

THEISTIC EVOLUTION IN THE POSTGENOMIC ERA

by *Georgi K. Marinov*

Abstract. How to reconcile the theory of evolution with existing religious beliefs has occupied minds since Darwin's time. The majority of the discourse on the subject is still focused on the Darwinian version of evolutionary theory, or at best, the mid-twentieth century version of the Modern Synthesis. However, evolutionary thought has moved forward since then with the insights provided by the advent of comparative genomics in recent decades having a particularly significant impact. A theology that successfully incorporates evolutionary biology needs to take such developments into account, because range of truly viable options among the many versions of theistic evolution that have been proposed in the past may narrow down when this is done. Here I present these previously underappreciated strains of contemporary evolutionary thought and discuss their potential theological impact.

Keywords: evolution; intelligent design; neutral and nearly neutral theory of molecular evolution; population genetics; theistic evolution

The reconciliation of the theory of evolution with Christian theology is a central theme in the relationship between science and faith. Prominent atheist writers have repeatedly insisted that the two are incompatible (e.g., Coyne 2012) while numerous propositions to the contrary under the general umbrella of theistic evolution (TE) have been advanced. Unfortunately, the debate has often suffered (though often both sides have not been fully aware of it) as a result of the misrepresentations of the theory of evolution that dominate its depiction not only in popular culture but frequently even in the writings of professional scientists.

First, a disproportionately large amount of time and effort in the area is spent writing about the works of Charles Darwin (Darwin 1859) even though, as monumental as their influence was in the past, they are only of historical interest at present and by no means reflect the current status of evolutionary theory, which has undergone some 150 years of development since Darwin's time. Second, the view of evolution that emerged in

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the middle of the twentieth century, usually referred to as the Modern Synthesis, in its hardened form with its emphasis on natural selection as the dominant evolutionary force and adaptation as its result, has come to dominate communications with the public and in turn discourse at the intersection of science and religion, even though this view is no longer tenable in the light of developments from the past several decades. At least part of the reason for this is that some of the most outspoken atheist authors hold panadaptationist views (Dawkins 1986, 1996), which has shifted the response on the part of theologians toward that particular position. This pattern of focusing on Darwin (and more recently, Dawkins) while ignoring critically important developments in evolutionary research continues up until the very present. For example, a recent article (Lamoureaux 2012), a portion of the abstract of which I quote below, dissects Darwin's writings in order to demonstrate their compatibility with theism:

According to famed atheist Richard Dawkins, "Darwin made it possible to be an intellectually fulfilled atheist." Many people today, both inside and outside of the church, follow Dawkins and assume that Charles Darwin ushered in a dysteleological view of nature with no ultimate plan or purpose and no place for God. [. . .]. In this two-part article, I will glean theological insights from Darwin's writings to challenge Dawkins's belief, and I will propose the provocative anti-thesis that Darwin made it possible to be an intellectually fulfilled Christian theist. Here in Part I, we will examine Darwin's views on (1) divine creative action and (2) his experience with and understanding of intelligent design in nature.

The obvious problem here is that in what way Darwin's writings are compatible with certain theistic positions has little relevance to how that question can be resolved with respect to the modern theory of evolution because it is no longer Darwin's theory of evolution.

Another contributor to this state of affairs is a peculiar aspect of the position of evolution among the sciences with respect to its understanding by nonspecialists. In the words of Michael Lynch:

Evolutionary biology is treated unlike any science by both academics and the general public. For the average person, evolution is equivalent to natural selection, and because the concept of selection is easy to grasp, a reasonable understanding of comparative biology is often taken to be a license for evolutionary speculation. It has long been known that natural selection is just one of several mechanisms of evolutionary change, but the myth that all of evolution can be explained by adaptation continues to be perpetuated by our continued homage to Darwin's treatise (6) in the popular literature. (Lynch 2007b, 8597)

