membrane to set up another local current. And so on. An action potential is a wave of electrical activity generated by local ionic currents as one bit of membrane after another depolarizes to admit positive ions further and further down the axon (Fig. 1).

In 1952 Hodgkin and Huxley (HH) published what became the most frequently mentioned elaboration of this idea. They maintain that in the squid giant axon the magnitude of the potassium current, \( I_K \), which flows outward to help repolarize the membrane and damp the action potential varies with \( \frac{1}{g_K} \), the membrane’s

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9 I’m ignoring action potentials in muscles.

maximum potassium current conductance, a weighting factor \( n^4 \), \(^{11}\) and a driving electrical force equal to the difference between \( E_m \), the membrane potential, and the resting potential for potassium \( (E_K) \). \( E_K \) is the membrane potential at which there is no net cross-membrane potassium current in either direction over any significant amount of time even though some potassium ions flow in and out of the membrane.

The HH equation for the potassium current is:

\[
1a. \quad I_K = n^4 g_K (E_m - E_K)
\]

Although his equation was derived carefully enough from empirical data to incorporate the qualitatively correct idea that \( I_K \) varies with \( (E_M - E_K) \), it is quantitatively inaccurate to a significant degree. Despite its inaccuracy, it has been indispensable to the study of the action potential. HH wrote equally useful equations of the same kind for \( Na^+ \) and other cross-membrane currents, and a more elaborate equation which describes the total cross-membrane current involved in action potential propagation and damping as the sum of the potassium current, a sodium current (described after the manner 1a), a leakage current due to the flow of other ions, and a capacitance current:

\[
1b. \quad I = C \frac{dE_M}{dt} + \frac{g}{k} (E_M - E_k) + g_n a^{m} h (E_M - E_{na}) + \frac{g}{l} (E_M - E_l)
\]

I is the total current, and \( CdE_M/dt \), the capacitance current; \( \frac{g}{k} (E_M - E_k) \) is the potassium current; \( g_n a^{m} h (E_M - E_{na}) + \frac{g}{l} (E_M - E_l) \) is the sum of the sodium and leakage currents respectively; \( m, n, \) and \( h \) are empirically estimated weighting constants (Hodgkin & Huxley, 1952, p. 518). The HH equations illustrate a crucial role for laws and lesser generalizations:

- indicating features of the phenomena of interest which mechanist explanations should account for.

1b does not explain; it describes. HH said they could not explain ion fluxes and permeability changes until more was known about the molecular biology of ion channels. They advertised their equations as empirically based kinetic descriptions intended to be simple enough\(^ {12}\) to make practical calculations of electrical results, yet sufficiently good to predict correctly the major features of excitability such as the action potential shape and conduction velocity. (Hille, 2001, p. 45)

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\(^{11}\) To see what the physical significance of the equation might be, HH say you might think of \( n \) as the proportion of hypothetical particles that occupy a position which facilitates ion flow (Hodgkin & Huxley, 1952, p. 507). Hille suggests interpreting it as the probability that the hypothetical particles are in such a position (Hille, 2001, p. 47).

\(^{12}\) To account for the changes in sodium conductance their data suggested, they found that they could employ a single variable which obeys a second order differential equation . . . [or] suppose it is determined by two variables \([m \text{ and } h]\), each of which obeys a first order equation’. They chose the latter because it gave them an equation which was computationally easier to compare with experimental results (Hodgkin & Huxley, 1952, p. 512). The changes in potassium conductance were also such that they could be described without second order differentiation by an equation which used only a single variable \((n)\). This illustrates the kind of simplicity HH had in mind.
They intended the total current equation to do no more than to put the results of their experiments on the giant squid axon into mathematical form . . . and to show that they [the potassium and other partial current equations derived from the experimental results] will account for conduction and excitation in quantitative terms. (Hodgkin & Huxley, 1952, p. 501)

In this passage ‘account for conduction and excitation’ does not mean explain conduction and excitation. Having claimed their equations could be used to predict with fair accuracy many of the electrical properties of the squid giant axon . . . (Ibid., pp. 540–541)

HH hastened to emphasize that agreement between predictions derived from their equations, and experimentally established values of the relevant electrical quantities 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 . . . (Ibid., p. 541)

To sharpen our intuitions HH said we could imagine physical factors which might correspond to some of the crotchets in their equations as they themselves had done to help guide their work. If there were particles whose positions within the membrane controlled the cross-membrane flows of specific kinds of ions, n^4, m^3, and h might correspond to proportions of flow permitting and flow inhibiting particles occupying the relevant positions (ibid., p. 512). But HH take pains to distance themselves from this physical interpretation.

[T]he success of the equations is no evidence in favor of the mechanism of permeability change that we tentatively had in mind when formulating them. (Ibid.)

The relations among electrical quantities they describe are characteristic of effects produced by an unknown neuronal mechanism. HH do not claim to know what it is or how it operates.

