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INDETERMINISM IN NEUROBIOLOGY*

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Abstract

I examine different arguments that could be used to establish indeterminism of neurological processes. Even though scenarios where single events at the molecular level make the difference in the outcome of such processes are realistic, this falls short of establishing indeterminism, because it is not clear that these molecular events are subject to quantum mechanical uncertainty. Furthermore, attempts to argue for indeterminism autonomously (i.e., independently of quantum mechanics) fail, because both deterministic and indeterministic models can account for the empirically observed behavior of ion channels.

1. Introduction. Is the brain a deterministic machine, or are neurological processes subject to chance events? If we mean by "chance" not merely our ignorance of the real causes of an event but a lack of causal determination in the objects themselves, do such chance events occur in a living brain? And if objective chance events occur in a living brain, are they relevant to its functioning? Answers to these questions would surely be of considerable interest for the philosophy of action, no matter whether determinism is considered to be compatible or incompatible with freedom of the will. The possibility of freedom is usually examined against an inherent determinism or indeterminism of the world (e.g., Van Inwagen 1983). However, it is possible that the world is not deterministic in its entirety, but that neurological processes are. If this were the case, that is, if only some highly remote or contrived processes were intrinsically indeterministic, while the brain is a fully deterministic machine, this indeterminism might not be relevant at all to the possibility of human freedom. Therefore, the salient question must be whether neurological processes are deterministic, not whether the world is deterministic. Furthermore, this question is important for the ongoing debates on the foundations of statistical theories and of probability in the philosophy of biology.[1] In spite of its philosophical importance, there are not many recent attempts to directly answer the question of whether neurological processes are fundamentally deterministic or indeterministic.

The goals of this paper are twofold. First, I critically examine some arguments that have been proposed to establish indeterminism about biological processes in general, as well as about neurological processes specifically. Second, I want to investigate whether recent empirical findings in molecular neurobiology could shed some new light on this old problem.

I begin with a discussion of different strategies that have been used to argue for indeterminism in biology (section 2). As one such strategy relies on quantum mechanics (QM), I then examine some older attempts to apply QM to neurobiology (section 3). Section 4 surveys a number of candidates for molecular neurological processes that could be indeterministic. In Section 5, I focus on a particularly promising candidate for such a process: the gating of ion channels located in neuronal membranes. Finally, in section 6 I determine the prospects of neuro-indeterminism given the current state of science.

2. General Arguments for and Against Determinism in Biology. Whether biological processes are generally deterministic or indeterministic is controversial. Determinists argue as follows (Rosenberg 1994, Horan 1994): Even though universal Laplacian determinism fails due to the "no hidden variables" proofs of QM, this indeterminism does not manifest itself in biological systems. Quantum indeterminism only affects the microphysical level, and only systems that are sufficiently isolated. Biological systems are macroscopic systems that strongly interact with their environments; therefore, their behavior is only subject to deterministic physical laws. Quantum effects disappear as we move upwards from the level of atoms and chemical bonds to systems the size of a living cell or above. Therefore, biological systems are fully deterministic. If biological systems behave stochastically – which they certainly do – this stochasticity is not of the *objective* kind known from QM, for example, as in radioactive decay. Instead, biological stochasticity is only *apparent*; it reflects our inability to predict the behavior of complex systems.[2]

If this reasoning is sound, we would have to conclude that the brain is a deterministic machine, and pay whatever metaphysical cost this may incur.

Indeterminists have produced two different responses to this argument (see Millstein 2003b). First, they have questioned the irrelevance of quantum indeterminism in biology by thinking up scenarios how quantum effects could "percolate up" to the macro-level. For example, Robert Brandon and Scott Carson (1996) describe a scenario where the fate of an entire population of organism depends on a single mutational event. Mutations, because they occur at the molecular (DNA) level, could be subject to quantum indeterminism, at least in theory (see also Stamos 2001). Second, there have been attempts to establish indeterminism autonomously, that is, independently of QM (Brandon and Carson 1996, Glymour 2001). On this other approach, quantum behavior may still provide the physical basis for indeterminism, but the grounds for holding indeterminism to be true are sought in the empirically observed behavior of biological organisms, not in any theoretical considerations involving QM.

