Toward a more general understanding of Bohr's complementarity: Insights from modeling of ion channels

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Abstract

Some contemporary theorists such as Mazzocchi, Theise and Kafatos are convinced that the reformed complementarity may redefine how we might exploit the complexity theory in 21^{st}-century life sciences research. However, the motives behind the profound re-invention of “biological complementarity” need to be substantiated with concrete shreds of evidence about this principle’s applicability in real-life science experimentation, which we found missing in the literature. This paper discusses such pieces of evidence by confronting Bohr’s complementarity and ion channel modeling practice. We examine whether and to what extent this principle might assist in developing ion channel models incorporating both deterministic and stochastic solutions. According to the “mutual exclusiveness of experimental setups” version of Bohr’s complementarity, this principle is needed when two mutually exclusive perspectives or approaches are right, necessary in a particular context, and are not contradictory as they arise in mutually exclusive conditions (mutually exclusive experimental or modeling setups).

A detailed examination of the modeling practice reveals that both solutions are often used simultaneously in a single ion channel model, suggesting that the opposite conceptual frameworks can coexist in the same modeling setup. We concluded that Bohr’s complementarity might find applications in these complex modeling setups but only through its realistic phenomenological interpretation that allows applying different modes of description regardless of the nature of the underlying ion channel opening process. Also, we propose the combined use of complementarity and Complex thinking in building the multifaceted ion channel models. Overall, this paper’s results support the efforts to establish a more general form of complementarity to meet today’s complexity theory-inspired life sciences modeling demands.

Keywords: Complementarity; Ion channels, Deterministic model, Stochastic model; Realist phenomenology; Complex thinking;

1 Introduction

Some complexity theorists and philosophers such as Mazzocchi (2010), Theise and Kafatos (2013) have recently argued for a new way of using complementarity to reconcile opposing conceptual frameworks in biology, hoping to improve biomedical research. According to them, the concept of "biological complementarity" indicates that no single research technique or theoretical position, or modeling strategy provides a complete account of all biological entity's features. Instead, these authors hold that the principle of complementarity introduced to quantum physics by Niels Bohr in 1928 (Bohr 1928) should occupy a much more important place in modern biological research than previously thought. As they see it, complementarity, as a relatively old conceptual framework, must embrace numerous complex system features such as nonlinearity, emergence, downward causation, multifactorialism, and complex causality. These features will not have only a theoretical impact but may pave the way to new medical and environmental interventions.

The inspiration for re-introducing "biological complementarity" these authors found in quantum physics where, necessarily in a particular context, two mutually exclusive perspectives or approaches are both right and not contradictory (since they arise in mutually exclusive situations) (Holton 1988; Roll-Hansen 2000; Grinnell et al. 2002; Camilleri 2007). Niels Bohr was the first scientist to use complementarity to bridge quantum physics's conceptual framework with those used in classical macroscopic physics (Camilleri 2007; Bohr 1928; Bunge 1955a, b). Afterward, Bohr's complementarity, the most crucial foundational principle of quantum physics, inspired physicists Max Delbrück and geneticists Timoféeff-Ressovsky et al. to look for its possible use in biology (Timoféeff-Ressovsky et al. 1935; McKaughan 2005; Domondon 2006).

The search for a general form of complementarity has continued to this day, usually at the outskirts of reexamination of quantum experimentation (see, for example, Wootters and Zurek 1979), including the quantitative understanding and experimental verification of complementarity in photonics (see Weston et al. 2013). However, since 2000, there is an increasing trend in the number of papers discussing this principle from the point of view of the latest experimental physics research findings, according to a quick survey through PubMed, Scopus, Web of Science, and Google Scholar.

A little part of the project was to describe the epistemological implications of the general form of complementarity. For instance, Adolf Grunbaum (1957) argued that the resolution of the determinism issue in light of physical theory ought to include a philosophical appraisal of the principle of complementarity and its generalization. Patricia J. Doty (1958) warned against applying generalized complementarity to what she calls secondary, less precise sciences (biology, psychology) at all cost, simply because this principle can mislead us to draw erroneous conclusions and explanations. On the contrary, Nathan Brody and Paul Oppenheim (1969) defended certain parallels between epistemic viewpoints on the mind-body problem and Bohr's epistemic views in physics. One of the more recent critical intellectual breakthroughs in this field is the realist phenomenological approach introduced by the philosopher Towfic Shomar (Shomar

2008, 2020). This fresh perspective strongly argued against a longstanding instrumental and vague "classical" realist understanding of complementarity.

However, to our knowledge, studious reflections on the possibilities of applying this principle in biology and medicine were rare in the second half of the 20th century. Among the occasional attempts is the one done by biologist Howard H. Patte, who argued that complementarity in biology has two significant expressions. One of them is structure-function dualism, and the other concerns the relationship between genes and phenotypes (Pattee 1978). However, things changed at the beginning of the 21st century as there has been a few attempts to revive "biological complementarity". This increased interest coincided with the growing adoption of the complex systems view of life.

Mazzocchi (2010) and Theise and Kafatos (2013) made a noteworthy attempt to re-actualize complementarity, mainly on the outskirts of their conceptual assessment of complexity-inspired biomedicine. The shots of these authors to reappropriate "biological complementarity" were, in the first place, epistemologically motivated but did not, however, exclude the potential that this conceptual tool has to offer when it comes to effective post-reductionist biomedical research practice. We hold that the motivation behind the profound re-invention of complementarity needs to be corroborated with solid empirical pieces of evidence. However, concrete examples from actual research were missing to test the possibilities and limits of complementarity in biology, biomedicine and neuroscience. Neuroscience is the perfect field for confronting the principles of complementarity and modern research practice. On the other hand, various theoretical principles such as complementarity are needed to ensure brain research data's reliability, legitimization, and reproducibility. Therefore, whether, how and, more precisely, to what extent this principle may stimulate and facilitate modeling experimentation in neuroscience and related biomedical fields requires further clarification.