HH’s equations are quantitatively inaccurate as well as non-explanatory. HH constructed them from current, voltage, and conductance values which they calculated from experimental data and plotted against one another. The equations describe the smoothest curves they could fit to the data. As usually happens with curve fitting, many values fell outside the curves. Furthermore, the data came from experimental preparations, rather than axons responding to natural stimuli in natural environments. Furthermore, HH experimented on squid giant axons which do not function like axons of other species even in natural settings under normal conditions. Finally, contrary to the equations, although the quantities they mention do co-vary, they do not co-vary uniformly. For all these reasons, the equations approximate poorly enough to the co-variations they describe for Hille to say that their ‘kinetic details cannot be taken literally’ (Hille, 2001, p. 55). Even so, he continues,
the HH model has important general properties with mechanistic implications that must be included in future models. (Ibid.)

Some examples:

- The HH equations led investigators to expect (correctly) that sodium and potassium currents reverse directions as cross-membrane voltages approach the values Nernst calculated would be just sufficient to prevent them from flowing across the membrane along their concentration gradients. Because Nernst calculated these voltages exclusively from thermal and electrical quantities, the HH equations suggest that

  the ions are moving passively with thermal and electrical forces . . . rather than being driven by metabolic energy or being coupled stoichiometrically to other fluxes. (Ibid., pp. 55–56)\textsuperscript{13}

- Despite their quantitative inaccuracies, the equations are right to say that sodium and potassium currents reverse at different membrane potentials. This suggests that separate mechanisms (different ion channels, as it turned out) are responsible for these currents (ibid.).

To repeat, the HH equations do not purport to explain anything. They are important because investigators can rely on them to suggest facts to be explained and tactics for explaining them. HH concluded that:

  fairly simple permeability changes [for sodium, potassium, and leakage ions] in response to alterations in membrane potential . . . are a sufficient explanation of the wide range of phenomena that have been fitted by solutions of the equations. (Ibid., p. 541)

To explain the crucial permeability changes investigators were to look for mechanisms that operate to change them in response to changes in membrane potential as required to account for the facts to which the HH equations are qualitatively faithful.

3. More epistemic uses for laws and lesser generalizations

A cardinal difficulty in understanding how an ion current varies with its driving force arises from the fact that the axon is sheathed in a hydrophobic bilipid membrane.

Charged molecules cross lipid membranes about as easily as people sprint up Mt. Everest: The amount of energy required makes it virtually impossible. (Miller, 2003, p. 2020)

\textsuperscript{13} Hille (2001), pp. 55–56. On the basis of measurements of ion currents through an artificial, non-organic membrane, David Goldman argued for this conclusion on similar grounds in Goldman (1943), p. 38.
The universally accepted solution to this is that

[t]iny ion channels . . . do the work of a thousand sherpas, allowing ions to skip through the membrane with ease. (Ibid.)

It is generally agreed that the channels which do this work are cylindrical cores embedded in the hydrophobic bilipid lining. One end of the core is exposed to the aqueous solution outside the axon, and the other, to the aqueous solution inside. The size of the core’s inner lining and the distribution of charges on its walls are among the factors that determine which kinds of ions can move through the channel when it is open. It is generally agreed that the changes in ion permeability which HH said were responsible for crucial features of the action potential are caused by the mechanisms which open and close these channels. The channels are voltage gated: they open and close in response to changes in membrane potential.

What has been the standard account (call it SA) of voltage gated potassium channels holds that once the membrane has depolarized enough to propagate an action potential, piston-like voltage sensors inside channel cores respond to the continuing depolarization by moving outwards. This unblocks the channel, allowing $K^+$ ions to flow out of the axon to help repolarize the membrane and damp the action potential. In response to repolarization, the sensors move back into their original core blocking position.\footnote{Kandel, Schwartz, & Jessel (2000), p. 167 illustrates the standard account for the case of a voltage gated sodium channel.} MacKinnon, Jiang, and their associates rejected SA when their crystallographic analysis of the structure of the KvAP potassium channel indicated that the voltage sensor was located outside rather than inside the channel core. Even though the KvAP channel belongs to organisms—\textit{Aeropyrum pernix} bacteria—that lack nervous systems and flourish in 95°C thermal vents which are unsuitable for mammalian life styles, most investigators agree that KvAP is voltage gated in the same way as its counterparts in mammalian neuronal membranes. Crystallographic and physiological evidence led Mackinnon, Jiang et al. to propose (MJ) that segments at the ends of the voltage sensors respond to depolarization by rotating upward through the lipid bilayer of the membrane. In so doing they pull open the inner lips of the core to admit $K^+$ ions and allow them to flow outwards. When the membrane has repolarized sufficiently to damp the action potential, they slide back down the outside of the core allowing it to close (Jiang et al., 2003a,b). MJ is controversial in a way that illustrates a second role for laws and lesser generalizations:

