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Two logics of experiment in biology & medicine: mechanistic/pathway versus populational

Shiping Tang[1]

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Abstract Two competing approaches, namely the New Mechanism/Mechanistic Philosophy and the "counterfactual + interventionist" (CF + I) approach, have dominated recent debates in philosophy of science. This article argues that the two approaches are underpinned by two logics of experiment. More concretely, there are two types and hence two logics of experiment in biology and medicine: a mechanism-oriented one and a populational one. The former seeks to identify and establish mechanisms or pathways (including entities, activities, and interactions) behind biological phenomena, whereas the latter seeks to establish whether and how much specific factors or variables impact outcomes at the populational level. These two types of experiment operate upon two different logics, and the word "experiment" means quite different things for them. Explicitly differentiating the two logics of experiment yields critical implications for a host of philosophical issues, including whether natural selection is a mechanism and whether the Hodgkin-Huxley model is explanatory.

Keywords Logics of experiment · Mechanism pathway populational · Counterfactuals · Causal explanation · Causal inference · Biology & medicine

1 Introduction

In the past two decades or so, historical and philosophical studies of experiment in *experimental* biology (biochemistry, cell biology, molecular biology, molecular genetics, and neurobiology) have firmly established that uncovering and establishing

✉ Shiping Tang
twukong@yahoo.com; twukong@fudan.edu.cn

[1] Fudan University, Shanghai, China

mechanisms or pathways (hereafter, M/Ps) has been a primary, if not the central, goal for biologists.[1] Along the way, the deductive nomological (D-N) model (Hempel & Oppenheim, 1948) has been firmly rejected as a valid model of scientific explanation, while the causal process (CP) or causal-mechanical (CM) model has become the major alternative (e.g., Wimsatt, 1976; Bhaskar, 1978 [2008]; Salmon, 1984), resulting in a "new mechanism/mechanistic philosophy" (hereafter, NMP; Glennan and Illari 2018; Glennan et al., 2022), at least in biology, history, and social sciences (e.g., Goertz & Mahoney, 2012; Kaiser et al., 2014).[2]

Opposing NMP, Woodward (2002, 2003, 2004, 2011, 2013) and his collaborators (e.g., Hitchcock, 1996; Woodward & Hitchcock, 2003) have advanced a counterfactual and interventionist (hereafter, CF + I) account of causal explanation, drawing mostly from the work of statisticians (e.g., Holland, 1986; Rubin, 1974, 1990, 2005) and philosophers of statistical reasoning (e.g., Pearl, 2009; Spirtes et al., 2000).[3] The CF + I approach emphasizes juxtaposing "ideal experiment" containing (ideal) manipulation/intervention/treatment with counterfactuals in deriving clear-cut causal inference. The differences between the NMP and the CF + I approach are real, and no easy solution to the debate between the two approaches seems at hand.

This article argues that these two competing approaches are underpinned by two types and hence two logics of experiment in biology and medicine: a mechanism-oriented one and a populational one.[4] Experiments in the mechanism-oriented logic

[1] While population geneticists (e.g., Mendel, Fisher) do conduct "(field) experiments", most biologists take "experimental biology" to perform laboratory-based experiments that focus on mechanisms and pathways. Hence, rather than adopting the more cumbersome term of "MPC-focused experimental biology" as suggested by a reviewer, I retain "experimental biology" for the sake of simplicity, as Weber (2005), Craver and Darden (2013), and may other have done. More contributions on mechanisms in biology are cited below.

[2] I thus take NMP to subsume CP/CM. The "New *Mechanism* Philosophy" should be preferred over the "New *Mechanistic* Philosophy", and certainly over the "New *Mechanical* Philosophy" (e.g., Craver 2007, pp. 86–93; cf. Glennan 2017; Glennan & Illari, 2018), if only to distinguish itself from the old mechanical philosophy (Roux, 2018). Implicitly, if not explicitly, NMP defends some versions of scientific realism. In fact, most proponents of scientific realism also explicitly emphasize mechanism, although their definitions of mechanism vary (e.g., Bunge 1967 [1998]; Harre & Madden, 1975; Wimsatt 1976; Bhaskar 1978 [2008]; Salmon 1984). The relationship between NMP and scientific realism is beyond the scope of this article. For earlier discussions, see Psillo (2002, chap. 4), Weber (2005, chap. 9), and Craver (2014). NMP also embodies a form of reductionism. For discussions on emergence and reductionism in biology, see Wimsatt (1976), Schaffner (1993, chap. 9), Rosenberg (2007), Mekios (2015), Glennan (2024), and Santo (2024).

[3] Woodward's (2003) CF + I approach explicitly builds on and extends David Lewis's (1973) counterfactual theory of causation. The relationship of the two approaches is beyond the scope of this article. For earlier discussions, see Psillos (2002, chap. 3), Woodward (2003, esp. chap. 5), and Illari and Russo (2014, chap. 9). Rubin (2005) has consistently preferred the term "potential outcome" over "counterfactual.".

[4] Notions of evidence, explanation, and causation that are at least partly underpinned by the two logics have been variously named: the former as (neo-)Aristotelian, mechanical/mechanistic, geometric-mechanical, production, power/capacity-based, and process-tracing; the latter as Humean, correlation/association/regularity view of causality, probabilistic, difference-making with treatment/intervention, (counterfactual) dependence, and causal inference with counterfactuals (e.g., Goertz & Mahoney 2012; Hall 2004; Illari 2011; Russo & Williamson, 2007; 2011; Steel 2008; Thagard 1998). In social sciences, these two logics have often been referred to as qualitative case study with process-tracing and quantita-

seek to identify and establish mechanisms (including entities, activities, and interactions) behind biological phenomena (Crick, 1988, p. 138). The ultimate goal of these experiments is to provide an explanation of phenomena, or "causes of effects", as complete and as deep as possible (Strevens, 2008). The major experimental tools in these experiments are treatments broadly defined, including a mixture of (re-)activation, (de-) inhibition, (de-)regulation, purification, and reconstitution (Baetu, 2016; Kaiser, 2016; Weber, 2016). These mechanisms and pathways are almost always presented as causal *diagrams,* or (crude) sketches or schemas that can vary from black box to gray box to glass box (Bechtel, 2006, pp. 33–40; 2008, pp. 17–22; 2015; Craver & Darden, 2013, chap. 3).[5]

In contrast, experiments in the populational logic seeks to establish whether and how much some factors or variables contribute to outcomes at the populational level (e.g., Fisher, 1935a, 1935b [1971]; Holland, 1986; Rubin, 1974, 1990). In other words, experiments in the populational logic are foremost concerned about establishing "effects of causes." (Holland, 1986) The key experimental tool in the populational logic is (ideal) interventions narrowly defined, under a perfectly controlled experiment in the field or within a population (e.g., clinical trial of drugs, testing social policies). Increasingly, causal relations within this logic are represented in structural equations as Bayesian Networks (e.g., Pearl, 2009; Spirtes et al., 2000; Woodward, 2003), after the rediscovery of pathway models invented by Wright (1920, 1921, 1922).

Thus, the same word "experiment" and other related words (e.g., control, treatment) mean quite different things for these two logics and biologists working within them. Indeed, scientists conducting the two types of experiment (and hence adherents of the two logics) rarely communicate with each other. Most mechanism-oriented experimental biologists only rarely cite population genetics and statistics (i.e., Ronald Fisher, J. B. S. Haldane, and Sewell Wright), whereas most population geneticists only rarely care much about what experimental biologists have been doing and discovering.[6]

Interestingly, although both types of experiment exist in the biological sciences and medicine, the mechanism-oriented one has traditionally dominated experimental biology, as the distribution of Nobel Prizes in physiology or medicine can testify (Appendix 1). The reason is simple: while establishing a causal relationship between

Footnote 4 (continued)

tive exercises with causal inference, with Goertz and Mahoney (2012) identifying them as two cultures. Hume (1777 [2007]) was certainly guilty of replacing causality with regularity AND counterfactual (causal) statement (Andersen 2018). "Difference-making" cannot differentiate the two logics because both logics of experiment use "difference-making" in their actual exercises.