On the other hand, simultaneous exploitation of conceptually distinct modeling strategies is quite a common practice today. For example, understanding ion channel activity in neuronal signal propagation pretty much requires the combined use of deterministic and indeterministic solutions, even in the same model (Guckenheimer and Oliva 2002; Austin 2008; Roy and Llinás 2009). In that sense, it is unclear whether neuroscientists could use complementarity to improve their research on neuronal signal propagation, especially considering the longstanding opinion that this principle can only be applied to mutually exclusive experimental or modeling setups.

In this essay we contend that, instead of the "mutual exclusiveness of experimental setups" perspective, scientists and philosophers could exploit phenomenological realism to appropriate Bohr's complementarity principle to meet ion channel modeling demands. Also, our goal is to discuss some empirical shreds of evidence from a biological domain that indicate a more general form of complementarity. This paper aims to move beyond discussions of complementarity's theoretical value and evaluate this principle significance to neuroscience from a purely practical perspective. The following discussion will begin by exploring some historical aspects of introducing complementarity to quantum physics and biology. The third section introduces readers to the deterministic/stochastic conceptual foundation of ion channel modeling.

The fourth section will discuss the examples that best reflect the current tendencies in these channel models. Finally, in the fifth section, we will answer whether Bohr's complementarity can be used at the ion channel modeling outskirts. This discussion will enable us to make detailed and general comments, conclusions, and recommendations concerning the usefulness of complementarity for managing computational neurophysiology practice.

Before proceeding, we want to stress that our goal in this paper is not to present a new account of complementarity neither for physics nor biology or neuroscience. Nor is our goal to criticize its long theoretical reach in these disciplines. Instead, here we want to suggest how actual neuroscientific practice, or some parts of it, could become accessible for deploying this principle. This realization probably opens the doorway for further substantial revision and re-conceptualization of "biological complementarity".

2 The historical and current reflections on complementarity: From physics to biology

It is quite a daunting task to discuss complementarity either from a philosophical or scientific perspective. As rational beings, we have an inner need to look for reasons why some things, concepts, and phenomena go hand in hand while others do not. Perhaps from such a constellation of our mind, the idea of complementarity was born. We can only speculate when precisely this happened. But what we know with great certainty is when complementarity found its place in science. Inspired by the paradoxical dual nature of the light as wave or particle depending upon the research method applied, Niels Bohr first publicly announced his view of complementarity in quantum mechanics (QM) in 1927 Congress of Physics held in Como, Italy (Bohr 1928; Holton 1988; Grinnell et al. 2002; Saunders 2005; Camilleri 2007). According to Bohr, complementarity should characterize the connection between the data obtained under different experimental conditions and may be interpreted pictorially only based on mutually exclusive concepts (Bohr 1928; Holton 1988; Vol'kensheten 1988). For as Bunge (Bunge 1955a, p. 2) observes:

> Owing to the fact that complementary aspects are mutually exclusive, it is impossible-thus Bohr argues -to afford a single well-defined picture of atomic phenomena, being on the other hand, indispensable to split the image of reality into two complementary models, or pictures, which can be applied in succession, never simultaneously in all rigor, and this simply because the aspects covered by each model are not simultaneously observed.

Bohr's scientific appropriation of complementarity was probably under the influence of German idealistic philosophy. For instance, Roll-Hansen (2011) and Sloan (2012) argued that Bohr's physics and philosophy of science could be traced back to Immanuel Kant's analysis of biological teleology in the second half of the *Critique of the Power of Judgment*. To be more precise, Roll-Hansen contends that it is likely that Harald Høffding's historicized Neo-Kantianism influenced Bohr's philosophical thought. According to Sloan (2012), this is still a highly debatable fact as it is not entirely clear how Bohr developed his views—whether from readings and discussions with his philosophical mentor Harald Høffding, or his reading of Kant or other sources, or directly from his reflections on these matters. Anyway, how Kant discusses and resolves Teleological Judgment's antinomy in the central sections of *Dialectic* has shown scientists and philosophers how they should treat conceptual contradictions in both science and philosophy. The apparent opposition between a mechanistic and teleological explanation of organisms in the manner Kant encountered these in the late eighteenth century - Cartesian-inspired biological mechanism, Stahlian vitalism, Leibniz-Wolffian teleomechanism, and Spinozistic hylozoism - lies in the heart of this *antinomy* (Sloan 2012). We are not going deeper into this subject, but it is possible that German Idealistic philosophy inspired Bohr to seriously start using this principle for scientific purposes.

On this philosophical trail, it might be said that complementarity as a method of "description" uses two or more mutually exclusive concepts of a specific realm (classical physics) to explain a phenomenon of another domain (quantum physics) that cannot be entirely defined by any one of these concepts (Bunge 1955a; Pan-Chiu 2002). In other words, the principle of complementarity does not contradict the longstanding Aristotelian philosophical insight that a "mutually exclusive nature cannot coexist within the same entity at the same time" (Park 1967; Pan-Chiu 2002). In contrast, Theise and Kafatos (2013) maintain that there is also an ontological level of Bohr's understanding of complementarity as he believed that the complementarity that was inherent in experimental research of the quantum world was a reflection of a more universal and fundamental complementarity, one that reflects in biological systems.

Many consider complementarity as Bohr's most significant contribution to the interpretation of QM. Some of Bohr's contemporaries, such as Pauli (Camilleri 2007), suggested that modern quantum theory should be called the "Theory of Complementarity". Others, such as philosopher and physicist Mario Bunge (Bunge 1955b), criticize Bohr's subjective-idealistic causal interpretations of complementarity-based QM (Copenhagen interpretation). He has argued that the usual understanding of QM is neither the only possible rational one nor agrees with scientific materialism but is consistent with the Berkeleian theory of knowledge. At first (in the introduction to the Como lecture), Bohr's idea was to use complementarity to deal with stationary states problems. He did not intend to use complementarity to deal with mutually exclusive experimental arrangements – this foremost moment scholars have tended to ignore (Camilleri 2007). In this vital lecture that changed the face of physics and science, Bohr employed complementarity to discuss the relationship between the atom's stationary state, characterized by its energy, and the determination of the electron's position in space at a given time (Camilleri 2007). For example, a free particle, e.g. an electron, may also be used to demonstrate the use of the principle of complementarity (Pan-Chiu 2002). It is well-known that "wave" and "particle" are mutually exclusive concepts in classical physics. According to the knowledge obtained in optics and electromagnetics, reflection, refraction, diffusion, and interference are recognizable characteristics of waves.