\begin{itemize}
  \item \textbf{Constraining mechanistic explanations.} Instead of moving short distances back and forth inside the aqueous channel core as SA supposes, MJ requires its outermost voltage sensor segments move a considerable distance through the lipid membrane outside the core even though they are decorated with arginine residues whose hydrophilic, positively charged components face into the lipid membrane lining and away from the aqueous fluid it contains (Miller, 2003, p. 2021). MJ’s critics object that this is energetically unrealistic. Lipid membranes are a ‘forbidden zone’ for charged molecules (ibid.; cp. Jiang et al., 2003a, p. 34, and Fig. 3 b,c, p. 35). It would take far less
energy for the arginines to move inside the core as SA says they do. Critics also object that it would take ‘an unrealistic amount of energy’ to move the sensors far enough through the lipid layer to open the channel (Miller, 2003, p. 2021). To respond to such objections, MJ’s friends must try to show that it is compatible with the constraints the electrostatic principles its opponents argue from place on accounts of voltage gating (Fig. 2).15

Coulomb’s law fits traditional characterizations of a fundamental law of nature so well that Regularists should expect it to figure in explanations of the action potential. But the only explicitly described application of Coulomb’s law I’ve found is its role in constraining estimates of the diameter of the narrowest part of an ion channel whose inner surface is decorated with charged residues.16 Coulomb’s law says the attractive or repulsive force one charge exerts on another in an electric field varies directly with their magnitudes and inversely with the square of the distance between them according to a permittivity factor which varies from medium to medium. In a simpler world investigators could use this law to estimate the distances between charges on the walls of a channel segment from measurements of the rate at which ions move through it under the influence of the forces the ions exert. Unfortunately, because ions in the channel form a counterion atmosphere which screens off the charges on the channel walls, the magnitude of the force they exert falls off too sharply with distance to calculate accurately from Coulomb’s law (Hille, 2001, pp. 545–546).

15 Opponents of MJ have been looking for alternatives to SA which don’t face these electrostatic difficulties (Blaustein & Miller, 2004).

16 I found no explicit applications of Coulomb’s law at all in Levitan & Kaczmarek (1977), Nicholls, Martin, & Wallace (1992), or any of the other textbooks I consulted except for Hille’s.
To correct for screening, investigators used a modified version of Coulomb’s law (the Debye–Hückel equation) which describes the potential at any given distance from a central ion as depending on the concentration and valences of the other ions in the medium as well as the distance from the central ion, its charge, and the medium’s permittivity (ibid., pp. 342, 546). Solving the Debye–Hückel equation for a highly unrealistic imaginary channel lined with three similarly charged ions, investigators calculated that if the radius of the narrowest part of the core exceeded 8Å, oppositely charged ions would not move through it at an empirically acceptable rate. This result enabled investigators to make crude but useful estimates of permissible diameters for real channel cores (ibid., p. 548). Coulomb’s law and the Debye–Hückel equation do not explain ion flow or its regulation. Instead, they help constrain the description of one part of the causal mechanism whose operation accounts for ion flow.

**Measurement.** John Roberts proposes that a distinctive function of the laws of a fundamental physical theory is the part they play in securing that crucial quantities can be measured, and determining how things must be if measuring procedures are to be reliable (Roberts, forthcoming). Although it fails even under ideal conditions for too many different conductors to qualify as a law in more than name, this is what Ohm’s law does for theories of neuronal signaling. In conductors which obey Ohm’s law the difference in potential between the ends of a conductor varies uniformly with the current running through the conductor and its resistance or conductance (the reciprocal of resistance). Investigators treat ion channels and other neuronal structures as if they were Ohmic conductors in order to measure their potentials, currents, resistance, and conductance. Voltmeters and other equipment used to measure electrical quantities are designed so that inputs into them produce readings in accordance to Ohm’s law. Their reliability depends upon how well they embody the law and how closely the electrical behavior of the conductor accords to it (Bureau of Naval Personnel, 1970, pp. 116 ff., 257 ff.). Although neuronal membranes and fluids are not perfect Ohmic conductors their electrical behavior does not deviate far enough from Ohm’s law to defeat the purposes for which they are measured (Hille, 2001, p. 426).

The Goldman, Hodgkin, and Katz (GHK) voltage and current equations are interestingly different examples of how measurements can depend upon generalizations. The **GHK voltage equation:**

\[
E_{\text{rev}} = \frac{RT}{F} \ln \left( \frac{P_K[K]_O + P_{Na}[Na]_O + P_{Cl}[Cl]_O}{P_K[K]_I + P_{Na}[Na]_I + P_{Cl}[Cl]_I} \right)
\]

is used to measure a quantity GHK called ‘relative permeability’. \(E_{\text{rev}}\), the reversal potential, is the cross membrane voltage difference at which the current constituted by potassium, sodium, and chlorine ion flows across the membrane reverse direction during depolarization or repolarization. \([K]_O\), \([Na]_O\) and \([Cl]_O\) are the concentrations