Finally, the reaction of general society to evolutionary ideas likely also played a major (perhaps even primary) role in shaping the current dominant perception of the theory. Although the history of resistance to evolution is much more complex than the often-told simplistic narrative of dogmatic

rejection of it on religious grounds from the very beginning, it remains true that creationism has been a constant cultural presence for most of the twentieth century and creationists have almost invariably equated all of evolutionary science with Darwin's theory of evolution. This seems to have forced evolutionary scientists to constantly defend Darwin and repeatedly go back to the original text of *The Origin of Species*. Unfortunately, Darwin never became aware of Gregor Mendel's discoveries of the principles of genetics (Mendel 1866) even though Mendel's work was available to him. As a result natural selection was the only evolutionary force extensively discussed in *The Origin of Species*, with the appreciation of the importance of the others having to await the development of population genetics more than half a century later. The end result has been that the excessive focus on Darwin's work in modern times, for reasons having little to do with its scientific relevance, has also, at least in part, been responsible for the disproportionate attention devoted to natural selection.

The goal of this article is to raise awareness of the overlooked aspects of modern evolutionary theory and their theological implications and to examine the way they affect the viability of some of the existing TE propositions. If a good understanding of the ways a God could create through evolution is to be achieved, the mechanisms of evolutionary change have to be fully accounted for. As these changes happen on the level of populations, through the interaction of natural selection, mutation pressures, and genetic drift, the disciplines of population genetics, molecular genetics, and comparative genomics have to feature prominently in any such discussion. I will first briefly explain some of the basics of modern evolutionary theory on the level of genomes and populations. I will then examine how the explosion of genome sequence data in the last two decades has empirically illuminated the relative roles that the different forces of evolution have played in human evolution, with particular focus on the importance of neutral processes. Finally, I will attempt to identify the most viable (in my view) TE ideas after accounting for these developments. I note that I write this starting with the premise that intelligent design (ID) as conventionally understood is not a viable proposition even though there is no way to completely reject that class of hypotheses.

POPULATION GENETICS AND THE FORCES OF EVOLUTION

A distinction is sometimes made between the fact of evolution and the theory of evolution (Gould 1981). The former refers to the common descent of all organisms on Earth including humans from earlier life forms that can be ultimately traced to a last universal common ancestor. This has been the scientific consensus since the time of Darwin (even if the topology of the phylogenetic tree of life has been drastically revised) and is

also agreed upon by all versions of TE. In contrast, our understanding of the mechanisms of evolution has undergone significant development.

At the time of Darwin, how inheritance works was not understood, and as a result where the variation to be acted upon by natural selection came from and how it was maintained was not clear. This presented a hurdle to the theory as the blending theory of inheritance that Darwin subscribed to would be expected to quickly reduce existing variation in a population. It was only after the rediscovery of Mendel's principles at the turn of the century that the issue was resolved and the path toward the later developments of the twentieth century opened. The theoretical basics of modern population genetics were developed in the next several decades based on the Mendelian principles of inheritance and basic probability theory (Fisher 1930; Haldane 1932). Eventually an evolutionary theory fully incorporating genetics was crystallized by the middle of the twentieth century, often referred to as the Modern Synthesis (Huxley 1942). The Modern Synthesis understands the process of evolution as a change in gene/allele frequencies in populations and recognizes several primary forces that drive such changes:

1. **Natural selection.** This is the most familiar evolutionary force, referring to the process in which environmental conditions determine the differential reproductive success of organisms carrying different genotypes, with a corresponding change in the frequency of alleles in a population. Note that selection can also happen due to factors acting within a population; for example, sexual selection, in which organisms within a population compete with each other for mating success, is a special case of natural selection (but not a separate evolutionary force).
2. **Mutation.** Mutational processes represent the major source of genetic variation in populations, and while they can be thought of as "random" in nature, they are not entirely unbiased. For various biochemical reasons, some mutations occur more often than others, which can have significant consequences for the outcome of evolution.
3. **Genetic drift.** Real-life populations are finite in size and in some cases quite small (discussed in more depth below). This means that allele frequencies can change (and alleles can eventually become fixed) simply due to the sampling error associated with the transmission of alleles from one generation to the next.
4. **Migration.** It is possible that two separated populations of the same species, with different distributions of allele frequencies, will eventually come in contact with each other and mix, leading to a change in the allele frequencies in the new population.

The population genetics framework of the Modern Synthesis is still the basis for all of modern evolutionary biology even if many of its interpretations have changed significantly. At this point, it is so well established and has proven its usefulness that it is reasonable to demand that all proposed evolutionary explanations have a solid population genetics basis. In this context, paraphrasing Theodosius Dobzhansky's famous quote into "Nothing in evolution makes sense except in the light of population genetics" (Lynch 2007b) is fully justified.