In contrast, a particle occupying a specific space in or around the atom does not possess these characteristics. Furthermore, physicists noticed that in some experiments light "behaves" like a wave. In contrast, in others, it behaves as a particle, thus suggesting that the concepts of classical physics ("wave" and "particle") cannot adequately explain the quantum world. For this reason, some physicists suggested abandoning the use of these concepts in the quantum realm (Pan-Chiu 2002). However, contrary to this view, Bohr insisted that we should keep them no matter how hard it would be to explain quantum phenomena in terms of classical physics (Pan-Chiu 2002).

Furthermore, the application of complementarity in quantum physics requires the implementation of mutually separate experimental arrangements. Indeed, according to Camilleri (Camilleri 2007, p.518), a good connoisseur of Bohr's work, it was only after 1935 Bohr would emphasize that in quantum mechanics (Bohr 1937, p. 293):

> We [must] use two different experimental arrangements, of which the only one permits the unambiguous use of the concept of position, while only the other permits the application of the concept of momentum, defined as it is solely by the laws of conservation.

Over the years, Bohr's view of complementarity evolved. While at first complementarity was seen through primary epistemological lenses, during the 1930s, Bohr moves on to consider the use of complementarity in solving the research problems of science (Bohr 1937; McKaughan, 2005; Domondon 2006). This paradigm shift coincided with Bohr's influence on a radical change of view about living organisms and biology during the '30s and '40s. He was one of three (the other two were Max Delbrück and Erwin Schrodinger) physicists involved in establishing molecular biology (Domondon 2006). He had a compelling scientific and philosophical influence on the development of Max Delbrück's view of complementarity. In particular, Niels Bohr's 1932 "*Light and Life*" lecture shaped his lifelong search for a form of complementarity in biology (McKaughan 2005). Max Delbrück, in collaboration with geneticists Nikolai Timoféeff-Ressovsky, and radiation physicist Karl G. Zimmer, published an article entitled "*On the Nature of Gene Mutation and Gene Structure*", also known as Three-man paper (3MP) in 1935 (Timoféeff-Ressovsky et al. 1935). We believe that some scholars read this paper as a contribution to the reductionist project in science and molecular biology development. Still, a careful reading reveals that the authors suggest two different ways of viewing biological processes. While the first analyzes the organism and its processes in parts and in isolated laboratory settings, the second way, at least heuristically, sees these processes as integrated and complimentary events crucial to the organism's functioning as a whole (McKaughan 2011).

In subsequent decades, undoubtedly, complementarity inspired scientists and philosophers to seriously reconsider our comprehensive understanding of reality in its entirety. Thus, besides in the natural and social sciences (Roll-Hansen 2000; Grinnell et al. 2002; Marchionni 2008; Theise and Kafatos 2013) and social ecology (Alrøe and Noe 2016), this principle fuels debates in theology and philosophy of religion (Pan-Chiu 2002). Complementarity has been and still is in the focus of physicists and philosophers of physics.

Even in quantum-mechanical discussions, philosophers and physicists have emphasized the need for a general form of complementarity (see, for instance, Wootters and Zurek 1979). In the context of establishing a broader form of complementarity applicable outside physics, the discussion between instrumentalists (see, for instance, Faye (2012) and realists (see, for example, Folse 1985) is particularly significant (Shomar 2008). Recently, as noted in the introduction section, philosopher Towfic Shomar (2008, 2020) made a considerable effort to establish a general form of this principle. Shomar holds that the apparent confusion between instrumentalists and realists, which prevents the extensive use of complementarity throughout scientific practice, arises because philosophers fail to recognize Bohr as a realist of a particular kind. Unlike instrumentalist and "classical" realist accounts, the realist phenomenology considers this principle outside the limits of "mutual exclusiveness" in a more "bottom-up" experimental spirit. For as Shomar observes (Shomar 2020, p. 406):

> "The notion of complementarity covers three levels of scientific practice: (1) the mutual exclusion of two experimental setups, (2) the mutual exclusion of modes of description, and (3) the mutual exclusion of pictures (the ways nature is revealed to us) combining, in the quantum system, the two classical properties of elementary particles: waves and particles."

Furthemore, Shomar (2020) suggests that these three levels can be related to the elements needed to build a phenomenological model. However, although Bohr initially did not have available the mathematical equipment required to build a model, he later found this in Heisenberg's uncertainty principle. Notably, a phenomenological model, according to Shomar, consists of (Shomar 2020, p. 406):

> "1) a low-level mathematical representation; 2) a story which can relate such low-level mathematical representation with the real elements of the phenomena; and 3) some boundary conditions. These components can be expressed in the case of complementarity as follows: 1) the uncertainty principle is the mathematical base for complementarity; 2) Bohr's elaborate story of the necessity of using classical language, leading to the idea of complementarity; 3) the quantum of action and the resulting but uncontrollable interaction with the measuring instruments that set the boundary conditions of each individual phenomenon.

In this regard, any theoretical description in Bohr's view, continues Shomar, if it should be accepted as a representation of the phenomenon, and not as a tool, ought to be built on a "bottom-up" approach. In other words, experiments and experience should be the foundation of any theoretical description, rather than a "top-down" approach commonly used by, for example, Albert Einstein and other hardcore theoretical physicists. We can only speculate how Bohr came to this understanding; perhaps his lifelong interest in experimental physics and biology helped him in the process.

Unfortunately, aside from Bohr, Max Delbrück, and a few other philosophers, particular interest in using complementarity in biology and medicine faded away for most of the second half of the 20th century (Theise and Kafatos 2013). However, as already indicated, at the beginning of the 21st-century, Mazzocchi (2010), Theise and Kafatos (2013), complexity thinkers and scientists, re-actualized the possibility of using this principle in complexity-inspired biomedical sciences.