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17 Ohm’s law, \(V = IR\), says that voltage varies with current and resistance.
of potassium, sodium, and chlorine ions outside the membrane. \([K]_i, [Na]_i,\) and \([Cl]_i\) are their concentrations inside the membrane. Ignoring subtleties, 2a says that \(E_{rev}\) depends on the ratios of these ion concentrations, three additional quantities, \(P_K, P_{Na},\) and \(P_{Cl},\) which GHK called ‘absolute permeabilities’ for \(K^+, Na^+,\) and \(Cl^-\) (Hille, 2001, p. 448).\(^{18}\) Algebraically rearranged, the voltage equation can be used to calculate relative permeabilities such as the ratio of \(P_K\) to \(P_{Na},\) or \(P_{Cl},\) to \(P_{K},\) and so on, from empirically determined values of \(E_{rev}\) and cross-membrane ion concentration ratios.

For ions of any species, the **GHK current equation**:

\[
2b. \quad I_S = P_S Z_S^2 \frac{E_M F^2}{RT} \frac{[S]_i - [S]_o \exp(-zSFE_M/RT)}{1 - \exp(-zSFE_M/RT)}
\]

can be used to calculate \(P_S\) the absolute permeability for \(S\) ions from membrane potential \((E_M), Z_S,\) the valence of \(S\) ions, and empirically determined values \((I_S),\) the cross membrane \(S\) current.

As said, relative permeabilities calculated from 2a were supposed to be identical to the ratios of absolute permeabilities calculated from 2b. GHK believed that an ion species’ absolute permeability corresponded to the membrane’s conductance for ions of that species, and that relative permeabilities corresponded to conductance ratios (ibid., pp. 445–446). But these equations unwittingly conflate two distinct quantities which vary independently of one another. One of them is mobility, the rate at which ions can move through a medium once they have entered it. The other is selectivity, the rate at which the medium admits them (ibid., pp. 449, 469). Furthermore, GHK used two incorrect assumptions to derive the equations. They assumed (homogeneity) that each ion channel is homogeneous with regard to all of the factors which influence ion flow. And they assumed (independence) that electrostatic and other interactions among ions flowing through a channel do not influence the rate at which they move. Because these assumptions are incorrect it is not surprising that the GHK equations are empirically inadequate (ibid., p. 449). Nevertheless, they ‘are used in most studies of membrane permeabilities to ions’ because measurements of the chimeric quantities (absolute and relative permeability) they describe ‘summarize . . . ion selectivity measurements made on many channels’ in ways which are useful for a number of different research purposes (ibid.). Unlike Ohm’s law which is essential to the measurement of quantities as fundamental to theories of neuronal signaling as mass, force, and velocity are to Newtonian physics, the GHK equations are used to measure quantities that are artificial, non-fundamental, but pragmatically useful. Unlike Ohm’s law, which is useful despite some small inaccuracies, the GHK equations are severely flawed. They play the following non-explanatory role:

- Using incorrect generalizations to articulate and develop mechanistic explanations.

\(^{18}\) In 2a, \(F\) is Faraday’s constant, \(R\) is the gas constant, and \(T,\) the absolute temperature.
While some generalizations are useful because they deliver empirically acceptable quantitative approximations, others are useful because they do not. Ionic currents don’t co-vary with membrane potentials in accordance with the current equation 2b. Worse yet, the voltage and current equations 2a, 2b can conspire to deliver mutually inconsistent permeability calculations. In one experiment the permeability of hydrogen relative to sodium was calculated by applying the voltage equation to data from a membrane bathed in a solution containing sodium ions to which hydrogen was gradually added. The results contradicted absolute permeability values for hydrogen obtained by applying the current equation to data from a membrane bathed in a sodium free solution containing hydrogen ions (Hille, 2001, pp. 476–477). Investigators used these and other GHK equation failures as problems to be solved by finding out more about how ion channels work. Fine-grained descriptions of exceptions to the GHK equations and the conditions under which they occur sharpened the problems and provided hints about how to approach them (ibid., Ch. 15, passim). For example, violations of the independence and homogeneity assumptions provided clues for improving descriptions of ion channels and their operations. Thus Hille says that since 1970, deviations from the GHK equations stimulated the major advances in the study of neuronal ion channels (ibid., p. 449). To summarize: the GHK equations do not explain anything. They were epistemically valuable even though they fall short enough of correctness to allow mutually contradictory calculations of values of the quantities they describe.

- Supporting and evaluating inductive inferences and practical applications of findings to new cases. This is the last of the epistemic uses of laws and lesser generalizations I’ll mention.

To learn about the action potential and the mechanisms responsible for it, investigators must rely on inductively supported generalizations about unobserved cases. It would be impossible to design or intelligently perform an experiment without relying on inductively supported conclusions about the behavior of the equipment, the reagents, and the material to be experimented on. Without inductive generalizations the results of experiments on one or more ion channels would tell us nothing about other ion channels. And so on.