[5] I take "diagram" to be less formal than "graph" (e.g., Menzies 2012, cf. Bechtel 2015). Pearl's (2009) directed acyclic graph (DAG) is an even more demanding form of graph. See also section IV below.

[6] Now a personal disclaimer. The author was trained in paleontology (mostly a field of populational logic), then molecular biology and genetics (mostly a field of M/P logic), and finally in social sciences (a field with both logics, often at war against each other). As a result, the author has worked with both logics. Moreover, the author has been called for and actually practiced combining the two logics (or "mixed methods") in empirical inquiries. Thus, although I underscore that the M/P logic has dominated in biology, I do not favor one logic over the other.

a possible cause and an outcome may or may not require scientists, discovering a mechanism almost always does. As Craver and Darden (2013, pp. 1–2), noted, while hunters in South America had long known that curare can kill animals (including humans), uncovering how curare kills took more than a century of scientific detective work by quite a few scientists. Most prominently, while our ancestors had long known that some things must have been passed from parents to their children (i.e., there is a causal relationship between parents' characteristics and their children's ones), establishing the central mechanism of inheritance (i.e., how inheritance really operates) took millenniums until the discovery of the DNA double helix in 1953 by Watson and Crick (1953a, 1953b). In other words, uncovering mechanism(s) behind a causal relationship is a much more formidable task than establishing a (possible) causal relationship.

Meanwhile, the population-oriented logic has laid much of the intellectual foundation of modern statistics, causal inference, and randomized controlled trials (RCTs) in medical sciences and social sciences (Fisher, 1925[1934]; 1935 [1971]; Neyman 1923[1990]; Rubin, 1990, 2005; Holland, 1986). The population-oriented logic is also the core foundation of machine learning and artificial intelligence (Pearl & Mackenzie, 2018). Explicitly differentiating the two logics of experiment therefore yields critical implications for key philosophical issues.

Several key caveats are in order.

First, I readily acknowledge that some implicit references to the two logics exist (see Sect. 3 below for details). More often than not, these references to the two logics are couched in the debate between the two approaches on causation, yet both sides of the debate have mostly failed to recognize that there are really two logics of experiment in biology and medicine and it is these two logics that underpin the two approaches. Thus, my central point is that the two logics have not been adequately explicated and a more explicit grasp of the two logics will help us resolve key contentious points in the debate.

Second, I construct the two logics as "ideal types" so that we can grasp their fundamental differences more explicitly. By no means am I suggesting that the two logics are incommensurable. Certainly, the two logics do agree with each other on some key issues and share some common elements. Also, although I single out the two logics, I am not suggesting that no other logics of experiment, discovery, and explanation exists in biological and medical sciences (Braillard & Malaterre, 2015). In fact, I readily admit that there may be limits to what NMP or CF+I can do for developmental biology, system biology, or even protein-folding. Addressing these issues, however, is beyond the scope of this article.

Third, although I stress that the two logics of experiment are different, I do not mean that these two logics are incompatible, in principle and in practice. Indeed, these two logics can work together in unraveling the causal structure of nature and society, precisely because these two logics are different (i.e., the two kinds of experiment perform different functions in science). For instance, the discovery process from the Hodgkin-Huxley (HH) model to the Na^+/K^+-ion channels has been a journey that combined the two logics (see Sect. 5 below).

Traditionally, however, few biologists have worked with both logics, partly because these two logics require quite different skills and instruments. More often than not, experiments with the two different logics perform distinct functions and

work for different (immediate) objectives in biological discoveries. Increasingly though, integration of the two logics, usually with some mathematical tools (including formal graphs), has become more common, especially in evo-dev biology and system biology (Bechtel, 2015; Brigandt, 2015; Meikos 2015; Gross, 2015).

Fourth, while admitting the two logics can work together, I reject Woodward's (2003, 2004; see also idem 2010; 2011; 2013) position that the M/P logic can be subsumed by or assimilated into the CF+I framework. *Because these two logics are different, they cannot be reduced to a single logic.* As such, the two philosophical approaches that reflect the two logics cannot be reduced to one, and neither one can subsume or assimilate the other (Bogen, 2004; Waskan, 2011; cf. Psillos, 2004; Campaner, 2006; Craver, 2007; Woodward, 2011, 2013).

Fifth, if my thesis that there are two logics of experiment in biology and medicine is correct, its implication will be wide and profound, epistemologically and methodologically. Issues that are related to the two logics range from the relationship between two kinds of evidence obtained from the two types of experiment, to the role of counterfactuals in causal analysis, the role of RCTs in medicine and policy, causes of effects versus effects of causes, and singularism versus pluralism stand toward causality at the level of ontology and epistemology. I cannot possibly engage them, other than alluding to some possible directions and potential implications (for earlier discussions, see Danks, 2005; Russo & Williamson, 2007, 2011; Bechtel, 2011; Illari, 2011; Illari & Russo, 2014; Glennan, 2017; Cordovil et al., 2024).

Finally, to support my arguments, I mostly use multiple but brief examples rather than focus on one or two key experiments. I do so to show that my arguments are applicable to a wide field (i.e., the entire field of biology and medicine). In section five, I do address two mini debates in more detail in order to show that explicitly differentiating the two logics does help resolve some critical difficulties within these two debates.

The rest of the discussion unfolds as follows. Section II presents a brief conceptual preparation, providing operational definitions of key concepts without getting into the details. Section III lays bare the two types of experiments and their corresponding logics. It also highlights the dominance of the mechanism-centric approach logic in biology, using the sample of Nobel Prizes in physiology or medicine and chemistry as evidence. Section IV underscores the lack of explicit appreciation of the two logics within existing discussions. Section V discusses whether natural selection is a mechanism and whether the HH model is explanatory, in light of the two logics. A brief conclusion follows.

2 Working definitions

Since different authors have deployed many of the terms below differently, for the sake of convenience, I enlist the working definitions of these terms here. My aim is not to impose (although I do suggest) any singular definition or interpretation regarding these terms but rather to avoid debating them. Since terms are many yet space is limited, I shall be as brief as possible by stating my positions without getting into the details.

For mechanism, I slightly modify Illari and Williamson's (2012, 120) minimalist definition: "A mechanism for a phenomenon consists of entities, activities, and interactions organized in such a way that they are responsible for the phenomenon." (See also Glennan, 2017, 17; Glennan and Illari 2018, 2; Glennan et al., 2022) A mechanism is thus always a mechanism for something within a particular system: a mechanism is something real, ontologically. This definition draws essential elements from earlier definitions but reduces inconsistencies among them (e.g., Bechtel & Richardson, 1993 [2010], chap. 2; Glennan, 1996, 2002; Thagard, 1998, 66–73; Machamer, Darden, and Craver [hereafter, MDC] 2000; Darden, 2008; Bechtel & Abrahamsen, 2005).[7]

A mechanism is often multi-leveled and spatially organized: entities, activities, and interactions are spatially and temporally arranged. A mechanism does not have to be unidirectional, but can be reversible or even cyclic (Darden & Craver, 2002; Darden, 2008; Bechtel, 2011; Illari & Williamson, 2012; cf. Glennan, 1996; Tabery, 2004).

