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Critical Focus

Evolution's Waiting-Time Problem and Suggested Ways to Overcome It—A Critical Survey

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Abstract

In recent decades, severe waiting-time challenges have emerged for explanations of complex biological change within the Modern Evolutionary Synthesis. Theorists continue to propose natural mechanisms which purportedly shorten these waiting times, but do the arguments for these improvements take account of all relevant factors? Here we consider four proposed mechanisms for rapid evolution: symbiogenesis, the action of transposable elements, horizontal gene transfer, and the use of alternative evolutionary pathways. In all four cases we find that the claimed evolutionary benefit fails to take all aspects of the proposal into consideration. On the other hand, when laboratory processes analogous to evolution benefit from the teleological insights of the experimenters, we find that time no longer poses an insurmountable obstacle. By extension, it seems reasonable to propose teleology as the solution to biology's waiting-time problem.

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INTRODUCTION

About sixty years ago, regarding the emergence of life on earth, Nobel Laureate George Wald said,

> Time is in fact the hero of the plot. ... Given so much time, the 'impossible' ... [becomes] virtually certain. One has only to wait: time itself performs the miracles[1].

It seems that many biologists and philosophers have long believed that Wald's perspective on the power of time applies equally to neo-Darwinism (sometimes called "the Modern Evolutionary Synthesis").

Is an evolutionary version of Wald's appeal to time still relevant, or has time actually become more of a villain than a hero, with respect to the neo-Darwinian story? The next section of this article will present some relatively recent representative examples of what has become known as the waiting-time problem. These examples are not insignificant, peripheral oddities, but rather central components of the evolutionary account.

Evolutionary biologists continue to propose non-teleological mechanisms that, when conjoined with the standard theory, purportedly shorten waiting times. The second section of this article will briefly examine a small sample of these mechanisms. The question guiding this examination is whether the claimed advantages of the proposed mechanisms take account of all relevant factors.

The final section will draw on our knowledge of human teleological activity to explore the possible role of purposeful action in overcoming the waiting-time problem.

THE WAITING-TIME PROBLEM FOR UNDIRECTED EVOLUTION

The failure of the Modern Synthesis to explain the origin of novel proteins, organs, and body plans[2][1] has been expressed by numerous scientists who favor naturalistic explanations of life:

> Clearly something is missing from biology. It appears that Darwin's theory works for the small-scale aspects of evolution. ... The large-scale differences of form between types

[1]In his "Notes" section for the Prologue, Meyer lists numerous books and articles by scholars and scientists admitting or inferring such problems with ND. See Notes 8 and 12

> of organisms ... seem to require another principle ... that gives rise to distinctly different forms of organism[3].
>
> In the post-genomic era, all major tenets of the Modern Synthesis are, if not outright overturned, replaced by a new and incomparably more complex vision of the key aspects of evolution. ... So, not to mince words, the Modern Synthesis is gone[4].
>
> Current evolutionary theory ... largely avoids the question of how the complex organizations of organismal structure, physiology, development or behaviour—whose variation it describes—actually arise in evolution[5].

The referenced authors, and many others [6–9], have proposed various solutions to the problems they see in the Modern Synthesis (discussed below). Interestingly, they all agree that the solutions are sufficiently far removed from classical neo-Darwinism as to constitute replacements of that theory, rather than mere enhancements of it.

Philosopher of science Stephen Meyer traces the root of the problem to information [2]. However, as others have noted, it can also be seen as a *time* problem:

> The question unanswered by the two well-established pillars of evolutionary theory (selection and heredity) is whether, given *the rate* and nature of changes in the DNA, enough of the right kind of phenotypic variation will occur to allow selection to do its work, powering complex evolutionary change. ... The Modern Synthesis ... lacks the third pillar required of a general theory of evolution, a pillar needed to explain the feasibility of evolutionary change [10] (emphasis added).

This perspective echoes the views of Erwin and Valentine from twenty years earlier:

> Explanations for the Cambrian radiation ... have focused on species selection or traditional microevolutionary processes. *The rapidity* of and low species numbers during the radiation render these explanations untenable" [11] (emphasis added).