Good and bad inductive arguments are formally indistinguishable. As John Norton argues, their cogency typically depends upon by more or less general matters of fact. Why, as John Stuart Mill wondered, is it reasonable to conclude that pure bismuth melts at 270° from the fact that a few samples melted at that temperature, when it is unreasonable to infer that wax melts at 91° from the fact that a few samples of wax melted at that temperature? The inference to the melting point of unobserved bismuth samples is licensed by factual generalizations which have no counterparts for the case of the wax. Bismuth is an element, and elements have stable melting points. The difference between the two inferences is that no such generalization holds for wax (Norton, 2003, pp. 649–651).

Recall that Mackinnon, Jiang et al. developed MJ from facts they established from a small sample of bacterial KvAP ion channels. Whether there is any good reason to believe what they say about voltage gating in unobserved KvAP channels, let alone mammalian potassium channels, depends on whether there is any good reason
to accept inductive arguments for generalizations of their findings. The required
inferences depend, as Norton would say, upon the truth of factual generalizations
about the ion channel family KvAP belongs to, and similarities among its members. If KvAP and mammalian K⁺ channels did not belong to the same family, or if mem-
bers of that family did not share certain structural and functional features, the infer-
ences would be no better than the inference from the melting points of a few wax
samples to the conclusion that all wax melts at that same temperature.

More generally, the cogency of an inductive inference from facts about a sample
to a conclusion about a population depends on whether the sample is representative
and whether its members were selected in a way that does not introduce bias. As Jim
Woodward points out, there is no way to make sense out of (let alone answer) the
question whether any sample meets these conditions without appeal to generaliza-
tions about the population and the sampling methods (Bogen & Woodward, forth-
coming, pp. 250 ff.).

4. Describing typical features of the operation of a mechanism

The generalizations in all of the forgoing examples do epistemic rather than
explanatory work. But general descriptions of mechanisms, their parts, the things
they do, the conditions under which they operate, and so on are also used to set
out causal explanations. For example, claims such as ‘potassium currents flow out-
ward when voltage gated potassium channels open’ and ‘voltage gated potassium
channels open when the axon membrane is depolarized and close when it repolarizes’
may figure in causal explanations of some of the effects we’ve looked at. General
descriptions of how arginine bearing segments are moved, and how their movements
help open and close voltage gated potassium channels may be invoked to answer
causal questions about how action potentials are damped.

This does not mean that regularity is constitutive of causality. Most if not all such
general descriptions are subject to exceptions at least with regard to their quantita-
tive details. The more reliable the mechanism that produces an effect, the more often
it will satisfy a general description invoked to explain its production. For mecha-
nisms as unreliable as the neurotransmitter releasers I mentioned earlier, exceptions
may be the rule. But no matter how irregularly the relevant mechanism may operate,
in order for a causal explanation to be acceptable, descriptions of its operation must
tell us (at least to a good approximation) what happens when it produces the effects it
explains. They can tell us that regardless of whether the mechanism satisfies them in
any, let alone every other case.

Few of the explanatory generalizations neuroscientists use are equivalent to uni-
versally quantified sentences as required by Hempelian and related logical empiricist
and other Regularist theories of explanation.¹⁹ I will call general descriptions that
figure in acceptable explanations but whose universally quantified counterparts are

¹⁹ The *locus classicus* is Hempel (1965), pp. 245–296. For a historical survey, see Salmon (1989).
false ‘generalities’. Like ‘women bear children’, the frequentative sentence Nancy Cartwright calls a ‘habitual’ (Cartwright, 1989, pp. 199–200), generalities tell us what things of a specified kind do without claiming that they do it always or usually (even under the same background conditions), or that every member of the kind do them even once. For example the generality

3. Electrical activity of a pre-synaptic neuron in one region (the CA3 area) of the hippocampus initiates electrical activity in a post-synaptic neuron in another (the CA1 area) can be used (for in vitro preparations at least) to explain CA1 neuronal activity. 3 is true of the CA1 firings it is used to explain, and of others as well. But generalizations whose truth requires every CA1 neuron in a properly functioning hippocampus to fire under normal circumstances whenever its presynaptic CA3 neurons fire are flatly false (unless one restricts their application to the relatively few occasions on which CA1 neurons actually have fired in response to pre-synaptic action potentials).

Generalities are general in the sense that they are true of more than one case. Some hold for many cases. For some there are principled ways to distinguish cases for which they can be expected to hold from cases for which they cannot. But the goodness of a causal explanation of one or more cases typically does not depend in any interesting way upon how many other cases satisfy the relevant generalities. Even if all the generalities used to explain several cases held for enough additional cases to satisfy a Hume or a Hempel, that would not be what distinguishes the causal sequences of events involved in cases which were explained from non-causal sequences. Generalities about voltage gating must be true (to a satisfactory approximation) of the production of just the channel openings they are used to explain.