In principle, both of these approaches can be applied to neurobiology. In other words, we can attempt to establish indeterminism of neurobiological processes both on the grounds of theoretical considerations pertaining to the relevance of QM to neurological processes, or by using biological knowledge about neurons, the CNS, and so on. In the following, I want to determine the viability of both strategies. I begin by examining some older attempts to show that QM could be relevant to the functioning of the nervous system.

3. Quantum Mechanics, Mind/Body-Interactionism, and Physicalism. Most existing attempts to apply QM to the brain were not primarily concerned with indeterminism, but with mental causation and freedom of the will directly. The idea that QM could rescue freedom from Laplacian determinism has been defended by a number of physicists (e.g., Jordan 1932; Penrose 1989, 1994) as well as by some neurobiologists and philosophers (Popper and Eccles 1977; Eccles 1994). However, this idea is quite different from the "percolation" scenarios suggested by philosophers of biology (mentioned above), for reasons that I shall now explain.

The classic attempts to save freedom with the help of QM are typically based on a very strong, problematic metaphysical assumption, namely mind/body-interactionism (Esfeld 2000). Interactionists believe, first, that mental states or events are not identical with nor realized by physical states or events. Second, interactionists think that mental states or events can causally influence physical states or events, and vice versa. On these assumptions, interactionists then call on QM in order to make room for influences from the mental into the physical world that do not violate the conservation laws that govern the latter. The eminent neurobiologist Sir John Eccles, for example, thought that mental states or events could alter the probability of neurotransmitter release at synaptic terminals (Eccles 1986). His idea seems to be that this could happen in a way that does not amount to the expenditure of energy at the synaptic terminal, thus avoiding a conflict with the law of energy conservation.[3]

On an interactionist theory of mental causation such as Eccles', however, the brain is not the control center of the human body. It is merely an organ that executes instructions received from a higher authority, namely the mind. Eccles only needs QM in order to avoid a conflict with the law of energy conservation. Thus, what he and others have defended is not indeterminism about neurological processes but a very peculiar account of the role of the central nervous system in human behavior. On this view, the nervous system is merely a mediator between the mental and physical world, not a control unit of its own.[4] It will barely need mentioning that such an account is not widely accepted today, neither in philosophical nor in scientific quarters. Neuroscientists today look at the brain as *the* control center of human behavior, not merely as a mediator (e.g., Crick 1994). In a similar vein, according to physicalist philosophers of mind such as Jaegwon Kim (1998), the brain provides the physical substrates or realizers for mental states. This attributes to the brain much more causal power than just a Cartesian executor of mental events.

The question of the possible relevance of QM to the philosophy of mind presents itself differently if we reject the Cartesian interactionist metaphysics that has traditionally been presupposed. We no longer assume that the brain as a physical entity receives its orders from a mental realm. On a physicalistic perspective, the brain has causal powers of its own. It is a machine that takes causal inputs and releases outputs, with a complex web of computational events standing in between (in the best cases). Physicalism is widely understood to imply the *supervenience* of all mental and biological properties on an organism's physical properties (Weber 1996). Supervenience means that any change in an organism's mental or biological properties requires a concomitant change in its physical properties. For the purposes of this paper, I shall assume that supervenience on physical properties actually holds. As we shall see in the following section, supervenience simplifies our search for indeterminism in the nervous system.

4. Indeterminism in the Nervous System: The Candidates. Which neurological processes could, in theory, be indeterministic? And is it conceivable that a possible indeterminism of neurological processes at the micro level (e.g. due to quantum effects) could "percolate up" to the organismic level? These are the questions to be addressed in this and the following section.

Among the thousands of cellular and molecular processes that occur in a living brain, the most relevant ones for my present purpose are those involved in the transmission and processing of signals by neurons. Neurons fire so-called action potentials down their nerve fiber or axon. An action potential is a wave of depolarization (carried by ionic currents) that spreads along the membrane enclosing the axon. An axon typically terminates in a number of synapses that connect to other neurons. When enough action potentials reach a synapse, intracellular storage vesicles that contain neurotransmitter are emptied into the cleft that separates the synaptic membrane from the neighboring neuron. The neurotransmitter rapidly diffuses across this cleft. When it reaches the membrane of the neighboring neuron, it binds to specific receptors that cause a depolarization of the membrane. The result is a so-called synaptic potential. If this potential reaches a certain threshold, the neighboring cell fires a new action potential. In this manner, a signal can move from one neuron to the next. This process forms the basis for neural computation.