More recently, Shapiro wrote that,

> molecular evidence about genome sequence changes tell us that the simplifying assumptions made in the 19th and early 20th Centuries are plainly wrong. ... Many change events have been *quite rapid*[12] (emphasis mine).

Waiting for Novel Proteins

Axe has studied the ability of neo-Darwinian processes to arrive at functional protein folds through purely blind searches [14–16]. Relevant to our purposes, Axe's research explores whether blind processes can plausibly cause a one-celled organism to produce the long sections of new protein sequences needed to produce a novel, functioning protein [16].

Using generous assumptions [15, 17][2] Axe calculates that there would be "at most 5×10^{23} opportunities ... for mutations to craft a protein that performs the function in question successfully [15]". He then calculates that purely random mutations would need to sample a minimum of 10^{104} sequences to reasonably expect to arrive at one new functioning protein fold [15].

Axe acknowledges that the rarity of a protein fold varies considerably with its complexity [14]. In his 2016 book, Axe calculates that even for a protein 153 amino-acid residues in length, a blind search would on average need about 10^{74} chances to arrive at a functional protein fold [18]. Therefore, dividing this number by his assumed number of 10^{14} chances per year (5 x 10^{23} opportunities divided by 5 billion years), a blind Neo-Darwinian search would need more than 10^{60} years for all 10^{74} chances to be realized. Thus, available time (5 billion years) is less than 10^{-50} as long as the time needed. Further research could possibly change that picture, but as things now stand, the waiting-time challenge seems formidable.

A waiting time challenge has also surfaced in a protein function co-option scenario. Reeves, Axe, and Gauger recently subjected two enzymes, Kbl2 (2-amino-3-ketobutyrate CoA ligase) and BIKB, to double mutations by the millions to see if any of these mutants perform the function of BioF2 (8-amino-7-oxononanoate synthase). Reeves, et al. judged these three enzymes to be among the candidates most evolutionally amenable to such a co-option [19]. After testing 70% (nearly 8 million both for Kbl2 and for BIKB) of possible doubly-mutated combinations, no detectible BioF2 function emerged [19]. Reeves et al., concluded that at least three mutations would be required. They then calculated that getting BioF2 function "by the classical recruitment mechanism" from a highly similar enzyme via three mutations would take 10^{15} years [19] – over 500,000 times the estimated age of the universe. Of course, biologists have not experimentally tested all potential co-option scenarios like this. However, this research produces quantitative data suggestive of the severe waiting-time barriers which may broadly be faced by the blind co-option the Modern Synthesis envisions.

[2] Axe's assumptions: 300-amino acid protein, a starting population of 10 billion, 1000 generations/year, mutation rate = 1 per cell, 5 billion years.

Waiting for the Emergence of Whales

A high-profile example of a neo-Darwinian waiting time problem—the evolution of whales—has been examined by Sternberg and Wells [20, 21]. Between them they list at least fifteen major adaptive modifications needed for a successful transformation of a land-dwelling Pakicetus into a fully aquatic whale. Based on the two-mutation waiting time for hominids calculated by Durrett and Schmidt [22], Sternberg estimates that to get just two coordinated favorable mutations in a whale-ancestor would take 43.3 million years [20]. Yet the time available for the entire Pakicetus-whale transition at most 9 million years [23, 24],[3] and possibly as short as 2 million years [20].

It is not currently possible to calculate how long the neo-Darwinian waiting time would be for the fifteen changes Sternberg and Wells list, plus all the other needed changes which they do not list. The main reason for this is that major morphological changes clearly require many more than two mutations. Nevertheless, the conclusion that the needed time greatly exceeds the available time is firm.

Waiting for Human–Chimpanzee Divergence

In both scientific and popular writing, it is commonly asserted that the similarity between the human and chimp genome (ranging from 95% to 99%) [25–27] is overwhelming evidence that the two species evolved from a common hominin ancestor. Three teams of researchers touch upon the question of waiting times for a series of two mutations in creatures with long generation times and small initial populations (such as hominins). Lynch and Abegg estimate the waiting time at about 500 million years [28**?**], Durrett and Schmidt at 216 million years [22], and Sanford, et al., at 84 million years [30].