The acceptability of MJ’s explanation of one or more channel openings does not derive from their application to any other instances. Perhaps investigators would not have come up with a good explanation for any given case unless the same causes operated in the same ways in enough other cases to provide them with adequate data. Perhaps it would be hard to find a good reason to accept the explanation unless one could rely on inductive inferences from other cases the generality describes correctly. But these are epistemic considerations. The correctness of an explanation does not depend upon what happened in any cases except those the generality is used to explain. The generality of the claim used to explain the effect(s) of interest is

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20 CA3 neurons influence CA1 neurons stochastically. At first, post-synaptic responses are quite infrequent. Their rate may increase with repeated pre-synaptic activity, but the process remains stochastic, and failures are by no means uncommon. (Kandel, Schwartz, & Jessel, 2000, p. 1264). There are true general claims to make about the statistical distributions of CA1 responses to CA3 firings, the probability that a response will occur, and so on. But it is non-statistical generalities such as 3 which are commonly used to set out explanations. As long as one is explaining one or more particular effects (as opposed to the rate at which they occur, or their probability, conditional on the relevant causal influences) there is no need to replace them by (or understand them as elliptical versions of) true statistical or probabilistic generalizations.
important, but not because the truths of general descriptions on natural regularities are constitutive of, or necessary for causality.\textsuperscript{21}

5. How much regularity does it take for a mechanism to produce an effect?

Suppose that during a time, $t$, a gating mechanism whose structure and operation conform to MJ opens a single voltage gated potassium channel just once in response to a change in membrane potential. $t$ will be a very short time; critics as well as friends of MJ agree that it takes only a tiny fraction of a second to open a channel. Ignore for now what happened before $t$ to produce the mechanism and put it in good working order in an environment suitable for its operation during $t$. Once everything is ready to go, the parts of the mechanism must stay connected to one another and retain a number of their features long enough to open the channel. Although parts of the mechanism change with regard to their locations, energy levels, and other features while the mechanism operates, the changes must not exceed certain limits. The arginine bearing voltage sensor segments must respond in an orderly way to the forces that rotate them through the bilipid layer. Whatever factors enabled them to defeat the unfavorable energy distributions MJ’s critics point out must operate with some uniformity. The same holds for causal influences in the immediate and wider environment in which the mechanism operates. For example the mechanism could not operate successfully if the forces exerted by charged particles in the neighborhood varied too greatly from the values Coulomb’s law requires. The mechanism could not do its work unless some regularities obtained to some extent throughout $t$. But $t$ is far too brief a time to accommodate the regularities that Regularists invoke to distinguish causal from non-causal co-occurrences. Since nothing can happen after the channel is open to bring it about that the gating mechanism didn’t open it during $t$, the regularities I’ve mentioned so far needn’t continue to obtain for more than a split second.

Before the ion channel opens, a great many factors must operate regularly enough during the time it takes to produce the gating mechanism, put it in good working order, and render its environment suitable for its operation. The voltage gating mechanism couldn’t open the channel without these regularities any more than Charley Parker could have played ‘Koko’ if the materials his horn was made of hadn’t behaved regularly enough during its manufacture. Any number of things had to behave regularly enough for as long as it took him to learn to play. Although he couldn’t have played if such regularities had not obtained, they are not what

\textsuperscript{21} Although I have no space to discuss it, I think roughly the same thing holds for explanations of general facts. The generalities used to explain, for example, why action potentials typically have such and such wave forms, or why depolarizations or repolarizations typically follow certain time courses, are required to be true (or approximately so) case by case, of typical cases. What makes them useful in explaining the general fact is their applicability to each instance they describe to a satisfactory degree of approximation. Their applicability to any given case does not depend upon their applicability to any of the others of which they are true.
distinguish playing ‘Koko’ from merely blowing into a horn and fingering the keys without causing the relevant sounds. Similarly, the regularities that made it possible for the gating mechanism to open the channel are not what make activities of its parts causes rather than non-causal accompaniments to the channel opening.

The only other way I know of in which regularity is required for causality is trivial. Since tokens of C are causes of tokens of E in all and only the cases in which the former make a causal contribution to the production of the latter, a regular connection of some sort must extend over all the cases in which Cs cause Es. You can’t learn much about causality from that. It would make no difference to one C token’s causal contribution to the production of an E token if every mechanism involved in the causal process broke down immediately afterwards and no further regularities obtained among Cs and Es.22

6. Counterfactual regularities make no contribution to causal productivity. They are not what distinguishes causal productivity from non-causal co-occurrence

Some Regularists will object that what I’ve been saying is irrelevant because the difference between causal and non-causal co-occurrences and sequences of events depends upon counterfactual rather than actual regularities.