Whereas interactions among entities do not have to be productive, activities (supported by entities) must be "causally productive activities": activities (and entities) thus have power or capacities (Bogen, 2008b; Glennan, 2009). In fact, enzymes such as ATPase, caspases in apoptosis (i.e., programmed cell death), DNA polymerase, and RNase etc. are named explicitly for their power or capacities to perform specific activities. Of course, activities can be positive (e.g., promotion, activation, synthesis) or negative (e.g., repression, inhibition, de-activation, degradation), and activities do not have to reside with a single entity.

While mechanism may be different from pathway or cascade (Ross, 2018, 2020), most biologists use "pathway", and to a less extent, "cascade" as synonyms for mechanism (Craver, 2007; Thagard, 1998, 2003). Alternatively, a pathway or cascade contains (possibly) many mechanisms (e.g., Skilling 2015; Ioannidis & Psillos, 2017; Boniolo & Campaner, 2018). For convenience, I use "mechanism" most of the time.

For the relationship between mechanism, regularity/pattern, and law (as statement),[8] I adopt Andersen's (2011, p. 325) position: "regularities are what laws describe and what mechanisms explain." Hence, "many generalizations that we have or might call laws are simply descriptions of the behavior of mechanisms; that is, the phenomena for which the mechanism is responsible is a lawful regularity, and the mechanism that is responsible for that regularity explains the law." (Glennan, 2017, p. 45) Mechanisms underpin regularities/patterns that are captured by laws. Hence, law (as statements) captures or states regularities/patterns but does not explain them: neither law nor regularity is causation or explanation (Anscombe, 1981; Bhaskar,

[7] Cartwright's (1999, p. 50) "nomological machines" contain similar elements, as Cartwright et al. (2020) noted. Bhaskar (1978 [2008]) also identified entities and processes (i.e., actions, interactions) as part of mechanism.

[8] Here, it is critical to distinguish laws as "metaphysical entities that produce or are responsible for regularities" and law statements as "descriptions of laws" (Craver and Kaiser 2013, p. 128).

1978 [2008]; Bogen, 2005, 2008b; Craver & Kaiser, 2013; cf. Hume, 1777 [2007]).[9] Consequently, a law does not have to contain any mechanisms.

A (statistical) correlation or co-variation as associative regularity is not causation, even if it is robust and stated as a law. A complete explanation for a phenomenon or a set of phenomena explains its regularities/patterns (as laws), if there are any. Yet, explanations do not require laws (Thagard, 1998; Bogen, 2005; Craver & Kaiser, 2013; cf. Woodward, 2002, 2004; Leuridan, 2010). Also, mechanisms can be generalized without laws (Bechtel & Abrahamsen, 2005).

An explanation does not have to explain regularities (as laws): a unique event or outcome such as the Cambrian Explosion, the origin of birds from dinosaurs, or the French Revolution can still be explained. Yet, an explanation for a unique historical event or outcome may still, and often must, contain mechanisms (Bechtel & Abrahamsen, 2005; Glennan, 2017, 44–48; Andersen, 2011, 2012, 2018; Ioannidis & Psillos, 2018; Cartwright et al., 2020).

There may be fewer laws in experimental biology than in physics and chemistry. Unsurprisingly, most experimental biologists are not very interested in laws: rather, they are mostly interested in explanations with mechanisms or pathways (Crick, 1988; Thagard, 1998, 2003; Craver & Darden, 2013; Glennan, 2017, pp. 44–48; cf. Weber, 2005, pp. 29–35).

A causal explanation seeks to provide an adequate, if not full, account for a single phenomenon, or more often for natural sciences, a set of phenomena (Salmon, 1984). In history and social science, the explanandum may be a singular event or outcome (Glennan, 2010; Gerber 2014; Little, 2018). A causal explanation is to establish "*causes of effects*".

In contrast, causal inference is to establish whether a factor or a variable contributes to an outcome within a sample or a population. In other words, causal inference is to establish *"effects of causes"* rather than *"causes of effects"* (for a debate, see Dawid et al., 2014). Causal inference is almost always done with statistical tools, with probability theory and Bayesian logic being part of its foundation. Also, it is within causal inference that Holland (1986) identifies the lack of real counterfactuals as the ultimate challenge (see also Woodward, 2002; Kluve, 2004; Psillos, 2004, esp. pp. 302–307). Thus, causal inference is explicitly modelled after randomized experiments with a heterogeneous population (Neyman 1923 [1990]; Fisher, 1935a, 1935b [1971]; Rubin, 1974, 1978, 2005; Holland, 1986). Working with a homogenous population, randomization is unnecessary.

Causal inference does not provide a full causal explanation, partly because it cannot uncover or capture mechanisms but can only establish statistical correlation or co-variation caused by possible mechanisms (Thagard, 1998, esp. pp. 62–73). Meanwhile, providing a causal explanation often requires causal inference, but the

[9] Most NMP's proponents take regularity and pattern to be equivalent or regularity to be a narrower form of pattern (i.e., a regularity is a pattern that can be expressed more formally). See, for example, Craver and Kaiser 2013, p. 128. Here, I follow the opinion of the majority. For a dissenting take, see Burnston 2017.

latter does not require the former. Hence, constructing a causal explanation can subsume causal inference, but the reverse is not true.

As becomes clear in section III below, the two logics of experiment hold very different ideas regarding the goal of experiment. For the population logic, the ideal experiment is to facilitate a clean and clear identification of the causal effect, or "causal inference" (Woodward, 2002, pp. 45–61). For the M/P logic, the central goal is to identify and establish the entities, activities, and interactions of a mechanism toward a causal explanation.

Probability theory is a foundational component of statistics, but statistics is more than probability theory. Whereas statistics cannot work without probability theory, probability can work without statistics, especially statistical causal inference (see below). Probability can be about both repeated observations of a single unit (e.g., coin tosses) and a sample/population of units and organisms. In contrast, statistics is almost always about a sample or a population of units and organisms (e.g., human, ants). Hence, probabilistic causality can be about a single event or outcome. In fact, there now exist formal approaches for estimating probabilities from case studies with process-tracing within a Bayesian framework (e.g., Fairfield & Charman, 2017). In contrast, statistical causality is always about a population (of units or observations) even though a statistical causality is always probabilistic.[10] In sum, while a statistical causality is always probabilistic, not every probabilistic causality is statistical (and populational). In this sense, the conventional term "probabilistic causality" might have conflated "probabilistic causality" and "statistical causality".

3 Two logics of biological experiment

I now explicitly differentiate the two logics. Before that, however, we need to grasp that there are two different types and hence meanings of population in biological sciences.

3.1 Population in biological sciences: two meanings

Behind the notions of law, regularity, and pattern, there must be a notion of population. Surely, without a population or a sample of observations, it is nonsensical to talk about law, regularity, and pattern. Yet, population is a polysemic term.

The statistical notion of population, perhaps more properly termed "universe", is the entire aggregation or complete set of any objects (e.g., individuals, items, events, and observations) from which a sample (as a subset) is drawn. For the statistical notion of population, objects do not have to be organisms, as Fisher (1925 [1954], chap. 1) had pointed out long ago.

The statistical notion of population, however, is not the meaning most biologists have in mind, even though handling a population always require statistics.

[10] Thus, Ariew (2022) argues that Darwin had statistical thinking, because Darwin had "population thinking" (Mayr 1959 [1976]). Yet, Darwin definitely had little explicit "probabilistic" thinking.

In biological sciences, population (almost) always means a pool or collective of individual organisms from the same species or subspecies.[11] When a population denotes a population inhabiting a given area or ecological niche, it is called a "local population".

Beyond the above, many philosophical discussions of biological sciences assume that population means the same thing for all biologists. Yet, for the two logics of experiment, population actually means very different things.