Estimates of the time available for the divergence of humans from chimps are far shorter, ranging from 6 to 13 million years [30–33].

Although these three cases do not in themselves show that implausible waiting times are typical of the Modern Synthesis throughout the history of all biological organisms, they may explain the recent tendency to propose non-classical (and non-teleological) evolutionary mechanisms in an effort to correct the problem.

PROPOSED CORRECTIVE AMENDMENTS TO NEO-DARWINISM

This section briefly evaluates four factors that have been offered as solutions to the waiting-time problem: symbiogenesis, transposable elements, horizontal gene transfer, and alternative pathways.

[3]Due to the 2011 discovery a surprisingly old, fully aquatic whale jawbone, a more accurate available waiting time could be 4 million years.

Symbiogenesis

Thomas Cavalier-Smith describes symbiogenesis as "the extremely rare, but permanent merger of two organisms from phylogenetically distant lineages into one radically more complex organism" [39]. He lists several examples of symbiogenesis, including emergence of the plant kingdom through converting absorbed cyanobacterium into chloroplasts, and emergence of cellular mitochondria through eukaryotes enslaving primitive bacteria [39].

However, since numerous modifications would have been needed to transform a newly acquired symbiont to an organelle [39, 40], it is unclear whether the required timescale is actually reduced by this hypothesis.[4] One can imagine the central absorption event happening quite rapidly, but, while Cavalier-Smith postulates how various stages of symbiogenesis might have occurred, he does not provide details about how long pre- and post-absorption stages must have taken in order for the changes to be fixed throughout the eukaryotes. In addition, he offers no calculation to show that required times are less than available times [39].[5]

Furthermore, the genetic systems of modern chloroplasts and mitochondria are distinct from the rest of the cell [41], indicating that there has never been "free-mixing" of the two genetic transcripts. Whatever genetically-hybridized functions the eukaryotic cell retains, they seem to be highly specialized, which again implies protracted waiting times.

Even if symbiogenetic events did cause chloroplasts and mitochondria in eukaryotic cells, these early events would not resolve subsequent waiting-time problems, such as the Cambrian explosion, the evolution of whales, or the evolution of humans from a hominin-ancestor. Cavalier-Smith acknowledges that symbiogenetic events are "extremely rare" [39].[6] He does not mention any specific ways those rare, early events helped shorten waiting times for evolving the later, problematic novelties.

Transposable Elements

Molecular biologist Nina Fedoroff describes transposable elements (TEs), as "DNA sequences ... having the ability to move to new sites in genomes either directly by ... transposons ... or indirectly through ... retrotransposons" [42]. TE relocations can significantly and rapidly enlarge genome diversity [42], thereby possibly enabling

[4]Cavalier-Smith's meticulous descriptions of numerous symbiogenetic scenarios bear out this point.

[5]Cavalier-Smith occasionally approximates how long ago he believes certain symbiogenetic transitions occurred, and at one point he suggests that an extra 400 million years allowed plastid DNA to evolve the ability to "retain more genes" than mitochondrial DNA. None of these address whether the time required for the multi-faceted symbiogenetic transitions is plausible.

[6]He asserts there are only 7 to 8 known cases, one incorporating mitochondria at the genesis of eukaryotes, and the other six "to make diverse algae."

evolution to arrive at novel, complex features much more rapidly than random mutations could.

Still, there are good reasons to question the ability of TEs to shorten overall waiting times for major biological innovations. In the first place, the time savings in one step of the process point to significant time costs in other steps. Besides moving DNA segments, transposition and retrotransposition require enzymes (transferase and reverse transcriptase, respectively). They also require numerous complex regulatory mechanisms [42, 43], many of which critically defend organisms from highly damaging effects TEs can cause when they are expressed [44–46]. Some of these protective mechanisms include "repressive protein complexes, histone methylation, RNA interference (RNAi), and RNA-directed DNA methylation, as well as recombinational regulatory complexes" [42]. Moreover, even if TEs speed diversity, Fedoroff admits, "The epigenetic mechanisms that control homology-dependent recombination ... slow the pace of genome restructuring to an evolutionary time scale" [42].