The simplest evolutionary model in the classic Fisher-Wright framework involves a population of synchronously reproducing randomly mating hermaphrodite organisms contributing to an infinite pool of gametes with free recombination. The selective advantage of an allele is modeled with the selection coefficient s where its frequency p in the next generation is expected to be $p_1 = (1 + s)p_0$. Positive values of s are therefore expected to lead to fixation of the allele while negative values to lead to its elimination. However, real populations are finite and the random sampling nature of gamete segregation and mating has the important consequence that neither the fixation of adaptive alleles nor the elimination of maladaptive ones is ensured. Mutations with negative values of s can still be fixed by chance and mutations with positive values of s may not go to fixation due to genetic drift.

The interplay between selection and genetic drift is well understood quantitatively. To proceed, further relaxations of the assumptions of the Fisher-Wright model are needed. Real-life populations have spatial, sex, and age structure; as a consequence the absolute size N of the population is not relevant to population genetics calculations. The "effective" population size N_e , which corrects for these factors and is in practice almost always lower than N (e.g., the total human population size is at present larger than 7×10^9 , but its long-term N_e is only $\sim 1 \times 10^4$), is used instead (Caballero 1994). Additional complications arise from the fact that genes do not exist as separate freely recombining entities but are physically linked on chromosomes, with decreased rates of recombination the closer they are to each other. This further decreases N_e (Gillespie 2000) and also makes it possible for strongly beneficial mutations to drive the fixation of tightly linked deleterious mutations and vice versa ("genetic draft"). Linkage has the effect of decreasing the fixation probabilities of adaptive mutations and increasing those of maladaptive ones (Hill and Robertson 1966). Finally, mutations are neither present all the time nor do they arise just once, but are better described by a continuous mutation rate per locus μ . This is important because, as mentioned above, the physical processes generating mutations can be biased.

Imagine a selectively neutral ($s \approx 0$) mutation arising in a diploid population of N individuals. Its initial frequency in the gamete pool is $1/2N$,

which is also the probability of its fixation by random chance in the absence of additional mutations as each of the $2N$ alleles in the population has equal chance of being fixed by a neutral random process. Incorporating the mutation rate into the model, the long-term fixation probability of a neutral mutation turns out to be independent of population size and equal to μ as in each generation $2N\mu$ such mutations are produced. What is the probability of fixation when $|s| > 0$? Such selective advantage only ensures that a new mutation of initial frequency $1/2N$ will have a frequency of $p = (1 + s)/2N$ in the gamete pool, which is still a small number. Thus there is a very significant stochasticity in the fixation of new mutations and most are eliminated by chance even if they are beneficial. Without going into technical details, the general probability of fixation of a new mutation is given by Kimura (1962):

$$p_f \approx \frac{\frac{2s N_e}{N}}{1 - e^{-4N_e s}}$$

Important corollaries of this are:

1. Even in very large populations, the fixation probability only asymptotes to $2sN_e/N$.
2. Taking into account μ , the limit of the fixation probability for beneficial mutations is $4N_e s \mu$, which increases with N_e .
3. Deleterious mutations with small values of $|s|$ will behave similarly to neutral alleles. The smaller N_e , the larger $|s|$ for which this is true.

It follows that the power of selection is limited by N_e and s . Comparing p_f to the neutral expectation $1/2N$, one can identify the regime in which selection dominates drift and vice versa. Specifically, when

$$|4N_e s| < 1$$

alleles will behave as effectively neutral irrespective of whether they are beneficial or maladaptive (Lynch 2006, 2007c). It is therefore expected that organisms with low long-term N_e will have accumulated a number of slightly deleterious mutations (Ohta 1973).