Once upon a time, Nelson Goodman discovered that all the coins in his pocket were silver. Why wasn’t his putting his coins in his pocket the cause of their silver content? Why was pouring silver into a coin factory vat a cause? The Counterfactualist answer would be that an invariant counterfactual regularity holds between silver content and ideal silver introducing interventions on similar coin factories while no such regularities hold between silver content and ideal versions of whatever introduced the coins into Goodman’s pocket. Because things go wrong sometimes in real world coin factories it is not required that silver coins are actually produced every time silver is poured into the vat. What is required is the truth of certain conditionals about what would have resulted if certain silver introducing interventions had occurred. The conditionals are counterfactual because their antecedents are false. The antecedents are false because they describe ideal interventions which did not

22 Carl Craver objected in correspondence that ‘[i]n order to understand how even a single action potential has the wave form that it does, I am going to have to appeal to properties of populations of receptors, exhibiting stochastic behavior, that jointly operate to allow a regular and repeatable phenomenon to occur’. This illustrates that a population of mechanisms, each of which fails more often than it succeeds in producing a certain neuronal effect, may nevertheless produce those effects often and regularly enough to generate an action potential. Furthermore, some causal explanations (in this case, explanations of action potentials) depend upon statistical generalities about the production of an effect (e.g., neurotransmitter releases) that hold for a great number of populations (e.g., of neurons). But it doesn’t follow that each and every effect (e.g., each and every neurotransmitter release) is produced by a reliable mechanism which regularly produces effects of the same kind. Nor does it follow that if a mechanism regularly produces an effect in a number of cases, it’s doing so is what enables it to produce the effect in any other case. Nor does it follow, as Regularists believe, that what makes something causally productive of an effect is the regularities it instances.
actually occur. According to the Counterfactualist, actually putting silver into a vat contributes causally to the production of coins in a real world factory only if the relevant counterfactuals are true. If they aren’t true, pouring in the silver is not a cause of the coins’ silver content.

How can the chemicals in birth control pills cause non-pregnancy in fertile females, when they can’t prevent non-pregnancy for males? Counterfactualists say it’s because an invariant counterfactual regularity obtains between non-pregnancy and interventions that introduce those chemicals into female, but not into male bloodstreams (Woodward, 2003, pp. 154 ff., 172–173, 198–220). Counterfactual reasoning can be *epistemically* important to the discovery of causal structures. But Counterfactualism is not an epistemological idea. It is an ontological idea, or a piece of conceptual analysis to the effect that there is no causality without counterfactual regularities.

Many of the causal processes I’ve mentioned in this paper operate indeterministically. I have argued elsewhere that for indeterministic causal processes there needn’t be any fact of the matter as to whether the regularities Counterfactualists believe essential to causal productivity obtain (Bogen, forthcoming, §iv, *passim*). Instead of repeating those arguments, here are some other reasons not to be a Counterfactualist.

- It’s hard to see how the causal efficacy of part of a real world mechanism or any of its parts could depend upon counterfactual regularities. What *actually* goes on is sufficient for the production a mechanism, the satisfaction of its operating conditions, and so on. What *actually* goes on when a mechanism operates is sufficient for the production of any effects it produces. How can it make any difference to any of this whether certain things that did not happen *would have* or *might have* resulted if other things that did not actually happen *had* happened?
- I suppose we’d have to accept Counterfactualism if nothing but counterfactual regularities could discriminate causally productive processes and non-causal co-occurrences. But Elizabeth Anscombe’s critique of Hume suggests the following alternative (Anscombe, 1981). It’s a matter of fact (as opposed to counterfactual regularity) that Goodman’s coins were produced by a mechanisms such that pouring silver into the vat at the right time introduced silver into them. It’s a matter of fact (rather than counterfactual regularity) that what Goodman did to put the coins into his pocket could not influence their chemical composition. The right answer to the question why the chemicals in birth control pills can prevent pregnancy in a fertile woman but not in men is also factual rather than counterfactual: it actually is the case that fertile women have reproductive mechanisms for birth control chemicals to disable, while males do not. More generally, it’s a fact that some things exert causal influences which others do not. It’s a fact that some

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23 But I am indebted to Stathis Psillos for telling me of a passage in which Judaea Pearl says the counterfactuals in Bayes net causal reasoning ‘are merely conversational shorthand for scientific predictions’ (Pearl, 2000, p. 34).
things belong to mechanisms in which they can make causal contributions to the production of certain effects, while others do not. These are facts about what the relevant mechanisms and their parts can do and what they cannot. Like the claim that birth control pills prevent pregnancy by interfering with the release of eggs from the ovary, thickening cervical mucus to hinder the movement of sperm, and rendering the lining of the uterus unsuitable for the implantation of fertilized eggs, descriptions of causally productive activities can be understood and put to practical use without explication or analysis in terms of counterfactual regularities. And for non-determinist causal processes I submit that such facts are easier to understand, test, and apply to practical tasks than counterfactual claims about what would or might have happened if things that did not actually happen had happened.