Horizontal Gene Transfer

Horizontal gene transfer (HGT) happens when genetic material is directly transferred between organisms. As in symbiogenesis, HGT can significantly and rapidly enlarge genome size and diversity, possibly enabling natural selection to start sorting genetic differences sooner, thereby shortening evolutionary waiting times [11].[7]

Some biologists claim that HGT promotes (and perhaps accelerates) evolutionary transformation [47, 48]. However, most of the genetic material transferred by HGT (at least in animals and plants) consists of transposons [47, 49]. Therefore, the difficulties that TEs face for substantially shortening overall waiting times apply equally here, the only difference being that in HGT the new genetic material originates exogenously.

As with TEs, HGT would require complex transposition and regulation enzymes (both in the source organism and in the host organism). Moreover, the likelihood of harmful effects is even greater with HGT, since the genetic material comes from a foreign body.[8] In order to mitigate damage to the host, the HGT process would require specialized mechanisms to inhibit or silence the transposons' expression [43, 48].[9] Fedoroff reports that prokaryotes (and presumably eukaryotes as well) possess "systems that discriminate endogenous DNA from that acquired through horizontal gene transfer and bacteriophage infection" [42]. As with transposition, the overall waiting times for evolving these specialized enzymes and mechanisms could offset any short-term time savings brought by the rapid influx of genetic material.

Alternative Pathways

The proposed mechanism of alternative pathways is based on the fact that the time required to evolve any given function is reduced if multiple pathways to that function exist. This mechanism thus asserts an innate genetic flexibility in living organisms. Using mathematical models, some studies have concluded that for organisms with large populations and short generation times, alternative pathways could result in adaptations within reasonable overall waiting times. Lynch and Abegg assert "the existence of many plausible pathways by which complex adaptations can emerge much more rapidly than expected" [28]. Durrett and Schmidt report that "significant changes in gene regulation can occur in a short amount of time," due to genetic flexibility" [22, 30].[10]

Can alternative genetic pathways really reduce waiting times sufficiently? Several considerations suggest otherwise. First, in his study of waiting times for novel protein functions, Axe has already recognized that many sequence routes to a given function are possible [16], and taken those alternative routes into account in his calculations. He still concludes, "Protein sequences that perform particular functions are far too rare to be found by random sampling" [16].

Second, as discussed above, Lynch and Abegg, Durrett and Schmidt, and Sanford et al. all agree that, for complex organisms with long generation times and small populations, waiting times for even two mutations are implausibly prohibitive. In the case of the purported chimp ancestor-to-human transition, Sanford et al. assert that even multiple alternative pathways do not solve the problem [30].

> The waiting time problem for a model hominin population is so dramatic that we cannot even begin to resolve the problem – not even when we invoke the special case of having many alternative strings that all meet the same need ... To completely dispel the waiting time problem, one would need to invoke the existence of vast numbers of alternative strings (all ... functionally equivalent), for every evolutionary challenge [30].

[7] Over thirty years ago, Erwin and Valentine wrote about HGT through viral infection as an accelerator of evolution, albeit clarifying that it would only happen with "the aid of other evolutionary processes."

[8] Mathematically speaking, this concern could be partly compensated for if the gross number of organisms experiencing HGT's were massive. Whether this compensating situation exists or has existed will require more research and calculation, in order to clarify how many HGT's would be necessary to overcome the deleterious effects.

[9] Fall, et al. claim that mechanisms in prokaryotes have the ability to "modulate acquisition of new DNA in different genomic positions." One might also reasonably expect that eukaryotes possess such a specialized capacity to discriminate.

[10] Sanford, et al., agree in part, with Durrett and Schmidt, admitting that alternative pathways should at least "reduce waiting times."

Regarding whale evolution, one could reduce Sternberg's estimated waiting time of 43.3 million years to 4.3 by positing 10 alternative, two-mutation pathways to the same function. While this about equals the best estimate of the time available for the transition to modern whales, it does not account for the time to evolve the full suite of changes (at least fifteen and probably many more) required for that transition. Moreover, these changes likely would require substantially more than merely two mutations each.

Returning to Durrett and Schmidt's argument, these authors acknowledge that "the [prior] existence of these so-called 'presites' is necessary for the evolution of new binding sites on a reasonable timescale" [22]. Apparently, without somewhat fortuitous preconditions, waiting times become unreasonable.