The dependence of the strength of selection on N_e was noted early in the development of population genetics (Wright 1931). However, natural selection was the focus of attention, both for historical reasons (it was the evolutionary force that Darwin focused on) and because it is the only force generating adaptation, to the neglect of the other three forces, especially in popular evolutionary accounts. That the consolidation of the Modern Synthesis happened just before the structure of DNA and the genetic code were worked out likely also contributed to this outcome. These advances

provided the first insights necessary for the development of an evolutionary theory that seriously considers the role of nonadaptive processes, for example, the observation that the genetic code is degenerate and multiple codons code for the same amino acid leaving the third position free to evolve largely neutrally. The neutral and nearly neutral theories of evolution (Kimura 1968; King and Jukes 1969; Kimura 1983) as well as the writings of Stephen Jay Gould and others (Gould and Lewontin 1979) attempted to break the adherence to panadaptationism. They only succeeded partially and largely within the circles of the population genetics and molecular evolution community, where nonadaptive evolutionary mechanisms are a foundational component of most current work in the field. The traditional popularity of natural selection and its usefulness as an explanatory tool (Mayr 1983) have helped keep its place as the dominant and often only mechanism of evolution in most nontechnical presentations. This was not, however, the only reason. The data needed to weigh the relative contributions of different evolutionary forces were not available until DNA sequencing was developed and later the genomes of large numbers of organisms could be sequenced, analyzed, and compared. The last two decades have seen an explosion of such data, still continuing today, and its analysis has forced researchers to formulate an updated view of the evolutionary process, in which nonadaptive mechanisms play a prominent role (Lynch 2007c; Koonin 2011).

ROLE OF NONADAPTIVE PROCESSES IN THE EVOLUTION OF MULTICELLULAR EUKARYOTES

DNA sequencing and comparative genomics have allowed the placement of many genomic and cellular features in the context of the population genetic environment of different lineages. This has revealed that numerous traits fundamental to the biology of complex multicellular organisms are primarily the result of nonadaptive evolutionary processes. To understand why this is the case, a brief overview of these features is necessary.

Cellular life can be divided into two groups: the prokaryotic bacteria and archaea, and eukaryotes (which include humans). Fundamental differences in cellular and genomic organization exist between them, the most relevant to the discussion here being:

1. **Intramembrane system.** Prokaryotes have a generally simple intracellular organization, with no membrane-bound organelles (except in some rare cases). In contrast, all eukaryotes possess a complex intramembrane system.
2. **Nucleus.** All eukaryotes contain a membrane-enclosed nucleus containing their genome, continuous with the endoplasmic reticulum intramembrane system.

3. **Mitochondria.** All eukaryotes contain a mitochondrion (or the remnants of one), an organelle vital for cellular respiration. It has its own (reduced) genome, bears a striking resemblance to a bacterial cell, and evolved as the result of an endosymbiotic event between the ancestor of eukaryotes and a member of the α -proteobacteria clade. This was perhaps the most important event in the evolution of eukaryotes, as will be discussed in detail later.
4. **Spliceosomal introns.** A striking feature of the genes of all eukaryotes is that they contain introns (though not all genes). Introns are transcribed, but are then excised from messenger RNAs (mRNAs) before translation into proteins through an intricate splicing process involving a dedicated machinery, the spliceosome, containing both RNAs and proteins. Bacteria do sometimes contain introns; however, they are few and rare and are self-splicing.
5. **Multicellularity.** Even though most eukaryotic lineages are unicellular, on several occasions multicellularity arose. In contrast, no prokaryotic lineage has evolved complex multicellularity.

In addition to these discrete, qualitative differences, prokaryotes and eukaryotes are differentially distributed on a continuum with respect to the following traits.

1. **Genome size.** The largest prokaryotic genomes contain ~ 10 million base pairs (10 Mb). In contrast, the human genome contains more than 3 billion bases (~ 3.1 Gb), with most mammals falling in the same range, there are plants and fishes with genomes larger than 100 Gb, and some unicellular eukaryotes have possibly even bigger genomes (Gregory 2005). Most unicellular eukaryotes, however, have small genomes of a few tens of Mb, and small invertebrates tend to lie somewhere in the hundreds of Mb range. It should be explicitly stressed that these are averages and even if it might seem that genome size is tightly correlated with organismal complexity, this is deceptive. The existence of unicellular organisms with genomes hundreds of times larger than the human genome is only one of a very large number of such discrepancies, often between very closely related organisms. The absence of absolute correlation between organismal complexity and genome size is referred to as the “C-value paradox” (Thomas 1971).
2. **Intron content.** Prokaryotes do not contain spliceosomal introns, while all eukaryotes do, but in addition to this, considerable variety is observed in the number and length of introns within eukaryotes. Many unicellular eukaryotes, particularly the ones with small genomes, contain only a few and often quite short introns. In

contrast, large multicellular organisms with big genomes have many and long introns. A continuum generally tracking the distribution of genome size is found in between.