In their view, complementarity should be readmitted and reconceptualized from the ground to articulate distinct viewpoints and research strategies found in the biological domain. Nonetheless, they contend that complementarity may resolve many current biological theory problems, including the relationship between proximate and ultimate causes, analysis, synthesis, noise, the epistemology of complexity, etc. Mazzocchi even considers complementarity as a general epistemological principle, which can compensate for the human perceptive, communicative, cognitive, and linguistic limits. In science, claims Mazzocchi (Mazzocchi 2010, p. 343):

> An epistemology that incorporates the notion of complementarity should be able to overcome the idea of an all-inclusive representation and acknowledge the several viewpoints and distinct levels of explanation that might be required for the understanding of a given phenomenon.

For Theise and Kafatos (2013), biology and medicine should rely more on describing the multilevel interactions between system constituents, working together in complementary relationships similar to quantum physics situations. Thus, in addition to Mazzocchi's epistemological considerations of complementarity in biology, they began and concluded within what Bohr labels, in the context of physics, an ontological dimension of complementarity: (Theise and Kafatos 2013, p. 19):

> As limits of knowledge or horizons of knowledge are approaches, through the application of nonlinearity in complexity theory, complementarity will be viewed as a fundamental cornerstone and necessity of life itself.

In this sense, we could even call Theise and Kafatos' stance as being "ontological" or perhaps "optimistic". An optimistic view here is opposed to the skeptical view about the human mind's limited capacity to explain the extraordinary complexity of the living world. Limited cognitive and computational abilities, which prevent us from identifying in the biological domain universal laws such as in physics or chemistry, interfere with a profound understanding of complex biological systems. In this light, the search for conceptual tools, which can help us think more efficiently about biocomplexity, is the holy grail of post-reductionist complexity-inspired science. One of these tools is complementarity, whose relevance for today's research and clinical interventions need yet to be proven.

So far, discussions seem to support the idea that the general form of complementarity might be central to a better understanding of biocomplexity. However, biology, medicine, and neuroscience are primarily practical sciences. Therefore, complementarity must find a strong refuge in both "classical" and automated experimentation (modeling) as the two most important means of interacting with biological systems (for an overview of automated experimentation, see

Radder 2009). We do not think that even the first steps have been taken to strengthen this principle's use in daily research. In particular, the use of this principle has not been examined from the aspect of modeling the activity of some of the molecular components of the brain, such as ion channels.

Moreover, assessing this principle's use-value in biomedicine requires thorough verification and validation within complex and diverse biomedical research practices. This practical verification is an essential pre-step underlying the introduction of this principle to complexity-inspired biomedicine. However, confronting complementarity with the real-life biomedical lab is missing in the literature.

3 Rethinking the fundamental assumptions of ion channel behavior

Classical and quantum physics should provide an explanatory framework for studying biological systems (Koch and Hepp 2006). But there is a catch. These two significant contemporary physics areas stand at the opposite spectrum of our most profound understandings of nature. For example, classical physics is often associated with determinism, while quantum mechanics is fundamentally indeterministic (Koch and Hepp 2006). Also, this means that the brain's physiology might utilize both deterministic and indeterministic principles. But the big question is whether the available empirical knowledge about brain behavior supports this reasoning.

According to young and still controversial quantum neurobiology, the central nervous system (CNS) quantum processes determine the diverse brain functions such as consciousness, memory, subjective experiences, and the processes of choice and decision-making (Tarlaci and Pregnolato 2016; Jedlicka 2017). It is also thought that experimental and theoretical focusing on the determinism/indeterminism issue should give us a clue whether the brain operates according to deterministic principles or perhaps is subject to chance events or stochasticity (Weber 2005). These insights, among other things, questions the validity of experimental and computational approaches in detecting quantum phenomena starting from the molecular level to the whole-brain functioning.

Marcel Weber (2005) introduced two methodological means used to test the brain's quantum indeterministic behavior. The first approach is based on the grounds of theoretical QM considerations relevant to neurobiological processes. The latter uses proper experimental knowledge about the brain. In the first strategy, we should prove that QM processes are directly responsible for significant biological phenomena. For example, he cited Robert Brandon and Scott Carson's scenario where the fate of an entire bacterial population might depend on a single mutational event. A fundamental assumption in this example is that a DNA mutation can be subject to quantum indeterminism.

In the other approach, the brain's quantum behavior is sought in the empirical facts about the CNS's functioning. Weber's argumentation to justify this second approach seems to lie in the fact that experimental neurobiology appears to be exciting for several reasons. First, the logical structure of the argument is based on a physicalistic understanding of supervenience. According to this understanding (Weber 2005, p.666), “any change in an organism’s mental or biological properties requires a concomitant change in its physical properties”. Second, the critical point of Weber’s argument is that if supervenience holds, then for a biological process to show intrinsic stochasticity or indeterministic behavior, it must be based on stochastic microphysical (biomolecular) processes. Molecular realizers such as photoreceptors, pre-and postsynaptic receptors, the voltage- and ligand-gated ion channel, and molecular diffusion processes are perhaps the only molecular sources of macroscopic biological stochasticity (Weber 2005). In other words, the observed stochastic behavior of these molecular components and processes underpins the brain’s quantum indeterminism.