AN EVIDENCE-BASED CASE FOR TELEOLOGY

Conceptually, teleological agency could drastically shorten waiting times for complex biological features. Teleology is neither blindly deterministic nor purely random, nor merely a combination of the two. Rather, it intentionally innovates by foreseeing goals and learning and inventing paths to overcome obstacles. Consequently, it can rapidly rule out large swaths of unlikely search space, focusing only on potentially successful solutions [51].[11]

Empirical evidence from genetic engineering and synthetic biology shows how at least some biological transformations can happen much more quickly through intelligent input and manipulation than through purely unguided processes. Over recent decades, this evidence has steadily narrowed the analogical gap between human-designed artifacts and the entities we observe in nature. These analogies may also indicate that teleological causation is the best explanation for the origin of complexity that would otherwise be inexplicable.

The experimental evidence highlighted here is limited to intentional (teleological) changes of key aspects of unicellular organisms by human researchers. Where available, we will broadly compare the waiting times for such changes with the waiting times estimated by researchers for analogous changes purported to result from purely non-teleological Neo-Darwinian processes. These putative non-teleological waiting times, while quite long, do not seem nearly as prohibitive as those calculated by Axe above (e.g. exceeding the age of the earth by many orders of magnitude). This is perhaps because different estimation approaches were used, or because the particular biological subjects of their respective calculations or estimates may be quite different. The purpose here is to compare times with and without teleological input in order to show from empirical data how drastically teleology *shortens* waiting times.

First, as reported in 2012, a set of viral-bacterial binding site experiments offer one brief example of the scale of time saved by teleologically-manipulated unicellular experiments. Justin Meyer et al., report that, on average, viruses on which they experimented were able to evolve the ability to bind to a new site on the outer membrane of *E. coli* within 12 days [52].

Although this is extremely rapid by evolutionary standards, it is important to account for the role played by the experimenters [52].[12] Biologist Dennis Venema, reporting on the experiments, comments, "*The researchers used a genetic trick* to almost entirely remove LamB from a population of *E. coli* hosts. ... *The researchers rigged it* so that every so often a susceptible host with LamB would be produced."[13] Meyer and his team do not mention how much these intentional steps contributed to the rapid binding site change.

Another very close analogy intimately linking human agency to rapid biological transformation can be derived from the results recently published by the Sc2.0 yeast genome project, which aims to build a streamlined, synthetic version of the *Saccharomyces cerevisiae* genome.[14] This project was initially estimated to take about 12 years to complete [53, 54], enlisting the efforts of laboratories in ten locations around the world [55].

The Sc2.0 project is replete with strategic and tactical goals, spanning all levels. From the project-wide mission, to the goals guiding each particular team's task of synthesizing separate chromosomes, down to the preliminary or component objectives for accomplishing small steps toward team goals. The project's educational mission is to further spur "systematic studies of eukaryotic chromosomes" [55] and discover how "genome-wide engineering" affects "living systems" [56]. The project's practical aims for building a basic yeast "chassis" include expanded and faster "production of many pharmaceutical and industrial compounds" [57].[15] Relevant to waiting times, other key objectives concern speed and innovation, including inducing "rapid and complex structural changes

[11] See Dembski's discussion of information as the product of ruling out possibilities.

[12] The 12-day waiting time does not include the 28 days during which the team "cocultured a virulent (non-lysogenic) derivative of phage λ and *E. coli* B in 10 ml of a minimal glucose medium in six replicate flasks ... with daily transfers of 1% of each community [etc.]." These are teleological manipulations of conditions and specimens.

[13] Emphasis mine. Researchers achieved the balance through careful, intentional manipulations.
http://biologos.org/blogs/dennis-venema-letters-to-the-duchess/the-evolutionary-origins-of-irreducible-complexity-part-4

[14] The journal *Science* included eight articles on the Sc2.0 project interim results in its March 10, 2017 issue. Numerous references from those articles appear in this section.

[15] See also the Frequently Asked Question "What kind of biological questions can be answered with this approach?" at the Sythentic Yeast 2.0 website (2017) http://syntheticyeast.org/faq/

of synthetic chromosomes" [56].

