Letters and Notes

Implications of Two Opposing Variations of Neutral Theory

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In evolutionary biology, neutral theory has been gaining more and more ground since it was originally proposed by Motoo Kimura in 1968 (Kimura, 1968). It was originally proposed as a mathematical way of understanding the relationship between allele variations and population sizes in population genetics, but was later applied to molecular evolution as well (Dietrich, 1994).

Popular theories sometimes shape the thinking about a subject far beyond what the technical aspects of the theory suggest. This is true both for popular and professional audiences, as even for professionals, popular principles oftentimes fill in the gaps in understandings (see Bartlett (2017) for a discussion of this).

While selection has previously stood in the gap for these types of understandings in biology, today neutral theory has begun to takes its place. Interestingly, in the case of neutral theory, the theory implied by the data is actually significantly at odds with the larger interpretation and application of it.

The question turns on whether neutral evolution is merely a description of the peculiar features that are found in the organisms present in the earth today, or if neutral evolution is due to general features of evolution itself (i.e., they would exist no matter how biology was configured). I will call the first theory "observational neutral theory" and the second one "comprehensive neutral theory."

In observational neutral theory, neutral theory merely points to observations about present mutations in present organisms. It makes no claims about evolution in general, evolution past, nor the requirements for neutral evolution to take place. It merely points out that most mutations we observe are nearly-neutral or of low effect (Eyre-Walker and Keightley, 2007), and therefore selection has very little effect on which mutations survive in the population (Sanford et al., 2007). Genetic drift therefore becomes the dominant mode of observable evolution. Selection, when it acts, is primarily purifying selection (Dietrich, 1994). This type of neutral theory does not speculate on *why* this is the case—more to the point, the reason for why neutral evolution occurs is basically outside of its scope. That is, it leaves out the specific molecular requirements that would lend themselves to neutral evolution.

In comprehensive neutral theory, the dominance of neutral evolution is not only in the observed present, but is also the key to all of evolution. That is, evolution *needs* no guidance from natural selection to do its work (though it may have some). According to this view, neutral mutations and genetic drift are all that is needed to get all of the precise mechanisms available within biology.

The reason that this distinction is important is that I have found that, in conversation, many biologists free-float between the two theories. Neutral theorists often start in the observational theory, beginning by saying that evolution as we observe it obeys the principles of neutral theory. Since neutral theory is dominant in the process of evolution today, many neutral theorists then generalize to the comprehensive theory and say that because it is dominant today that neutral theory must have been equally dominant in the past. Therefore, neutral evolution *must* be really powerful, because all of biology is the result of neutral evolution. However, one can then point out that the reason neutral evolution works in the present is because mutational hot-spots are contained in less-sensitive areas of the genome. When pressed, the neutral theorist quickly switches from a comprehensive theory back to an observational theory, usually citing natural selection as the reason for such a propitious distribution of hotspots. Recognizing the distinction between the observational and comprehensive theories of neutral evolution is important for critical thinking about neutral theory. This is somewhat amusing because one of the supposed benefits of neutral theory is getting around problems of selectionism and adaptationism in evolution. However, when pressed on shortcomings in neutral theory, this is precisely where neutral theorists often go.

Comprehensive neutral theory is unworkable, because the machinery in cells and organisms are precise mechanisms. Therefore, random wanderings in genome space will not produce them in any amount of time. My own viewpoint is that the observational neutral theory is a fairly accurate representation of what we know about modern evolution, but it needs to be underpinned by something other than selectionism for a foundational theory of how it came to be that evolution has such a neutral focus.

One possibility is that neutral theory works precisely because organisms contain sufficient information to target mutations in areas that are less likely to be problematic—i.e., in areas where modifications are expected to occur and accounted for. However, this presupposes the existence of information within the cell to do the targeting. Neutral theory cannot hoist itself up by its own petard to perform this, and neither can neo-Darwinian selectionism.

Constructive Neutral Evolution (Stoltzfus, 2012), abbreviated CNE, is an attempt to get around this, but winds up falling into the same trap. It aims to be more comprehensive in the small scale, specifically accounting for complexity. It is interesting that the *models* of CNE show how complexity can form, but leave out how those complexities turned functional—it is merely assumed that they often do. Interestingly, this mirrors the same process described in this paper with earlier forms of neutral evolution, with researchers passively switching back-and-forth between whether the theory only describes a process or whether it is a comprehensive solution to the problem of complexity.

A better research program for neutral theory is to recognize the limitations of neutral theory's role in evolution, and determine the necessary conditions for neutral theory to work. The most rigorous descriptions of what makes evolution workable in a general sense focuses on the information present in organisms (Marks II et al., 2013; Ewert and Marks II, 2017; Dembski and Marks II, 2009; Bartlett, 2010; Dembsking and Marks II, 2010). As the Evolutionary Informatics lab points out, "information makes evolution possible" (Evolutionary Informatics Lab, 2019).

Ultimately, either neutral theorists need to say that this introduction of information is beyond the reach of biology (similar to the stance of Yockey (2000)) or, like Intelligent Design, propose a valid source or mechanism for such information to have been included into organisms (Meyer, 2009). Eternally punting to mechanisms known not to be able to produce the effect in question, however, does not make for an effective research program in the long term.

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