Within the M/P logic, population is rarely mentioned. Why? Because biologists working within this logic assume that the population at hand is essential homogenous, at least for their key experimental goals. In other words, for a population of *Escherichia* ***coli*** (*E. coli*), *Neurospora crassa (N. crassa)*, *Saccharomyces cerevisiae* (*S. cerevisiae*), *Caenorhabditis elegans* (*C. elegans*), and *Drosophila melanogaster* (*D. melanogaster*) of the same strain, experimental biologists who focus on mechanisms and pathways assume that each individual *E. coli, Neurospora*, yeast cell and each individual *C. elegans* or *D. melanogaster* organism is identical or nearly so to each other, at least for their experimental goals.

Thus, when Beadle and Tatum's (1941) were investigating "one gene for one enzyme" with *N. crassa*, although they worked with different strains of *N. crassa*, each strain of *N. crassa* is essentially homogenous for their experimental goals. Likewise, when Jacob and Monod (1961) were experimenting with the lactose (*lac*) operon, although they worked with different strains of *E. coli*, each strain of *E. coli* is essentially homogenous for their experimental goals.

Hence, although experiments within the M/P logic can and do work with populations, experiments within the M/P logic mostly work with "essentially homogenous populations". As a result, scientists working within the M/P logic rarely have to think with the populational logic and hence have little usage of statistics.

Of course, by "essentially homogenous populations", biologists working with the M/P logic do not really assume that each individual organism of a single strain (as the population) is identical. Instead, what they assume is that the differences among the individual organisms within the strain are not so significant or meaningful that they impact the phenomenon and the mechanisms underpinning the phenomenon. Most of the time, biologists working the M/P logic make sure a strain is an "essentially homogenous populations" by propagating different batches of the same strain from a single mother population (e.g., the Hela cell line).

In contrast, within the population/treatment logic (e.g., population genetics, ecology etc.), population (or sample as a fraction, and hopefully, a representative fraction of the total population) is the starting point for any inquiry. Most critically, it is almost always assumed that the population is heterogeneous, that is, each individual organism with the population or sample is different from each other, at least for some characteristics.

[11] Some philosophers of biology call for conceptual pluralism for population (e.g., Stegenga 2016). But this does not change the fact that biologists (almost) always take a population to be a population of the same species.

Thus, when Mendel and Fisher performed their field experiments, they were experimenting with a heterogeneous population with different strains. Likewise, when a potential drug is tested in clinical trials, the populations are by definition heterogeneous. Similarly, when social scientists study how a social policy impacts different communities, they are working with different populations of human beings that are inherently different from each other.

In sum, in lab experimental biology, biologists within the M/P logic almost always work with "essentially homogenous" populations. In contrast, in populational genetics, biologists with the logic of populational/treatment almost always work with heterogeneous populations. This fact is a fundamental reason why the former does not bother with randomized controlled trials (RCTs) whereas the latter is almost obsessed with RCTs. The logic is simple: with an "essentially homogenous" population, randomization is unnecessary. In contrast, with a heterogeneous population, randomization is quintessential for an ideal experiment. This also explains the fact that ever since Fisher (1925 [1954]), most sophisticated statistical techniques out there have been developed for situations in which randomization or even experiment is not feasible (e.g., Holland, 1986; Pearl, 2009; Rubin, 1974, 1978).

3.2 Two logics of experiment in biology

In biology, the dominant logic of experiment is undoubtedly the one that seeks to uncover and establish mechanisms or pathways behind biological phenomena such as cell division, development, cancer, and others. This has been well documented by leading advocates of NMP (e.g., Bechtel & Richardson, 1993; 2010; Darden, 2007; Craver & Darden, 2013).

A key feature of this logic, however, has gone largely unnoticed: experiments with this logic have little, if any, populational thinking at all.[12] For these biologists, an established mechanism (e.g., the Central Dogma, i.e., information flows from nucleic acid to protein) needs no populational support: it has to be correct, sometimes across the entire biotic world. As such, biologists working with this logic seldom use probability theory and statistics. Most critically, for these experimental biologists, causal inference with statistical tools is not a concern at all.

In contrast, the populational logic of experiment in biology explicitly aims to understand population-level outcomes, with its most prominent example being population genetics. Within this logic, the key concern is causal inference with statistics. Population-level experiments aim to determine a factor's effect upon a population outcome (e.g., a fertilizer on a crop's output), often measured as the "(local) average treatment effect" (LATE). Like a mirror image, biologists working with this logic care little about the mechanisms beneath the populational outcomes.

[12] This fact is entirely consistent with the possibility that a complex mechanism (e.g., protein synthesis) can be "split" into more fine-grained sub-components (including more specific mechanisms) at different levels as our knowledge about the complex mechanism gets deeper. I thank a reviewer for pressing me to clarify this point.

The foundational figure for the populational logic was Ronald Fisher (1890–1962), who was first and foremost a mathematician and statistician. Fisher (1925 [1954]) laid much of the foundation of modern statistics. In fact, Fisher carried out many field experiments with crops in the Rothamsted Experimental Station while developing his statistical-genetic theory of natural selection (Fisher, 1926, 1930).[13] Besides Fisher, both Haldane (1892–1964) and Wright (1889–1988), the other two founding fathers of population genetics, also contributed to statistics foundationally. As Brandon and Ramsey (2007, p. 66) put it, "Population-level theories of evolution—the stock and trade of population genetics—are statistical theories par excellence."

In experiments within the population logic, the goal of the (ideal) experiment is to facilitate *causal inference as the statistical identification of the causal effect(s) of factors or variables.* Pearl (2009, p. xv) asserted, "the central aim of many studies in the physical, behavioral, social and biological sciences is the elucidation of cause-effect relationships among variables or events".[14] Rubin (2005, p. 323), who did not always agree with Pearl (or Fisher), put it even more bluntly by titling one of his subsections, "The Causal Estimand = Science"!

When this is the case, experimental design and statistical procedure must go hand-in-hand. None put it better than Fisher (1935a, 1935b [1971], p. 3): "Statistical procedure and experimental design are only two different aspects of the same whole, and that whole comprises all the logical requirements of the complete process of adding to natural knowledge by experimentation." Put it bluntly, a RCT experiment (e.g., a clinical trial of a drug) has to be designed very carefully and implemented precisely according to the design (i.e., the experiment is or at least close to being "ideal"), if it is to provide meaningful information for evaluating the effect of a drug.

Hence, the ideal experiment for the population logic is RCTs in the field or within a population, as done in perfectly designed and conducted clinical trial of drugs and testing social policies within a local population (e.g., Fisher, 1935a, 1935b [1971], pp. 17–21; Rubin, 1974, 1978; Woodward, 2002, 2003, pp. 94–99, 172–173, 198–220; 2011; for critiques, see Craver, 2007, pp. 93–104; Cartwright, 2010; Deaton & Cartwright, 2018). In Woodward's (2002, 2003) terms, the ideal experiment within the population logic demands "modularity".[15]

In contrast, for the M/P logic, the key goal of experiment, which is almost always done in a laboratory, is not about establishing the causal effect or even estimating the "(local) average treatment effect". Rather, the key goal is to identify components or entities (e.g., a protein, a gene, RNAs, and other molecules

[13] In fact, had Fisher not worked in the Rothamsted Experimental Station, he might not have developed his foundational contributions to statistics so rapidly in a mere seven years (1919–1926).

[14] Strikingly, Pearl (2009) did not cite a single article or book on mechanisms in biological sciences. One must wonder what Pearl would have written if he has read a single detective story behind the discovery of a single mechanism in biology such as the Krebs cycle, the lac operon, or just the DNA double helix!