Sc2.0 was designed to display three broad features: stability, flexibility, and fidelity. In order to reduce non-teleological change, teams intentionally designed features into Sc2.0 to reduce "sources of genomic instability" in the native genome by removing or isolating tRNA's, retrotransposons, and LTR repeats [55]. Sc2.0 project leaders also aimed to design the genome to be flexible in order to generate diverse sequences in different yeast cells [55]. Specifically, teams inserted numerous (sometimes hundreds) of loxPsym sites into Sc2.0 chromosomes, which "enable inducible evolution by SCRaMbLE (synthetic chromosome rearrangement and modification by loxP-mediated evolution)" [56]. The result is "a robust, high fitness, engineerable chassis for unbiased exploration of the viable genotype-to-phenotype space" [58]. Finally, project leaders designed Sc2.0 to largely maintain "wild-type" phenotypic functions, and gene content and arrangement [55, 56]. This was intentionally done to enable rapid detection and correction of deleterious bugs introduced through the synthesized genes [55, 59].

Sc2.0 Increased Speed

In addition to the key components of teleology and design features to induce transformation, the various teams also designed Sc2.0 to generate those diverse functions at a rapid pace. Mercy, et al. report that the SCRaMbLE system is "aimed at accelerating genomic plasticity" [56]. Dymond and Boeke similarly comment on the feature of speed: "Sc2.0 is highly plastic and can generate a wide variety of genome variants with little additional expenditure of time or money" [57].

Early in 2017, biologist Ben Blount, a project team member noted, "The design changes we've made ... will allow us to induce rapid evolution within our synthetic strains" [59]. Blount then provided experimental evidence of such rapid evolution. Using the SCRaMbLE protocol to test yeast cells already containing a partially synthetic chromosome, and subjecting those cells to abnormally high temperatures, Blount's team discovered that while most cells had died, one apparently well-adapted strain had grown "absolutely huge colonies overnight," which was "quite a dramatic phenotypic change for yeast and we've not seen evidence in the literature ... of yeast cells growing this fast overnight on a plate" [60].

In a related series of experiments, Ali Awan, along with Blount and other colleagues, redesigned a pathway from another bacterium and then used it to induce yeast to produce penicillin (a new function for yeast). Utilizing the SCRaMbLE protocol on the partial version of Sc2.0 yeast with that same pathway, they quickly optimized the bioactive penicillin yield to well beyond levels commercially available for fighting *Streptococcus pyogenes* [60, 61]. The final optimization step in this process produced the most striking effect on the waiting time, owing to the synthesized Sc2.0 chromosome's capacity for radical genomic flexibility. In two days, that step produced a strain which doubled the yield; a result which the team had previously needed four years to induce when they started from a native (non-synthesized) yeast cell [60]. Admittedly, these experiments and their results are still in their incipient stages. However, they do provide positive prototypical evidence of teleologically-manipulated, rapidly-induced biological transformation.

For centuries, people have intentionally cultivated and extensively engineered yeast for producing useful substances, just as they have cultivated or bred countless other organisms. What stands out about Sc2.0 for this discussion is the drastic accelerations it facilitates for attaining favored, adaptive functions. On one hand, Yue Shen, et al., comment that the wild-type version of their team's chromosome, from which the Sc2.0 version was copied and redesigned "has naturally evolved over millions of years" [58]. In contrast, if Sc2.0 is completed in 2018, a group of intelligent agents – within about twelve years – will have produced not only one yeast chromosome, but an entire streamlined and highly-adaptable genome which is already producing sub-strains with functions novel to the species. Roughly calculating based on Shen, et al.'s claim, teleology will have accomplished highly analogous changes in a little over one one-hundred-thousandth of the time he estimates it took non-teleological processes.

Further, teleology also shortens waiting time in synthetic biological research through the research teams learning and sharing new time-saving methodologies from their laboratory experiences. Blount comments, "The synthetic yeast project itself has taken a long time, but both because of background factors with technology increasing and also the technologies that have come out of this project itself, ... if you were to make another genome now, it would take you a fraction of that time" [60]. Non-teleological processes like Neo-Darwinism and its proposed supplements discussed above do not learn through experience nor share their most effective methods with each other.