Are there hard shreds of evidence to suggest the indeterministic behavior of particular molecular processes in nerve cells, including ion channel activity? So far, many neuroscientific papers have described what appears to be physiologically appropriate stochastic behavior of complex neural processes, including neurotransmission and action potential (AP) generation (Roy and Llinás 2009; O’Donnell and Rossum 2014; Kavalali 2015; Epstein et al. 2016). For instance, based on relevant scientific findings, Kavalali (2015) noted that spontaneous neurotransmission has an autonomous role in interneuronal communication, quite distinct from AP-induced release. The critical macromolecular machinery underlying presynaptic neurotransmission is the cytoskeleton of the presynaptic neurons. In 1994 Penrose (Penrose and Hameroff’s hypothesis) proposed that the microtubules, filamentous protein polymers that form the cells’ cytoskeleton, implement quantum computations (Penrose 1994; Weber 2005; Koch and Hepp 2006). Indeterminists often cited this hypothesis to prove the quantum nature of neurotransmitters release (Weber 2005; Koch and Hepp 2006). However, according to current knowledge, the cytoskeleton is involved in delivering vesicles to the synapse, not in the neurotransmitters’ release mechanism (Weber 2005; Kavalali 2015). Indeed, the presynaptic active zone recruits and docks synaptic vesicles loaded with specific neurotransmitters to their future sites of release, close to highly-localized presynaptic calcium channels (Wong and Kaeser 2014). To make things even more complicated, synaptic terminals can release neurotransmitters randomly in the absence of stimuli due to low-probability conformational changes in the vesicle fusion machinery (Kavalali 2015). Besides, extensive scientific studies reveal differences in release probability between different synaptic vesicles within the same presynaptic axonal terminal (Körber and Kuner 2016). All these findings indeed cast doubts on Penrose and Hameroff’s quantum hypothesis.

One of the most considerable arguments cited to support the thesis of quantum neuro-indeterminism comes from the apparent stochastic behavior of neural ion channels, which underpins AP generation and propagation. For example, Roy and Llinas (2009) argued that the Nelson process (the time-reversible Markov process associated with Schrödinger equation) used to describe ionic channel permeation could, indeed, be considered an intermediate between quantum and classical time reversible processes. In principle, the voltage-gated sodium (Na^+) and potassium (K^+) ion channels underlie AP generation and propagation in neurons. However, scientists are firmly convinced that many other channels, including other voltage-gated channels, regulate the physical characteristics of AP, including the response to synaptic input (Milescu 2015). Some modeling studies suggest that ion channels' stochastic noise is, directly or indirectly, responsible for spontaneous AP (spike) generation, information processing, spike time reliability, firing irregularity, etc. (O'Donnell and van Rossum 2014; Goldwyn and Shea-Brown 2011). This random stochastic fluctuation appears in the absence of neurotransmission and subsequent voltage changes across membranes. Yet, experimental and theoretical neuroscientists still disagree on how noise affects single neuron dynamics and which ion channel type is primarily responsible for its occurrence (O'Donnell and van Rossum 2014). At this time, we can only speculate how far we are from understanding the implications of stochastic ion channel fluctuations on integrative brain behavior.

Nevertheless, indeterminists cite these data to support their thesis that single-channel quantum behavior directly affects the brain's higher functions. Overall, the use of neurochemical transmission and ion channel behavior data as arguments for QM-based neurobiological indeterminism is not as promising as it seemed at first glance (Weber 2005; Koch and Hepp 2006). In the following passage, for example, Koch and Hepp summarize this skepticism (Koch and Hepp 2006, p. 611):

> Two key biophysical operations underlie information processing in the brain: chemical transmission across the synaptic cleft, and the generation of action potentials. These both involve thousands of ions and neurotransmitter molecules, coupled by diffusion or by the membrane potential that extends across tens of micrometers. Both processes will destroy any coherent quantum states. Thus, spiking neurons can only receive and send classical rather than quantum information. It follows that a neuron either spikes at a particular point in time or it does not, but is not in a superposition of spike and non-spike states.

This section's discussion is very important for understanding the physical (quantum) nature of neurobiological processes. However, considering that our focus here is on modeling strategies to explain nerve cell behavior, we should examine in more detail if and how computational models of ion channel activity simultaneously incorporate deterministic and stochastic solutions in their core.

4 Promises and difficulties in ion channel modeling

Thanks to the progress made in experimental, computational, and mathematical neuroscience, much of the attention in brain research has been paid to understand how neurons process information (Koch and Schutter 1999; Scott 2007). However, less attention has been paid to understand how these growing interdisciplinary efforts at the intersection of biology, physics, mathematics, computational science, and chemistry may be used to test the practical usefulness of recently rediscovered theoretical principles such as complementarity for neuroscience. This specific research domain may answer whether it is possible to use Bohr's complementarity in daily research or whether philosophers and scientists should continue to insist on its reformulation in biomedicine.

As we have already seen, according to the “mutual exclusiveness of experimental setups” form of Bohr’s complementarity, when the experiments involve mutually opposed concepts, it makes sense to use this principle only to concepts belonging to or arising from the separate experimental occasions. For this reason, according to this narrow view, we speculate, it is impossible to use this principle in the same model if that model combines two extremely opposing conceptual frameworks, such as determinism and stochasticism (indeterminism). A more detailed analysis of the research practice and relevant modeling results will confirm or reject our thesis.

Both stochastic (indeterministic) and deterministic models are currently used in modeling ion channel activity. Many of these models have been proven suitable for certain aspects of ion channel behavior. Below we will mention only some of the most critical models. The most common indeterministic model is the aggregated continuous-time Markov process with discrete states (Goldwyn et al. 2011; Epstein et al. 2016). A Markov model describes the dynamics of biological processes quantitatively by assuming that a set of discrete states transits through time from one state to another (Linaro and Giugliano 2015). It is believed that Markov chain models can successfully describe stochastic spiking activity (Goldwyn et al. 2011). But before Markov chain models were introduced, the dominant cellular neurophysiology model was the Hodgkin-Huxley (HH) model of nerve excitability. When the HH model was proposed in the 1950s, it failed to capture ion channel noise fluctuations and a far more complex (and higher-dimensional) description of channels’ chaotic behavior (Goldwyn and Shea-Brown 2011). In the last decades, tremendous efforts have been made to revise the canonical HH model in the light of deterministic chaos theory. Goldwyn and Shea-Brown (2011) argued that many of these approaches produce quantitative errors compared to physic-chemical kinetic equations; These equations are the natural setting for describing conductances and thus a perfect tool for predicting fluctuations in conductances and stochasticity in the resulting AP. Although the dominant effort is to bridge the HH model and chaos theory, some researchers continue to devise stochastic solutions in the HH model. For instance, Ronald Fox (1997) extended the HH equations to include stochastic solutions.