[15] Note that Woodward's (2003) notion of "modularity" is strictly technical for the sake of causal inference. In biology, the notion of "modularity" rests upon a belief in the ontological properties of biological structures and functions as "modules" and then an epistemological commitment for identifying these modules (e.g., Hartwell et al., 1999). For discussions on modularity in biology, see Schlosser and Wagner (2003), Callebaut and Rasskin-Gutman (2005), Mitchell 2005; Cartwright 2007; Braillard 2015.

or complexes), link activities and interactions (e.g., the binding of ligand with its receptor, transcription factors binding to DNA sequences) with the entities, locate them spatially and temporally, dissecting them structurally, and hence establish part or even the whole pathway (Craver & Darden, 2013). Hence, major experimental tools in the M/P logic include a mixture of purification, deactivation, disruption, inhibition, regulation, reactivation, acceleration (with enzymes or chemical compounds as catalysts), and tracing (e.g., with isotope or florescence labeling) that targets entities, activities, and interactions (Baetu, 2016; Bechtel, 2006; Craver, 2002; Darden, 2006).

Moreover, for the M/P logic, while some experiments can be understood as elegant and decisive (hence "ideal"), many, if not most, great discoveries had only been achieved by many (non-ideal) experiments with trial-and-errors. Thus, while the experiment to establish the exact model of DNA replication by Meselson and Stahl (1958) was elegant and decisive, the experiments behind the discoveries of the double-helix structure of DNA (Watson & Crick, 1953a, 1953b), the *lac* operon (Jacob & Monod, 1961), the chemiosmotic mechanism of oxidative phosphorylation, and the Calvin-Bense cycle of photosynthesis (Scholl & Kichelsen, 2015) had been anything but elegant or "ideal".

In sum, there are two logics of experiment in biology, and the word experiment means quite different things for the two logics. More often than not, these two types of experiment have operated independently from each other. For mechanism-focused experimental biologists, populational level outcome is at most an afterthought; they assume that mechanisms or pathways underpin populational level outcomes (but not vice versa). For them, regularities (and laws) are superficial, and the more foundational goal is to establish the mechanism or pathway behinds those regularities or patterns (Andersen, 2011; Bogen, 2005).

Thus, after Watson and Crick (1953a, 1953b) elucidated the double helix structure of DNA and concluded that DNA is the genetic material (of most organisms), they did not bother to think whether their extrapolation is valid among other: they had little doubt. Likewise, after Meselson and Stahl (1958) established the mechanism of semi-conservative replication of DNA with *E. coli*, they did not bother to test whether the same mechanism holds in other organisms.

Indeed, both the model of DNA structure by Watson and Crick and the results from Meselson and Stahl (1958) were almost immediately and universally accepted as valid by (molecular) biologists without further testing. It is this very possibility that mechanism-focused experimental biology can proceed almost entirely without referring to evolutionary biology, especially population genetics (Weber, 2005, pp. 2–3).

Like a mirror image, population genetics or field experiment can proceed almost entirely without referring to molecular pathways or mechanisms. In fact, Fisher (1930), J. B. S. Haldane (1924–1934), and Wright (1931) had completed their foundation work in population genetics long before the discovery of the DNA double helix as the molecular mechanistic foundation of genetic inheritance and natural selection. In short, there are two logics of experiment in biology, and they rarely interact with each other.

Here, it is worth noting that almost all the Nobel Prizes in physiology or medicine have gone to scientists who discovered key pathways or components of key

pathways (Appendix 1). In fact, no population geneticist has ever won a Nobel Prize in physiology or medicine: not even Fisher, Haldane, and Wright. In short, the first logic has indisputably dominated biology. "*Many (perhaps most) of the important discoveries in the biological sciences have been discoveries of mechanisms*." (Darden & Craver, 2002, p. 25). Deep down, therefore, most experimental biologists hold that molecules (as entities), mechanisms, pathways, and cascades are more foundational than populational outcomes (Thagard, 1998, 2003). After all, outcomes at the populational level (almost) always depend on mechanisms at the molecular level to operate (e.g., DNA replication, gene expression, and protein interaction), even though outcomes at the populational level cannot be reduced to mechanisms at the molecular level alone.

Finally, it is worth noting that the two logics are not limited to biology. As long as a science deals with phenomena at both the mechanism/pathway level and the populational level that are underpinned by mechanisms and pathways, the science contains contain both logics. Chemistry, geology, medicine, psychology, social sciences, and even physics all contain the two logics.

4 Lack of appreciation of the two logics and its consequences

The differences between the two logics are real. Consequently, failure to grasp the two logics and their differences can lead to unnecessary misunderstandings and squabbles.

Obviously, earlier philosophical discussions of experiment were all about physics and mostly focused on physical laws (e.g., Popper, Kuhn, Lakatos, Salmon, Bunge, Cartwright, to name just a few), and they could not possibly lead us to this understanding because there are foundational differences between physics on one side and chemistry, geology, and biology on the other side.[16] For instance, Steinle (2002, 2016) has mostly examined experiments in physics thus cannot lead us to the two logics.

Similarly, Franklin (2016) examined sixteen experiments from physics out of total eighteen cases and was mostly interested in what makes an experiment critical and good. Franklin (2016) actually examined two seminal biological experiments from each logic, Mendel's experiments with peas and Meselson and Stahl's (1958) experiments to establish the mechanism of semi-conservative replication of DNA. Evidently, the former followed with the population logic, whereas the latter the M/P logic. Because Franklin was into physics so much, it is quite unlikely that he could have appreciated the two logics.

[16] Weber (2005, pp. 2–3) noted that evolutionary biology, especially population genetics, is more similar to physics because it focuses on regularities as stated in laws (e.g., the Hardy-Weinberger law, Mendel laws). I am not sure this is always the case: discovering basic particles in physics is akin to establishing entities in biology, so is discovering elements in chemistry. The problem, I think, has been that early philosophy of science has focused on physical laws rather than entities and forces (as part of mechanism). Further, experimental biology also contains regularity as captured by laws (Andersen 2011). For instance, the Central Dogma that the information flow has always been from nucleic acids to proteins, but never the reverse way, is arguably a law.

Meanwhile, Illari and Williamson (2010) explicitly compared protein synthesis and natural selection as two different mechanisms. Apparently, the former is purely M/P-oriented whereas the latter populational (with individual foundation). They, however, hold that the two mechanisms "are more closely analogous than they appear."

There have been some implicit references to the two logics. Thagard (1998) came close to identifying these two logics when he examined mechanisms versus correlations in explaining diseases. O'Malley (2015, p. 10, 275, esp. table 1) noted the two different logics in passing when addressing the implications of endosymbiosis for evolutionary theory. When questioning Menzies' (2012) attempt to capture mechanisms with structural equations, Cartwright (2017) might have also come close (see also Cartwright, 2007, part II).

More recently, separate contributions on mechanism in evolutionary biology (DesAutels, 2018) and mechanism in molecular biology (Baetu, 2018) in the *Handbook of Mechanisms and Mechanical Philosophy* (Glennan and Illari 2018) seem to implicitly admit these two logics. Indeed, Baetu (2020) correctly argued that there are two types of (causal) inference in biomedical research (i.e., a non-statistical one in basic biomedical search and a statistical one in clinical research). Yet, he focused on the issue of comparability with these two types of causal inference rather than their different underlying logics.

The closest place for explicating the two logics has been the debate initiated by Russo and Williamson (2007), who insisted that when seeking to establish causal claims in health sciences, scientists often need to integrate two types of evidence, that is, probabilistic/statistical and mechanistic/process-oriented (see also Campaner, 2011; Illari, 2011; Russo and Williams 2011; Campaner & Galavotti, 2012; Clarke et al., 2014; Illari & Russo, 2014; Williamson, 2019).