3. **Transposable elements.** Transposable elements are DNA sequences capable of copying themselves to new locations in the genome. They do exist in prokaryotes but are rare. In contrast, eukaryotes with large genomes contain extremely large numbers of them. Half of the human genome consists of transposons (International Human Genome Sequencing Consortium 2001). Eukaryotes with smaller genomes belong to a continuum in between these extremes.

Differences in intron and transposon content provide part of the explanation for the C-value paradox. The fraction of the human genome occupied by decayed transposable elements and other nonconserved non-coding DNA fits well with theoretical expectations that most of the human genome consists of “junk” DNA (Ohno 1972), the sequence of which does not serve an important function for the fitness of the organism. (Given the size of the human genome and the per-generation mutation rate, if all of it was functional, there would be an unbearable number of deleterious mutations in every generation; this is not the case, thus the sequence-constrained component of the genome has to be a minor fraction of it). An explanation, well supported by data, for the observed variation in intron and transposon content as well as the evolutionary origin of many of the other differences between prokaryotes and eukaryotes has been derived from a straightforward population genetic analysis of the evolutionary dynamics of their appearance and maintenance or elimination by natural selection and genetic drift.

Recall that selection dominates evolution when $4N_e \gg 1/|s|$ and drift dominates it when $4N_e < 1/|s|$. To determine the importance of these forces for a given mutation, we need to know $4N_e$ and s . Intuitively, physically smaller organisms should have larger N_e than large ones. The volume of a eukaryotic cell is about two orders of magnitude larger than that of a prokaryote one, and unicellular eukaryotes are orders of magnitude smaller than large-bodied multicellular ones. These differences in size translate into inversely proportional differences in total population size N . It is often noted that the human body contains more prokaryotic cells living on and in it than the number of its own cells. But the complex relationship between N and N_e necessitates the empirical estimation of the latter, and this is extremely difficult to do directly. Fortunately, another quantity, $4N_e\mu$, can be empirically derived. At equilibrium, new mutations (introduced at a rate 2μ in a diploid organism) balance with fixation by genetic drift (of magnitude $1/2N_e$). The levels of variation at fourfold degenerate codon positions within a species can be used to estimate $4N_e\mu s$ (Lynch and Conery 2003; Lynch 2006). N_e can then be calculated from estimates of

μ . The average estimated N_e is $\sim 10^8$ or more for prokaryotes, $\sim 10^6$ – 10^7 for single-celled eukaryotes, on the order of 10^6 for invertebrates and 10^4 for vertebrates (Lynch 2006, 2007c). A similar difference (10^6 vs 10^4) is observed between annual plants and trees. Thus a defining population genetic characteristic of eukaryotes is their generally low N_e , with N_e being extremely low for large-bodied multicellular organisms such as humans.

How has this impacted their evolution? The following is a partial list of fundamental features of their biology which are at present best explained as the result of nonadaptive processes and low N_e .

1. **Transposable elements proliferation and noncoding DNA expansion.** Transposable elements have been exapted into new regulatory elements or even new genes on numerous occasions in eukaryote evolution (Rebollo, Romanish, and Mager 2012). However, such cases, in which they turn out to be useful, are very few compared to their total numbers and also cannot explain why they persist and proliferate in certain genomes and not in others. New transposon insertions can be highly detrimental to the fitness of an organism if they happen to disrupt a vital gene, and even intergenic insertions affect fitness negatively by their mere presence, as they increase the size of mutational targets (the same mechanisms of exaptation into new regulatory roles can also lead to misregulation of gene expression). A testament to their negative effect is the existence of very elaborate and vitally important small RNA-based systems for countering their spread (such as piRNAs; Aravin, Hannon, and Brennecke 2007). One would therefore naively expect that transposons would be rapidly eliminated from populations by natural selection. That this is so efficient in bacteria, and not happening in large-bodied eukaryotes, is readily explained by differences in N_e . As $|s|$ of each individual insertion in intergenic space is low, natural selection cannot purge them from the genomes of lineages with small N_e and they are free to proliferate. In bacteria, N_e is very large, selection is highly efficient, and transposons are rare.
2. **Introns.** The evolution of introns has long been a puzzle. Introns allow for alternative splicing and the production of multiple protein products from the same gene, and it has been suggested that this provides a long-term evolutionary advantage. However, even though alternative splicing events seem to be widespread in mammals (Wang et al. 2008), a major fraction of them may well simply be the result of biochemical noise of the splicing machinery. More importantly, such an explanation does not explain how introns evolved initially, why they are completely absent from bacteria and the distribution of their number and length within eukaryotes. The mere presence