In principle, stochastic processes could occur at any stage of the neurotransmission pathway, and anywhere in a neural circuit. For example, chance could intrude in the generation of synaptic potentials, receptor potentials (the equivalent of synaptic potentials at sensor neurons), or endplate potentials (the equivalent of synaptic potentials at neuromuscular junctions), the propagation of action potentials, the release of neurotransmitter by exocytosis, the diffusion of neurotransmitter across the synaptic cleft, and in the action of neurotransmitter receptors. Furthermore, chancy events could occur in a whole neuron, or in a whole neural circuit.

Where should we look for indeterminism in this complex picture? I suggest that the problem is simplified considerably if we appeal to the supervenience of biological properties on physical properties, already mentioned in the previous section. If supervenience holds, there can be *no stochasticity without micro-level stochasticity*. This means that for a biological process to show intrinsic stochasticity,[5] it must be based on stochastic microphysical processes, that is, they must be manifestations of quantum indeterminism. Thus, if we accept supervenience, we are left only with molecular processes as sources of intrinsic stochasticity. This means we have to deal only with the *molecular realizers* of neural processes. For the purposes of this paper, I shall group the molecular realizers of neural processes into two classes: (1) neurotransmitter transport, (2) ion channel gating. I will now briefly examine the former, while the latter will be discussed in more detail in the following section.

As I have mentioned, neurotransmitters are released at synaptic terminals from internal storage vesicles and subsequently diffuse across the synaptic cleft. Vesicle transport is believed to involve the cytoskeleton at certain stages. The physicist Roger Penrose has suggested that the cytoskeleton could be subject to quantum effects (Penrose 1994). He argued that microtubules, being hollow structures, could create a sufficiently isolated environment for quantum coherence in their interior. Another eminent physicist, Stephen Hawking, objects to this that biological structures such as microtubules are not sufficiently isolated for quantum coherence to be possible.[6] But without such coherence, biological macromolecules will behave classically, that is, deterministically.

Penrose's ideas are highly speculative, as there is no evidence for such a mechanism for quantum coherence as he envisioned. In recent years, cell biologists and molecular neurobiologists have gained many new insights on the various roles of microtubules in the cell. They seem to function mainly as structural and mechanical devices of the cytoskeleton. For example, microtubules interact with a class of proteins called kinesins and dyneins. Kinesins and dyneins are tiny molecular motors that allow the cytoskeleton and associated structures to generate mechanical forces. Kinesins seem to be involved in the transport of vesicles along the cytoskeleton, including neurotransmitter vesicles (Hirokawa 1998). However, these motor proteins interact with microtubules on the *outside* of the latter. The microtubules act like cables on which transport vesicles crawl along with the help of the motor proteins. Furthermore, it seems that this transport system is involved in delivering vesicles to the synapse, not in the release mechanism of neurotransmitters. These findings make Penrose's speculative mechanism for quantum coherence in microtubules rather unlikely.

Another candidate for an intrinsically stochastic process involved in neurotransmission is molecular diffusion. As we have seen, it is involved in the transport of neurotransmitter molecules across the synaptic cleft. All that can be said, at present, about this process is that diffusion can be and is treated as a deterministic process in statistical mechanics.

In the following section, I shall examine what I consider to be the strongest candidate for quantum effects in the nervous system.