Yet, while these authors seem to realize that these two types of evidence come from two types of experiment, which in turn are based on two different logics, they did not explicitly differentiate the two logics. Indeed, Illari (2011, p. 144) was adamant that "while there are distinctions in evidence-gathering methods that useful track something important about the kinds of conclusions the evidence supports, *there is no useful general distinction between mechanistic- and difference-making-evidence-gathering methods*." (Emphasis original; see also ibid, pp. 141–144, with the same sentence appeared in 141 without emphasis.) By doing so, Illari (2011) has indirectly denied that the two logics of experiment are different because the differences of (experimental) methods are really underpinned by the two different logics.

Our failure to explicitly grasp the two logics has led to several misunderstandings. The principal misunderstanding, often implicit, is that there is only one logic of experiment. More concretely, these two logics have been taken up by the two approaches toward causality (i.e., NMP and CF + I), and some proponents of the two approaches insists that their preferred approach is the only valid approach toward causality.

On the one hand, the NMP literature has primarily examined experiment within the M/P logic (i.e., establishing mechanisms, pathways, and cascades). As Levy (2013, pp. 105–106) noted, most NMP theorists do not examine population

phenomena, including "population genetics, ecology and other macro-biological populational disciplines." Yet, discovering mechanism is not the only game in biological sciences: discovering regularities and patterns is surely another.

On the other hand, and like a mirror image, most proponents of the populational CF+I logic do not really engage with the M/P logic. For instance, Woodward (2003, pp. 302–307 and pp. 312–313) examined only two biological and medical discoveries briefly, Mendel's law of segregation and the association between smoking and lung cancer. Apparently, both discoveries were about outcomes at the population level. Moreover, all the key causal inference works underpinning Woodward (2003), from Rubin (1974, 1978) to Holland (1986), Pearl (2009), and Spirtes et al. (2000), have been written by statisticians or philosophers of statistical logic and hence more about the statistical techniques and logics of statistical reasoning (see also Morgan & Winship, 2015; Rosenbaum, 2009),[17] and none of them examined experiments in the M/P logic. Unsurprisingly, Woodward too has failed to admit the two logics and their key differences (see also idem 2011; Woodward & Hitchcock, 2003).

Thus, when Woodward (2002) tried to squeeze the mechanistic logic into his CF+I logic, his interpretation of the classic experiments on the *lac* operon conducted by Jacob and Monod (1961) was mostly mistaken (Baetu, 2016, pp. 3316–3321). Moreover, the *lac* operon, intricate as it is, is an extremely simple mechanism, compared to many other mechanisms such as the pathways of programmed cell death, which includes apoptosis, necroptosis, and pyroptosis, not to mention the extensive cross-talk between the three specific pathways (Bertheloot et al., 2021).

Another misunderstanding has been that one logic can subsume the other because one logic is superior to the other. This sentiment is especially strong among proponents of the populational logic, often explicitly or implicitly based on their supposedly more quantitative and hence more "scientific" and "rigorous" logic.[18] For many proponents of the CF+I approach, mechanism can be reduced to the CF+I logic, via causal modeling with probability distribution and structural equations. Thus, many proponents of the CF+I approach have questioned the value of mechanism in constructing explanation (e.g., Pearl, 2009; Reiss, 2007; Woodward, 2002, 2011). Unfortunately, no amount of statistical manipulation can reduce the fundamental logic of mechanism to CF+I because the two logics are fundamentally different (Bogen, 2004; Waskan, 2011; Bateu 2016; see also Thagard, 1998; Russo & Williamson, 2007).

[17] Unsurprisingly, therefore, all these texts cite Fisher (1935a, 1935b [1971]) and Campbell and Stanley (1963 [1966]), with the latter being instrumental for bringing experimental and quasi-experimental methods to psychology and social sciences. In contrast, these texts have rarely cited any mechanism-oriented experiments.

[18] The sentiment was perhaps already present in Fisher (1935a, 1935b [1971]), who mostly used the term "scientific inference" for causal inference, thus (implicitly) suggesting that only (statistical) causal inference is scientific!

5 Natural selection and the Hodgkin-Huxley model

This section will try to shed some new light on two mini debates in the philosophy of biology, in light of our differentiation of the two logics. By doing so, I further underscore the payoffs of differentiating the two logics.

5.1 Is natural selection a mechanism?

Because the MDC (2000) definition of mechanism was mostly inspired by mechanisms, pathways, and cascades from molecular and neural biology, it cannot readily accommodate natural selection, which (at least partly) reflects a populational logic. As a result, some have argued that natural selection is not a mechanism, at least not according to MDC (Skipper & Millstein, 2005; Matthew & Ariew 2009; Havstad, 2011; Pérez-González & Luque, 2019; cf. Millstein, 2006, 2013).[19]

Once we grasp that there are two logics of experiment and that MDC (2000) developed their definition of mechanism to capture mechanisms in experimental biology, we can confidently identify natural selection as a typical mechanism—just not a molecular or cellular one—with only some minor modifications of the definition of mechanism (e.g., Bechtel & Abrahmsen 2005; DesAutels, 2016; Illari & Williamson, 2012). Certainly, Darwin's (1859) various terms for natural selection, such as "action," "power," and "process" can be understood as synonyms of mechanisms. Moreover, Darwin did use "machine", "mechanical", and even "mechanism" in other contexts. Unsurprisingly, most biologists since Darwin, from Dobzhansky, to Huxley and Williams, have identified natural selection as a typical (causal) mechanism (e.g., Ruse, 2005, pp. 290–299; Bell, 2008; Futuyma, 2013; Herron & Freeman, 2014). Indeed, most biologists would have found philosophers' argument that natural selection (as a phase within variation-selection-inheritance, or VSI) is not a mechanism to be extremely odd, to put it charitably (e.g., Schurz 2013).

To begin with, natural selection does have entities, activities, and interactions. Individual organisms (including their phenotypes and genotypes) and their environment are entities. Organisms' reproduction, competition, and perishing are activities. Moreover, organisms not only interact with their environments but also other organisms. Finally, entities, interactions, and activities in natural selection are also both spatially and temporally organized (Barros, 2008; Illari & Williamson, 2010). By any measure, therefore, natural selection is a mechanism.

What makes natural selection different from a typical mechanism in molecular biology is that it produces emergent outcomes at the population level, although it operates upon individual organisms (via their phenotypes and then genotypes). In other words, natural selection is a typical mechanism at the individual level but manifest itself *as if* a mechanism at the population level (Bourrat, 2019; Otsuka, 2016a, 2016b). Also, natural selection produces outcomes at the population level not deterministically but only in a *biased stochastic* fashion (Barros, 2008; Glennan,

[19] Millstein (2006; 2013) identified natural selection as "a population-level causal process", without citing Skipper and Millstein (2005). One wonders whether she has changed her mind. After all, for NMP, a mechanism always contains processes.

2009; Matthewson & Calcott, 2011, esp. pp. 752–754; Illari & Williamson, 2010; Levy, 2013, esp. pp. 109–112; Millstein, 2006, 2013; Wang, 2013; Walsh et al., 2017; DesAutels, 2016, 2018). This is why the main approach toward natural selection has been population genetics underpinned by probability theory and statistics (Brandon & Ramsey, 2007; Weber, 2005). When this is the case, the reason why the molecular and neurobiology biology-inspired MDC (2000) definition of mechanism seems incapable of accommodating natural selection as a typical mechanism at a first glance becomes quite understandable.