The time savings illustrated in this project (as well as in the opening example regarding intentionally shifted binding sites) highlights the point of this paper: Teleology achieves biological changes similar to those claimed for the Neo-Darwinian mechanism, yet in dramatically shorter time. By extension, these examples offer proof-of-principle, analogical support to the proposal that teleology could provide a far better explanation than the non-teleological mechanisms of the Modern Synthesis for the appearance (or development) of novel biological structures and systems.

Objection: Merely Copying an Existing Genome?

A thoughtful critic might find fault with using the Sc2.0 experiments as an example. One might assert that one cannot credit intelligent agency with speeding up waiting times when human researchers have merely copied (or streamlined) an already-existing, functioning genome. Should we wonder that Neo-Darwinism waiting times are longer than the waiting times for the Sc2.0 project when blind mutation and selection did the lion's share of the hard work evolving the Sc genome in the first place? This objection highlights a correct observation but misses several key points. First, the example above of Awan, Blount and their team's "trial-run" experiments do not merely illustrate duplication of an existing natural pattern in a chromosome. Their experiments also consisted of two innovative phases. The first phase included four years of rigorous learning through trial and error, not merely cutting and pasting genes from *Penicillium chrysogenum.* The team redesigned the five-gene metabolic pathway so that it would work in a different organism, and ultimately produce a bioactive amount of penicillin, a novel function for yeast [61]. The second, much briefer phase utilized the teleologically-innovated SCRaMbLE system to produce numerous variants, one of which was, again, teleologically chosen (not merely copied) because of its dramatically higher penicillin yield [60]. Thus, while the generic Sc2.0 genome is largely a replication of a natural genome, one of its prototype variants, a truly novel yeast strain, required not mere duplication but significant teleological, innovative manipulation.

Second, while the generic Sc2.0 genome is largely a replicate, it is also important to remember that such replication closely mimics standard evolutionary processes. Sc and its closest living relative species *Saccharomyces paradoxus* share most of their DNA. The two species "appear to be biochemically indistinguishable, have the same chromosome number, and appear to be largely syntenic" (having the same genes that share the same approximate chromosomal location) [64].

Further, since functional change happens either by randomly mutating and selecting duplicated genes [65][16] or by horizontally receiving genes or even whole genomes either transferred (by HGT) or absorbed (by symbiogenesis) from neighboring organisms [66], non-teleological evolution itself relies on large-scale duplication of pre-existing genetic information. In this sense, the Sc2.0 example is highly analogous. Awan et al.'s penicillin-producing yeast could reasonably be thought of as an example of *teleological* horizontal gene transfer, or even perhaps teleologically-guided convergent evolution.

The purpose of including the example above of Sc2.0 and the penicillin generated by one of its variants is not to show how intelligent designers can create brand new organisms with completely novel functions entirely from scratch. Rather, the purpose is to illustrate that intelligent designers can closely mimic one small part of what non-teleological mutation and selection and their proposed supplemental mechanisms are purported to do, only much, much faster. Viewed in this light, it seems fair to compare Sc2.0 with Neo-Darwinian mechanisms and their accompanying supplements.

CONCLUSION

The blind mechanisms of the Modern Evolutionary Synthesis are confronted by seemingly insurmountable obstacles of time. Faced with this, many biologists advocate an "extended synthesis" which supplements classic Neo-Darwinism with new, additional naturalistic mechanisms [67].[17] However, a full consideration of these additions reveals that the decreases in waiting time ascribed to them are more than offset by time increases that tend to be overlooked. Teleological mechanisms, on the other hand, clearly can shorten waiting times drastically. This conclusion is now well demonstrated by research in synthetic biology and genetic engineering. The challenge for those still seeking a resolution of the waiting time problems via non-teleological mechanisms is to show quantitatively how such mechanisms can plausibly overcome the formidable waiting-time problem they face.

[16] However, see Leisola's list of problems that accompany gene duplication, which would likely incur long waiting times, p. 156.

[17] This volume includes contributions by biologists advocating a range of supplementary non-teleological mechanisms including many of those listed under Proposed Corrective Amendments.

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