5. Ion Channels: Some Good and Some Bad News for the Neuro-Indeterminist. The exchange of signals between neurons essentially involves the opening and closing of different kinds of ion channels. Such channels are comparatively large protein molecules that are embedded in the neural membrane. They are selectively permeable for specific kinds of hydrated ions, typically, sodium, potassium, calcium or chloride ions. Ion channels have different states, typically a state of low ion conductance ("closed"), one of high ion conductance ("open"), and an inactivated state. Depending on the specific type of channel, its state is influenced by the presence of ligands (e.g., a specific neurotransmitter molecule) or by the voltage across the membrane. All electrical excitation in neural membranes is controlled by different classes of ion channels: Action potentials spread mainly by the help of voltage-gated sodium and potassium channels. The generation of receptor potentials involves ligand-gated or mechanically gated ion channels. Neurotransmitter release is initiated by voltage-gated Ca^{++}-channels. Neurotransmitter receptors are essentially ligand-gated ion channels.

Given the importance of ion channels in all neural processes, they are an interesting place to look for indeterministic behavior. This is what I turn to now.

In recent years, molecular biologists and biophysicists have learned a great deal about the properties of ion channels (Hille 2001, Yellen 2002). A particularly important technique for the study of ion channels was developed in the 1970s and 80s and is known as "patch-clamping" (Neher and Sakmann 1976). In this technique, a small patch of membrane containing channel molecules is sucked onto the tip of an extremely thin pipette. If the membrane is tightly sealed to the mouth of the pipette, tiny ion currents can be measured. With this technique, is has been possible to record currents from single ion channel molecules.

Patch-clamping experiments showed that ion channels behave stochastically. What this means is that the opening and closing of ion channels follows an irregular pattern, as long as we focus on a single molecule. However, there is a fixed probability that any given channel will open if it is in the closed state, and a fixed probability that it will close if it is in the open state. These probabilities are independent of a channel's previous states. Thus, ion channels satisfy the Markov condition. Biophysicists have successfully modeled the dynamics of ion channels with Markov models (Colquhoun and Hawkes 1981).

These findings are good news for indeterminists. For the first time, it was shown that an important class of biological macromolecule behaves stochastically. What is more, it could even be shown that chance events in ion channel molecules could "percolate up" at least to the level of neurons. For example, it was shown that single-channel events can trigger spontaneous action potentials in cultured cells (Johansson and Arhem 1994; Chow and

White 1996). This raises the theoretical possibility that a single chance event, perhaps a quantum event, could make some difference in the behavior of a complex animal.

Unfortunately (for the indeterminist), the good news from ion channel biology is neutralized by some bad news. The bad news is that deterministic models can fully account for the behavior of ion channels, too (Liebovitch and Toth 1991; Cavalcanti and Fontanazzi 1999). In a deterministic model, a system's state variable evolves according to a function that takes a determinate value at all times.[7] Deterministic models of ion channels feature a state variable representing the protein's conformational state. The channel conductance is assumed to depend non-linearly on this state variable. Furthermore, the state variable responds to changes in current flow with a certain delay time. Under these assumptions, it was shown that ion channels could exhibit the phenomenon of *deterministic chaos*. This means that there are combinations of model parameters that will result in aperiodic, unpredictable behavior. The modeled channels flip open and shut in an apparently erratic fashion, in spite of the assumption of determinism built into the models. Statistical analyses of the simulated time evolution of individual systems gives results that are well in line with the behavior of ion channels as observed in patch-clamp measurements. Thus, the observable behavior of ion channels can be fully accounted for by deterministic models.

The mathematical models of ion channel gating are not based on chemical or structural information on ion channel proteins;[8] they just make some very basic assumptions about the dynamics of conformational change in a protein molecule. In spite of this, these models teach us an important lesson: It is evidently not possible to decide the issue of determinism vs. indeterminism on the basis of kinetic analysis in combination with dynamic models, if Markov models and deterministic models can both be adapted to the kinetic data. The choice between deterministic and indeterministic models is underdetermined by the evidence.

What are the exact implications of this result for the attempts to establish indeterminism in biology? This question is the subject of the final section.

6. Prospects for Neuro-Indeterminism. The findings reported in the previous section have severe implications for both the "percolation" and "autonomous" strategies (see Section 2). They spell bad news for the "percolation" strategy because defenders of this approach have rested their hopes on scenarios where single events at the molecular level could make the difference in the outcome of a macroscopic process. Unfortunately, even though empirical evidence from neurobiology suggests that this is possible, we are nowhere near to having established neuro-indeterminism. For we still don't know whether the relevant *molecular* events are indeterministic or not. It is not enough to show that single events at the molecular level could make the difference between different macro-states; indeterminists must also demonstrate that these molecular events are intrinsically stochastic.