In this sense, populational genetics models of natural selection, with Fisher, Haldane, and Wright as their foundation, are statistical descriptions but never causal explanations of populational change, partly because they do not integrate molecular and cellular foundations from molecular genetics and cell biology, which operate mostly within the M/P logic. Matthen and Ariew (2009, p. 223) put it bluntly: "*Mathematical population genetics is, in large measure, an application of probability/frequency theory…This is why it is a mistake to think that Fisher's Theorem (or any other theorem of population genetics) describes a unitary causal process*." (Emphasis added; see also Brandon & Ramsey, 2007; Walsh et al., 2017).

Here, it should be pointed out that natural selection is only a phase within VSI. Moreover, variation, selection, and inheritance all require more specific mechanisms at the molecular and cellular level (e.g., DNA replication, mutation, meiosis, crossover, mitosis, transcription, and translation).[20]

5.2 The Hodgkin-Huxley model: a populational model in need of mechanisms

In the past decade or so, a mini-debate has been going on regarding the Hodgkin-Huxley (HH) model of membrane potential (1952c; Hodgkin & Huxley, 1952a, 1952b). On the one hand, Bogen (2005, 2008a) and Craver (2006, 2007, 2008) insisted that the HH model, as elegant and fundamental as it is, is not explanatory, at least not in the mechanistic sense. On the other hand, Pence (2017) argued that the model is explanatory but not deep, while Weber (2005, 2008) and Schaffner (2008) staked positions in-between.[21]

The HH model is a set of equations that integrate several physics and chemistry laws, including the Ohm's Law, the Coulomb's law, and the Nernest equations. According to the HH model (Hodgkin & Huxley, 1952c), the total current equation (I_m), in its simplest form, is:

$$I_m = C_m \frac{dV}{dt} + I_K + I_{Na} + I_l \tag{1}$$

[20] It is worth pointing out that the CF+I approach cannot square with VSI as the central mechanism of evolution, partly because there is no possibility of "ideal intervention" for natural selection alone, not to mention VSI as a whole. Only the NMP approach can accommodate VSI as the central mechanism of evolution. To my best knowledge, Woodward has never addressed VSI within his CF+I framework. This fact itself it quite telling.

[21] Levy (2014) seems to fault Craver for not paying more respect to the HH model. I am not sure Craver agrees. In the end, the positions of Levy and Craver did not really differ from each other that much.

In Eq. (1), $C_m \frac{dV}{dt}$ captures the capacitative current, I_K the potassium current, I_{Na} the sodium current, and I_l the so called "leakage current" by other ions.

The HH model, in its slightly more complex form, is:

$$I_m = C_m \frac{dV}{dt} + g_K\left(V_m - V_k\right) + g_{Na}\left(V_m - V_{Na}\right) + g_l\left(V_m - V_l\right) + g_l\left(V_m - V_l\right) \quad (2)$$

In Eq. (2), $I_K = g_K\left(V_m - V_k\right)$, $I_{Na} = g_{Na}\left(V_m - V_{Na}\right)$, $I_l = g_l\left(V_m - V_l\right)$, $g_K = \overline{g_K} n^4$, and $g_{Na} = \overline{g_{Na}} m^3 h$. The HH model is a populational model because "[the HH model] summarized in one neat tidy little package the many thousands of experiments done previous to 1952, and most subsequent ones." (Cole (1992, p. 151) In fact, the HH model had been perhaps the only purely population-level discovery that was awarded a Nobel Prize in physiology and medicine in the past eight decades (see Appendix 1).

Moreover, the HH model is a fitting, thus a statistical model. Hodgkin and Huxley (1952c) had detailed their efforts to fit a model to the data from thousands of experiments with many figures and tables of data, even though they certainly started with several laws in physics. Indeed, Hodgkin and Huxley (1952c) stated this fact quite explicitly and repeatedly.

> "*This is a satisfactory degree of agreement, since the equations and constants were derived entirely from 'voltage clamp' records, without any adjustment to make them fit the phenomena to which they were subsequently applied. Indeed any such adjustment would be extremely difficult, because in most cases it is impossible to tell in advance what effect a given change in one of the equations will have on the final solution*." (Hodgkin & Huxley, 1952c, p. 541; emphasis added.)

> *"The voltage clamp data obtained previously are used to find equations which describe the changes in sodium and potassium conductance associated with an alteration of membrane potential. The parameters in these equations were determined by fitting solutions to the experimental curves relating sodium or potassium conductance to time at various membrane potentials."* (Hodgkin & Huxley, 1952c, p. 543; emphasis added.)

In fact, for the total current equation to capture the results from thousands of experiments, (statistical) fitting is essential, as Weber (2008, pp. 997–998) admitted "Hodgkin and Huxley obviously fitted them to the experimentally determined curves." Notably, "while $\overline{g_K}$ and $\overline{g_{Na}}$ are empirical parameters that were directly measured by Hodgkin and Huxley, gating variables [i.e., h, m, and n] are fitted expressions." (Levy, 2014, p. 474).

Hodgkin (1964, p. 42) explicitly emphasized this exercise and its achievements in his Nobel Lecture: "*Examples of some of the properties of the axon which are fitted by the equations are: the form, duration and amplitude of the action potential; the conduction velocity; impedance changes; ionic movements; and subthreshold phenomena including oscillatory behavior*."

The total current equation is thus a fitting model, and hence a statistical summarization, of a population of observations (Bogen, 2005; Craver, 2006; Levy, 2014). Indeed, the hallmark of a statistical equation is to fit a curve to the data from a population of observations.

Understood as such, *the HH model is a statistical model within the populational logic with treatment* (its treatment being the electric shock that activates the membrane potential) rather than a model within the M/P logic, even though activating and measuring the membrane potential is done within a lab. In this sense, the HH model seems to fit with the covering law model of explanation more than the mechanistic model (Craver, 2007, pp. 49–62; see also Hille, 2001, pp. 52–53). Moreover, because the HH model did not have the crucial mechanisms (esp., the ion channels as entities in place), it is a model in need of mechanisms.

Now, some readers may object to my position that the HH model is a statistical model within the populational logic because it contains both derivative and power functions. Because the HH model captures a statistical law of thousands of experiments with membrane potential, however, it has to be a model within the populational logic. In fact, the "leakage current" term within the total current equation of the HH model is essentially the error term in a statistical model, and a hallmark of statistical model. Here, the exact mathematical form of the total current equation of the HH model, whether derivative or power functions, does not invalidate the fact that the overall equation is a fitting, and hence a statistical, model. By the same token, the fact that the HH model integrates laws from physics and chemistry such as the Ohm Law, the Coulomb law, and the Nernest equations, does not invalidate the fact that the overall equation is a fitting, and hence a statistical, model either.[22]

As a populational model, most of the parameters in the HH model cannot be interpreted mechanistically (in terms of entities, activities, and interactions), other than Na^+, K + ions, and the cell membrane. In his Nobel lecture, Hodgkin (1964, p. 1152) was also unequivocal about their lack of knowledge of the molecular foundation of the membrane potential. *"We hoped that the analysis might lead to a definite molecular model of the membrane, However, it gradually became clear that different mechanisms could lead to similar equations and that no real progress at the molecular level could be made until much more was known about the chemistry and fine structure of the membrane."* (Emphasis added.)

Unsurprisingly, Hodgkin and Huxley (1952c, p. 541) explicitly admitted their equations do not constitute an explanation: "*The agreement* [between the model and the data gathered from numerous experiments] *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…Certain features of our equations were capable of physical interpretation, but the success of the equations is no evidence in favor of the mechanism of permeability change that we tentatively had in mind when formulating them.*" (Emphasis added.)[23]

[22] I thank a reviewer for pressing me to emphasize this point with more clarification.