- A third reason for suspicion is that when investigators such as Hodgkin, Huxley, Goldman, Katz, Kandel, MacKinnon, and Jiang, write about the action potential, they say next to nothing about counterfactual regularities. Although it’s plausible that implicit counterfactual reasoning is important to the development, evaluation, and practical application of their causal accounts, they are not explicitly included in causal explanations of the action potential. Nor do any of the authors I’ve mentioned in this paper report research engaged in to develop, evaluate, or find practical or theoretical applications for counterfactual generalizations. Neuroscientists who study the action potential try to discover regularities among actual rather than counterfactual sequences of events. I submit that this would not be so if counterfactual regularities were necessary for the truths of the causal claims they develop.

- It is certainly plausible that counterfactual reasoning is important to the design, and execution of experiments, and to interpreting data, modifying old hypotheses, developing new ones, and so on. The following illustrates a typical role for counterfactuals in theory evaluation. HH intended their equations to provide calculations of

  the [electrical] behavior of a model nerve whose properties are defined by the equations which were fitted . . . to the voltage clamp records described in earlier papers of this series. (Hodgkin & Huxley, 1952, p. 518)

- The model nerve is imaginary and highly idealized. Its electrochemical behavior conforms perfectly to the equations and depends exclusively upon the factors they mention. It is natural to think the calculations of its electrical behavior involve counterfactuals whose antecedents describe changes in one quantity (e.g., membrane potential) in the model neuron, and whose consequents describe changes in another (e.g., potassium ion flow or total current). The HH equations determine the truth or falsity of such counterfactuals by stipulating how the values of one or more of their variables must be changed when new values

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24 For more about this, see Machamer (forthcoming).
are assigned to others. HH hoped their imaginary neuron would resemble real neurons closely enough to make their equations useful in describing and predicting their actual electrical behavior. To evaluate their usefulness for this purpose, they manipulated electrical quantities in real world experimental preparations, calculated the magnitudes of others, and compared the results to values calculated for their model. The empirically derived results agreed with the counterfactual calculations in some respects and disagreed in others. In neither case were the counterfactuals used to explain anything. The task of finding out how useful the HH equations might be for predicting and calculating real world neuronal activity is epistemic, not explanatory. There is no suggestion here or in the subsequent literature that the factors responsible for the relations between the electrical quantities HH studied depend for their causal efficacy on counterfactual regularities.

This is only one example, but it is not atypical. I submit that it is as easy to find examples of counterfactual reasoning used for epistemic purposes as it is difficult to find causal explanations which explicitly include descriptions of counterfactual regularities, or which must be understood as implicitly including claims about counterfactual regularities whose non-obtaining would render the explanations unacceptable.

7. Recapitulation

• In the neuroscientific examples I’ve sketched, generalizations of different degrees of precision, accuracy, stability, and range of applicability were essential to the discovery of causes and the elaboration, evaluation, and practical application of causal explanations. Many of these uses were epistemic rather than explanatory.
• To the extent that these examples are representative of other areas, they support Mitchell’s idea that the usefulness of the laws and lesser generalizations biologists use derives from their giving rise to expectations which are reliable enough to further the biologist’s scientific purposes. How widely they must apply, and to what degree of accuracy or precision varies from case to case depending as it does upon the work to which the generalizations are put. As the GHK equations, Coulomb’s law, and other equations we’ve looked at illustrate, foundational neuroscientific investigations were well served by generalizations that do not approximate particularly well to the things they were used to study, and that gave rise to expectations which were not particularly accurate.
• The production of causal mechanisms and the satisfaction of conditions for their successful operation depend upon more or less widespread natural regularities. But once a mechanism in good working order is located in a setting that is suitable for its operation, the regularities it needs to produce an effect need not last any longer than the time it takes for the mechanism to complete its operation. For voltage gating this is no more than a tiny fraction of a second.
• Generalities are used to set out causal explanations. The generalities are not equivalent to the universally quantified sentences featured in Hempelian and related Regularist accounts of explanation. Using a generality such as ‘the voltage sensor opens the channel by pulling its inner lip’ to explain one instance of a neuronal effect does not commit one to its truth with regard to other instances.

• The case for the Counterfactualist view that regularities must obtain counterfactually in order for mechanisms to produce their effects in the actual world or for causal happenings to differ significantly from non-causal happenings has yet to be established.

• The laws and lesser generalizations in our examples were treated by neuroscientists who used them almost exclusively as descriptions of actual rather than counterfactual regularities. HH can be thought of as using counterfactuals to derive predictions from the imaginary neuron their equations define. But contrary to Counterfactualism, they were not used to explain neuronal effects. Instead they were used to evaluate the HH equations as instruments for predicting and describing actual neuronal behaviors whose causes HH insisted remained to be discovered.

8. Conclusion

Although natural regularities contribute to the production of an effect, regularity is one thing and causal productivity is another. It is to Mechanism’s credit that it enables us to appreciate the difference, and to adjust our ideas of the roles of laws and lesser generalizations accordingly.

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