But these findings also spell bad news for the "autonomous" strategy of arguing for indeterminism. This strategy has been pursued, for example, by using examples involving plant growth (Brandon and Carson 1996) or random search behavior in animals (Glymour 2001). In these cases, the manifest behavior of biological organisms was used to argue for indeterminism. But, as Millstein (2003b) shows, all of these examples are consistent both with determinism and with indeterminism. Analogously, the empirically observed behavior of ion channels is consistent both with determinism and with indeterminism; thus the "autonomous" strategy fails for the exact same reason in the context of neurobiology. To establish indeterminism, it would have to be shown that conformational changes in protein molecules such as ion channels exhibit indeterministic quantum effects. However, ion channels are very large complexes of molecules that interact with millions of solvent and other molecules at any time, at least in their functional state. No scenarios favorable for quantum effects such as those envisioned by Penrose for microtubules (see Section 4) seem to be forthcoming.[9]

There seems to be a widespread belief in contemporary philosophy that physics has proven the universe to be fundamentally indeterministic and that this must have far-reaching consequences for traditional metaphysical problems such as the nature of causation and freedom of the will. Furthermore, many philosophers of biology think that indeterminism rules in the biological domain, affecting the way we ought to think about probabilistic theories in biology and related matters. A crucial underlying assumption in this was that the indeterminism of QM,[10] since it affects the ultimate constituents of all matter, would manifest itself in biological systems. This would be necessary for quantum indeterminism to have the kind of metaphysical implications that it is generally thought to have. However, my analysis of the current state of neurobiology in this respect shows that this assumption is not warranted.

In recent years, neuroscientists and cell biologists have learnt a great deal about the molecular mechanisms of neurotransmission and signal processing in the central nervous system. So far, they never had to turn to QM in order to explain the phenomena they were observing in their laboratories. The only exception known to me is structural biology, i.e., the discipline that studies bio-molecular structures. The reason is that this discipline is interested in the structure and stability of chemical bonds, e.g., in DNA and protein molecules. Chemical bonds are based on interactions between electrons and atomic nuclei, thus QM is indispensable. While the motion of subatomic particles may thus be subject to quantum indeterminism under certain (measurement) conditions, there is no evidence that this may affect the behavior of the functionally relevant macromolecules in the brain. Classical physics seems to be sufficient for dealing with processes such as neurotransmitter transport or ion channel gating. But *these* are the functionally relevant processes out of which phenomena of metaphysical interest such as consciousness or intentionality emerge. Of course, we cannot know what science has in store for indeterminists in the future, as even determinists have to admit. But for the time being it is necessary to set the record straight on indeterminism in neurobiology. At present, its prospects are not so good.

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FOOTNOTES

[1] See, e.g., Rosenberg (1994, 2001), Horan (1994), Brandon and Carson (1996), Graves, Horan and Rosenberg (1999), Millstein (1997, 2003a), Weber (2001).

[2] This does not imply that probabilities, as they feature in some biological theories, are subjective, nor does it challenge realism about biological theories (Weber 2001).

[3] Paul Hoyningen-Huene points out to me that energy conservation is not the only physical constraint on such interactions; they would also have to obey laws of motion. Furthermore, it is far from clear how such an interaction could occur without violating laws of *quantum* mechanics.

[4] There is a strong resemblance between Eccles' and Descartes' philosophy of mind. Eccles has basically substituted synaptic terminals for Descartes' (1899, 19, 47f., 263ff.) pineal gland, and QM for Cartesian physics. Apart from these scientific modifications, the underlying metaphysics is basically Cartesian.

[5] By "intrinsic" I mean that the stochasticity is not based on our inability to predict the behavior of a system. The only intrinsically stochastic processes recognized by modern physics are quantum measurement processes. Other processes sometimes described as "stochastic" or "random" are not *intrinsically* stochastic or random. For example, Brownian motion is usually treated as a deterministic process. The "random walk" of a Brownian particle is only apparently random because it is impossible to predict the trajectory of such a particle.