It is important to note that the models and modeling strategies might give us a clue to assess whether neurons and, ultimately, the brain behaves deterministically or indeterministically. For instance, Marcel Weber (2005) argued that the experimental evidence to prove neurobiological indeterminism fails because both deterministic and indeterministic models can account for ion channels’ empirically observed behavior. Indeed, the use of nonlinear modeling negates the idea that ion channels operate exclusively by chance events. Also, it was shown by many studies that the slight variation of initial nonlinear model parameters might result in the unpredictable behavior of these channels (Guckenheimer and Oliva 2002; Mendonca et al. 2016). To illustrate this point, let us look at the following example. In addition to the direct effect of stochastic channel noise, specific nonlinear deterministic processes underpin the time-dependent irregular spiking activity of cortical neurons (Mendonca et al. 2016). It depends on the nonlinear interaction of the particular potassium ion channel Kv4 with sodium ion channels around the action potential threshold (Mendonca et al. 2016). However, a literature survey suggests that most synaptic integration models based on ion channel activity appear to be deterministic (Dudman and Nolan 2009). Besides, Guckenheimer and Oliva (2002) demonstrate a previously unknown aspect of the HH model: unstable, chaotic solutions, even with its original parameters.

On the contrary, Austin (2008) demonstrated the consistency of the deterministic and stochastic processes predicted by the HH model. He shows that in a suitable limit, as the stochastic components of the stochastic model increase and their contributions decrease, they converge to the trajectory predicted by the HH model's deterministic equations. In a more general way, Steinmetz, Manwani and Koch express observed consistency and convergence between stochastic and deterministic predictions of the HH model (Steinmetz et al. 2001, p. 91):

> The stochastic Markov version of the HH model converges to the classical, deterministic model as the number of channels grows large, but for realistic channel numbers, the stochastic model can exhibit a wide variety of behaviors (spontaneous spiking, bursting, chaos, and so on) that cannot be observed in deterministic model.

These findings support the idea that both deterministic and probabilistic aspects of ion channels' behavior can be represented in single neurons' information processing model. Thus, Austin's model that includes both stochastic and deterministic processes can provide much better and more detailed predictions of how ion channels generate and modulate AP. Steinmetz, Manwani and Koch (2001) also defend the advantages of combining deterministic and stochastic models in predicting ion channel activity. Moreover, deterministic and stochastic solutions offered by the reformed HH model could be used, among other proofs, to test the applicability of Bohr's complementarity to some ion channel modeling efforts. We will return to this problem later in section 5.

There are other advantages of nonlinear deterministic models in explaining the empirically observed behavior of ion channels. The ion channel interactions with the nerve cell's multimolecular machinery and the preexisting functional status of pre-and postsynaptic terminals are two critical events that may cause changes in their activity. Now, this claim is substantiated by many research studies. For instance, researchers reported that clustered patterns of spikes (AP), as a part of the stochastic model of stellate neurons (inhibitory neurons found in the cerebellum), are driven by activation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Dudman and Nolan 2009). To simplify, the previous activation of HCN channels increases the likelihood of subsequent AP generation and propagation in stellate neurons. HCN channels are activated by membrane hyperpolarization; they are permeable to Na^+ and K^+ ions, and their activation is facilitated by cyclic adenosine monophosphate (cAMP) (Benarroch 2013). This contradicts stochastic Markov models, which assume that ion channels are memoryless, dependent only on the current state and not on past events (Kispersky and White 2008).

Besides, there is a problem with the efficiency and predictability of both deterministic and indeterministic models. Due to all nontrivially interacting components of nerve cells and preexisting physiological conditions, it is also challenging to describe ion channel dynamics in a broader sense. In short, it is the biological context or boundary conditions that significantly complicate the modeling of the physiological processes. These deterministic and indeterministic simulations may give good predictions about some aspects of ion channel gating dynamics and individual neuronal computations. Still, they fail to reproduce all the critical contextual factors (boundary conditions) that may affect the behavior of single neurons and macroscopic neural networks, including top-down information processing in the brain (Herz et al. 2006; Gerstner et al. 2012). Considering that the brain is a nonlinear dynamical complex system with many feedback loops, its mathematical modeling and representations are challenging (Scott 2007; Jedlicka 2017). Many representative models, such as Austin's improved deterministic HH model, ignore possible external effects acting upon axons. Austin (2008) wonders whether this convergence between stochasticism and determinism is sustainable when many stimuli are projected on that same axon. More specifically, Austin raises the question of what would happen with convergence when the signals arrive from the soma along the axon or a trans-membrane current along the axon's length because these stimuli could be deterministic or stochastic. He concludes that one could expect that the stochastic model converges to his improved deterministic HH model's trajectory in the former case. In the case of stochastic stimuli, even the limit model would have stochastic components. Therefore, as already mentioned, Austin's model can resolve many possible scenarios and give better predictions. However, what happens when many integrated stimuli that arrive in a more extended period are considered or when numerous cellular mechanisms modulate ionic activity? It is known that many networks of complex signaling pathways (for instance, G-protein coupled receptor signaling cascades) are involved in axonal voltage-gated ion channel modulation that, in return, affect AP initiation and propagation, and thus the release of neurotransmitters (Burke and Bender 2019).