[23] While quoting this exactly same paragraph, Marcel Weber (2008, pp. 999–1000) has mistakenly replaced "interpretation" with "explanation".

Building upon these statements by Hodgkin and Huxley and being consistent with the NMP approach, Bogen (2005, p. 404) thus contended: "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." For Bogen, the HH model is essentially a (statistical) equation that summarize many measurements of membrane potentials but not a genuine explanation even though it contains some elements for a full explanation. At the very least, the HH model is not a sufficient or deep explanation, but a mostly phenomenal model or a shallow explanation (i.e., mechanistic sketch) with how-possible statements on possible mechanisms, *even if it may possess predictive power* (Bogen, 2005, 2008a; Craver, 2006, 2007, pp. 49–61, pp. 114–122; 2008; Kaplan & Craver, 2011).

Getting the two logics of experiment right helps us understand why a statistical law (captured in an equation) is not an explanation. A statisical law must be within the populational logic and hence does not have to contain mechanisms. As such, a statistical law does not have to be explanatory although it may be part of a full explanation with mechanisms.

Indeed, Weber (2008) could only claim that the HH model is explanatory by relying on Woodward (2003)'s claim of invariance and modularity, thus importing the populational logic. But modularity is only a component of, or a small step toward, an explanation. In fact, it is even debatable whether the HH model captures modularity (Craver, 2008). Similarly, Schaffner (2008) merely repeated Cole's (1992) argument that the HH model was a phenomenon unifier, hence a statement of regularity. Yet, regularity is not explanation: explanation needs to explain regularity (Andersen, 2011, 2012, 2018).

Likewise, Pence (2017, pp. 1181–1185) could only claim that the HH model contains explanatory elements by adopting the approach of a counterfactual-regularist (i.e., Pearl, 2009; Woodward, 2003). Yet, even Pence had to admit that the HH model did not provide a deep explanation for membrane conductance: only a model based on ion channels could. Hence, even Pence admits that the HH model, despite being an elegant correlational model, is still a shallow explanation according to the mechanistic standard.

Perhaps a final piece of evidence supporting that the HH model is not an explanation, at least not a deep one, is that the Nobel Prize for chemistry in 2003 went to the discovery of key entities and activities behind the membrane potential: Peter Agre for discovering the water channel (aquaporin) in 1992 and Roderick MacKinnon for solving the structure of the K^+-Ion channel in 1996. Only with these key discoveries did biologists come to know the central mechanisms of membrane potentials.

Finally, the making of the HH model has been anything but "ideal". The discovery of the potential and the making of the HH model had been years in the making. Most critically, the HH model had been the result of trail-and-error. *Thus, even a populational model with treatment does not necessarily entail "ideal experiment", and a key reason is that RCT with modularity is not possible with a population of heterogenous neurons*.

6 Conclusion

There are two logics of experiment in biology, medicine, and the broader natural science and social sciences. For too long, these two logics have not been explicitly differentiated and much confusion has resulted. Once we grasp these two logics, it becomes clear that the two major approaches toward causality, the NMP approach and the CF+I approach have often talked past each other because they have failed to grasp the two logics explicitly. Stating these two logics explicitly and grasping their implications therefore not only clarify important issues but also point to several issues that are worth more attention from philosophers.

For instance, while scientists working with the two types of experiment deploy counterfactual reasoning when interpretating evidence, hypotheses, and theories, they do counterfactual reasoning quite differently. As such, there is no single logic of counterfactual reasoning in science (Tang, 2025). Likewise, scientists working with the two types of experiment may approach the initial clue or sign to a potentially interesting phenomenon or puzzle. Similarly, scientists working with the two types of experiment may also assemble evidence quite differently. All these differences point to important issues for future philosophical inquiries.

As Bechtel and Richardson (1993 [2010], xx) noted, "the history of science can be approached two ways, as a reservoir of examples to illustrate a prior conception of science or as a source of insight into features of science that an adequate philosophical account of science needs to incorporate." My hunch is that most scientists would argue that the more fruitful way is perhaps the second one. While philosophers of science taking the first way have gotten some (perhaps many) things right, they almost inevitably get some things wrong, mostly critically because they try to impose an ideal structure upon the actual processes of doing science, which are almost always far messier and thus far more frustrating for scientists in the real world than philosophers could have ever imagined.

Thus, philosophers of science should take the actual processes of doing science as puzzle-solving and problem-solving more seriously (Simon, 1966 [1977]). Of course, it will be great if more scientists can contribute to the philosophy of science and make the dialogue between philosophers and scientists a more two-way affair, but I doubt this will happen any time soon.

Finally, as noted in the introduction, there are other logics of discovery in biology. Indeed, for many challenging questions in biology such as the origin(s) of the first protocell to the "last universal common (cellular) ancestor" (LUCA; e.g., Tang, 2020, 2021; Woese, 2002), the origin of the first eukaryotic cell (O'Malley et al., 2019), the origin of the first multicellular organism (Michod, 2007), and all the landmark events in the "major transitions" (Maynard Smith & Szathmary, 1995), there is no possibility of ideal or even decisive experiments. Yet, biologists have continued to pursue these fundamental questions with experiments and other means (e.g., whole genome sequencing, genomic comparison via computation, and computer simulation). Arguably, some of the most exciting progresses for these foundational questions in biology have been almost exclusively driven by whole genome sequencing and genomic comparison via computation (broadly known as bioinformatics). If

philosophy of biology takes the actual conduct of science and the actual process of scientific discoveries seriously from the standpoint of scientists, these endeavors that have received little attention from philosophy of biology in either the M/P approach or the CF+I approach should become part of philosophical inquiries, and they may well prove to be fertile grounds for exciting philosophical progresses.

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Declarations

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Appendix 1

Nobel prizes in physiology/medicine and chemistry: the dominance of the mechanism/pathway logic

Because no prizes were awarded from 1940 to 1942 (due to WWII), my account starts from 1943. I code discoveries into either those related to mechanisms or those related to other issues, according to the two rules that can be derived from the modified MDC definition (MDC 2000; Illari & Williamson, 2012). If a discovery was about entities (enzymes, antibodies, proteins, genes, hormones, viruses, cell organs), activities, and interactions, it is classified as a discovery related to mechanisms and pathways. If a discovery was not about either entities or activities/interactions, then it is not classified as a discovery related to mechanism.

From 1943 to 2023, a total of 81 years, 70 out of the 81 Prizes awarded went to discoveries of mechanisms. The only purely population-level prize was given to the Hodgkin-Huxley model. There were eight prizes awarded to medical treatments, and these discoveries at least partly reflected the populational logic. Yet even here, mechanisms have played an important role in some of these discoveries. After all, a full causal biological explanation can aid the discovery of medicine or cures for a disease, often dramatically and decisively (Thagard, 2003; Müller-Strahl 2014). Finally, one prize was awarded to discoveries in animal behaviors and another one to human evolution. Strikingly, there was not even a single prize given to population

genetics or biostatistics, even though both Fisher and Haldane were alive until 1962 and 1964 respectively, with Wright being alive until 1988.

The Nobel Prize in chemistry has an even heavier preference for mechanism. In fact, from 1943 to 2023, all 81 prizes in chemistry were divided between discoveries of mechanisms (e.g., compounds, proteins, and processes) and inventions of new techniques based on mechanisms, without a single one going to discoveries at the populational level. Moreover, a significant number of the chemistry prizes went to discoveries about the structure of biomolecules and other mechanism-related discoveries in biology, especially in molecular biology.

In fact, many statements given by the Nobel Prize committee to the Nobel laureates were explicitly about their discovery of mechanisms. All original data are available upon request.

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