Precisely, this challenge questions the entire epistemological and technological infrastructure available today to interact with the repertoire of ion channel different dynamic states, including their interactions with the cellular mechanism which regulate their activity. In this case, scientists would need supercomputers and considerable resources to model these bonding interactions. In philosophical terminology, perhaps the concept of *epistemological probabilism* can best describe this situation. Accordingly, neuro-indeterminism arises when we fail to explain the interactions between billions of neurons and an even more significant number of their molecular constituents, including ion channels (Weber 2005). Epistemological probabilism reflects our limited cognitive and computational capacity to study the brain as the most complex structure in the universe (Weber 2005). Perhaps, if this account of probabilism is correct, then indeterminists might lose ontological support for their views. In the absence of cognitive and technical solutions to deal with complex interactions between the brain's constituents, we will hardly distinguish the *ontological probabilism* woven into the very fabric of space and time from the epistemological one that results from our limited ways of interacting with the brain. If, by any chance, we succeed in discerning between our cognitive limitations and the laws of nature "independent from us", then we could give a more precise answer to this question. However, these issues go deep into the realm of scientific realism, which we will not discuss here because that is not our goal. Our cognitive (in)ability to understand complex brain dynamics has a significant share when deciding between determinism vs. indeterminism and corresponding modeling strategies. Also, resolving the determinism/indeterminism distinction would be hard to imagine without questioning the effectiveness and validity of ion channels' computational models.

To sum up, judging from the above considerations, neuroscientific research often requires integrating distinct modeling solutions in the same model. More precisely, the modeling representation of the same phenomena, such as ion channel activity, needs deterministic and stochastic approaches to ensure predictability, validity, and objectivity. This recognition leads us to ask ourselves how to accommodate these opposing modeling strategies to ensure a smooth research process. Perhaps, complementarity may seem like an excellent means of achieving this goal. However, we fear that complementarity might not be up to this task if used and interpreted only through the "mutual exclusiveness of experimental setups" form.

5 Complementarity in ion channel modeling?

The question remains: What about using complementarity for closing the gap between deterministic and indeterministic strategies used in ion channel modeling? What are the above examples telling us?

According to Bohr, we need complementarity in a situation when two mutually exclusive perspectives or approaches are both right, necessary in a particular context, and not contradictory as they arise in mutually exclusive conditions (mutually exclusive experimental setups) (Bohr 1928; Bunge 1955a; Holton 1988; Roll-Hansen 2000). The deterministic and stochastic modeling solutions used in cellular neurophysiology are both right and necessary in a particular context. However, their combined use quite often occurs in mutually nonexclusive situations, in a single experimental arrangement. This observation contradicts the narrow understanding of complementarity we provide at the beginning of this paper. The main reason for this notion is that some scientists and philosophers consider complementarity a "top-down" tool to deal with mutually exclusive experimental arrangements in quantum physics (see Shomar 2008). As Bunge noticed, when we have an experimental setup for determining one feature, we destroy the possibility of setting up a complementary experimental arrangement that would allow us to assess its conjugate attribute (Bunge 1955a). In the meantime, scientists have discovered that ion channels' measurable activity can, to some extent, exhibit quantum behavior. However, these quantum effects are still somewhat "lost" in the cellular environment and "masked" by deterministic macroscopic processes. For this reason, it is sometimes necessary to assume the deterministic and indeterministic behavior of ion channels in the same experimental condition. Bohr could not have had such knowledge at the time when he introduced complementarity to physics and science.

On the contrary, our study shows that quite often, mutually opposed experimental (modeling) arrangements in neuroscience are not separated. More precisely, there are cases when deterministic and indeterministic models are used separately. Still, ion channel researchers do not hesitate to simultaneously use opposing deterministic and indeterministic solutions in the same model. To corroborate this statement, let us remind ourselves of the Mendonca et al. (2016) paper. These authors confirmed that a model that accounts for stochastic noise in ion channels could be nicely combined with models describing nonlinear deterministic processes of irregular spiking activity of cortical neurons. Therefore, two opposite models are used to predict macroscopic spiking activity produced by the operation of thousands of ion channels. Furthermore, attempts to prove the consistency of chaotic and stochastic aspects of the improved HH model by Guckenheimer and Oliva (2002) and Austin (2008) also support our claim that two utterly different conceptual frameworks could be combined in the same modeling setup. However, from our examples, we have also seen that even this versatile and integrative modeling practice is not enough sometimes to provide us with a thorough understanding of the molecular physiology of ion channels, mainly when the function of these channels is observed in a broader biological context.

The simultaneous use of conceptually distinct and opposed models in computational neurophysiology, which are expected to be used in entirely different and separated experimental settings, is becoming neuroscience's daily practice. In other words, many models of ion channel activity combine deterministic and stochastic solutions, quite the opposite of how Bohr perceived quantum experimentation in the '20s and '30s. Seemingly from Bohr's "mutual exclusiveness of experimental setups" perspective, it would not be possible to consolidate a single experimental arrangement that would simultaneously determine mutually opposed global attributes of ion channel behavior. More precisely, the combined use of deterministic and indeterministic solutions in the same experimental or modeling setup would result in a contradiction. But based on the above examples, this obstacle in no way interferes with researchers' determination to use both solutions in the same ion channel activity model.

Moreover, thanks to Shomar's (Shomar 2008, 2020) "bottom-up" realist phenomenological approach, Bohr's complementarity can be deployed to present a descriptive account of ion channel activity using two mathematical models. As Bohr says: "regardless of what is the reality of the 'objects-out-there', the reality that we can account for is that of two descriptions that can be presented in a complementary way". Shomar's realist position set aside "mutual exclusivity of experimental setups" as the only correct interpretation of Bohr's complementarity. In fact, without going into whether the "objective" nature of the opening of ion channels is stochastic or deterministic, the practice of modeling these channels suggests that there is no mutual exclusion of modes of description of their activity. Thanks to realist phenomenological understanding, we think it is possible to go beyond the "mutual exclusivity of experimental setups" version of complementarity that limits its applications in our case. This notion is fundamental considering that one crucial research area of complexity-inspired biology, "bottom-up" systems biology, has incorporated modeling and reconstructing higher levels of organization based on interacting components at lower levels to be its primary epistemological and methodological goal (see Bruggeman 2007; Noble 2012).

Nevertheless, the simultaneous use of opposing experimental arrangements is not an exception in neuroscience reserved only for ion channel modeling. For example, neurophysiologists often combine opposing linear and nonlinear measures to the electroencephalographic (EEG) signals collected from the same experimental condition (Kesić and Spasić 2016). While the system's proportional responses account for linearity, disproportionality between input and output specifies nonlinearity and the corresponding nonlinear analysis of EEG. Most importantly, modern "complexity theory", which lacks universal consensus (Chu et al. 2003), combines different opposing theoretical principles, including linearity and nonlinearity. Some of these other conceptual and research frameworks used to interact with the complex organism are "bottom-up" and "top-down" systems biology, reductionism, holism, systems-theoretical biology, pragmatic systems biology, the epistemology of complexity, etc. (Mazzocchi 2008; 2010; 2011; Bruggeman et al. 2007; Noble 2012; Kesić 2019). Attempting to unite as many approaches and ideas as possible, previously thought to be an impossible task, stimulates interest in studying living complex systems. It encourages scientists to incorporate different principles and strategies and increases their expectations to legitimize existing and acquire new comprehensive research data.

In this articulation process between the parts and the whole, opposing theoretical principles, research object, and the researcher, complementarity may play a key role (Mazzocchi 2010). However, the principle must go through a kind of departure from the "mutual exclusiveness of experimental setups" to increase its usability range to capture opposing concepts in the single experimental setup. We believe that various theoretical and practical frameworks such as Morin's complex thinking can assist philosophers and scientists in searching for the general form of complementarity.

Noteworthy, Complex thinking does not necessarily imply that "everything is complex", meaning "what cannot be understood". In other words, complex thinking as a conceptual tool allows scientists to articulate the whole and the parts simultaneously, to distinguish complex from complicated and contingency from determinism (Ferrara 2010; Morin 2014; de Melo 2020). It provides a combination of several factors at the same time (Ferrara 2010, p. 3):

> Where principles of regulation and non-equilibrium are combined, where contingency and determinism, order and disorder are; where levels of the organization and nonlinear dynamics can be identified by feedback between the levels.

As a coupling mode between the world and observer, Complex thinking informs the development and coordination of new tools and strategies to support the practice and evaluation of Complex thinking across natural, biological, and social domains (de Melo 2020, p. 34):

> It produces further information through the creation of differences: (i) one's own state in relation to the World/System; (ii) the emergent view of the world, and the system-of-interest, in relation to our own previous views or those of other observes; (iii) the

> organization of the relationship between the observer and the world and the experience of its effects. The creation of this information may lead to changes in the thinking and, in turn, lead to more differentiated and integrated perspectives, offering more possibilities for effective action through a more congruent coupling.

According to Complex thinking, in principle, no logical obstacles interfere with the simultaneous use of concepts such as determinism and indeterminism in the same experimental setting. The reason is simple; the simultaneous differentiation and integration of a complex system's properties happen in the observer's mind, which is then transferred to scientists' practical actions. In this way, the differences between the stochastic and deterministic behavior of ion channels are recognized in the observer's mind while simultaneously searching for integrative mathematical and computer solutions that would minimize these differences. Thus, we suspect that Bohr's complementarity comprehended in a purely theoretical and antirealist manner cannot turn differentiation and integration into a single valid experiment or model consisting of opposing solutions.

On the contrary, complementarity's phenomenological framework may account for simultaneous differentiation and integration similarly to Complex thinking. The use of these two principles together, however, can intensify efforts towards the reconciliations between profound dualities scientists encounter across biological theory and practice. In this respect, Mazzocchi's, Theise's and Kafato's appeal for generalized complementarity and extensive use of conceptual tools such as Complex thinking to accommodate 21st-century biology are pretty justified.

6 Conclusion

This paper has suggested a general form of Bohr's complementarity to meet 21st-century ion channel modeling demands. However, scientists and philosophers should take the proper philosophical interpretations of this principle and examine its relevance for current scientific research before any applications in practice occur. Our study, at least, provides much-needed empirical support to understand how neurophysiologists may exploit complementarity to facilitate everyday research tasks. Hence, some of the modeling-related experiments presented in our paper indicate a more general form of complementarity.

Combining deterministic and indeterministic solutions in the same ion channel model is the most crucial landmark of today's computational neurophysiology. Based on deterministic or indeterministic solutions, these channel models are correct and necessary in a particular context and are expected to be part of separate modeling setups. However, according to this paper's results, some of these models simultaneously include opposing solutions. This state of the matter reduces the complementarity principle's application domain in this particular brain modeling area, or so it seems at first glance. In this respect, we hold that the narrow "mutual exclusivity of experimental setups" version of Bohr's complementarity limits its application to ion channel modeling practices. Hence, if we adopt this interpretation of principle as only valid, it would be difficult to explain how this principle can be relevantly applied in ion channel modeling.

However, a practically-oriented realist phenomenological position opens space for a more general complementarity suitable for diverse experimental and modeling applications, including neuroscience.

The paper's other important finding is the suggested joint use of complementarity and Complex thinking. The first allows the use of seemingly different "bottom-up" solutions in a single model, while the second forms a bridge between different conceptual frameworks used to frame that model. Even so more, as Rychlak (1993) argued in the field of psychology, complementarity enters at the formulative point of a scientific investigation, even before experiments are designed and conducted. The similar applies to neurophysiology; in addition, we argue, this also might be said for Complex thinking.

Although this paper explores the limits of applying complementarity in modeling practice, one can read it as an evidence-based contribution to frame a general form of complementarity. Once we consider all the pieces of evidence about the procedures in ion channel modeling, we're left with one inescapable conclusion. It appears that Bohr's complementarity might be suitable for ion channel modeling practice and should be further accommodated to meet the demands of rapidly expanding computational neuroscience research. At the very least, this is possible from the point of view of a realist phenomenology.

In this paper, we have only superficially touched on this principle's use in neuroscience. Moreover, considering that this article is a work of conceptual analysis, it is clear that the conclusions are drawn from a limited number of examined scientific and philosophical papers. Therefore, the claims and statements presented in the article are open for revision, confrontation, and further discussion.

Data Availability This paper is a work of conceptual analysis and, as such, does not contain any experimental data. However, all materials cited are available in academic databases, university libraries, or free online sites.

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