of an intron results in an increase in the complexity of the task of maintaining the proper expression of a gene as it has to be spliced out correctly for a functional protein to be produced. On its own this affects fitness negatively. The fidelity of splicing depends on the presence of splicing signals in DNA and on a complex spliceosome machinery to carry out the excision. If some bases necessary for correct splicing are mutated, the result is often a nonfunctional protein. Thus introns present a mutational burden, and one would expect that they would be selected against. This is illustrated well by the large number of human diseases due to mutations affecting splicing (Cooper and Mattox 1997; Douglas and Wood 2011). This negative effect on fitness can be quantified by considering the total number of base pairs n required for proper splicing and the mutation rate μ . Then $|s| \approx n\mu$. As alleles evolve effectively neutrally if $N_e < 1/4|s|$, if $1/n > N_e\mu$ the selective disadvantage of an intron is below the threshold at which selection is able to remove it. The value of n is between 20 and 40 (Lynch 2002). The value of $N_e\mu$ is significantly lower than the 0.05 threshold this implies in land plants and vertebrates, it is around it for unicellular eukaryotes, and well above it for bacteria due to the differences in both the typical N_e and the mutation rate of these groups (Lynch 2006). This explains very well why introns are absent from bacteria, why they are often short and few in number in unicellular eukaryotes and why they are so abundant in land plants and metazoans.

The above explains why introns persist in certain groups, but does not provide an account of how they were initially established in eukaryotes. Our current best understanding of how that happened is very interesting and relevant to the larger topic of this essay. It is reasonably well understood that spliceosomal introns evolved from Group II self-splicing introns (Lambowitz and Zimmerly 2004), retrotransposable elements with enzymatic activity as RNAs (ribozymes) to catalyze their own excision from mRNAs, leaving the mRNA into which they are inserted functional. This is evolutionarily beneficial for the Group II introns themselves—if they are not excised, they might cause the host's death through the disruption of vital genes, and with it their own extinction. The structure of Group II introns is remarkably similar to the structure that spliceosomal RNAs adopt and both reactions employ similar biochemical mechanisms carried out by RNA. This is strong evidence that the spliceosome and spliceosomal introns evolved from Group II introns after the latter lost their self-splicing ability and instead became reliant on *trans*-acting factors, which eventually evolved into the spliceosome (Cech 1986). But how and when did this happen? The most likely scenario is based on the following observations. First, eukaryotes

probably originated as the result of an endosymbiosis event between an archaeon (or a related lineage) and the α -proteobacterial ancestor of mitochondria. Second, Group II introns are found in bacteria, but are rare in archaea, and when they are present in the latter, they seem to be the result of recent horizontal gene transfer (Dai and Zimmerly 2003). Third, during the coevolution of mitochondria and their host, there has been massive transfer of genes from the mitochondrial genome to the nucleus, a process that still continues to this day (Hazkani-Covo, Zeller, and Martin 2010). Thus spliceosomal introns likely originated from Group II introns migrating from the α -proteobacterial endosymbiont and inserting into the genome of the protoeukaryote. The fixation of these insertions by genetic drift was likely facilitated by its existence in a state of low N_e during its early evolution (Martin and Koonin 2006). Some insertions lost the ability to self-splice and the spliceosome evolved from the remnants of *trans*-acting Group II Introns and archaeal proteins. Strikingly, extensive analysis of orthologous genes has revealed that numerous intron positions are conserved across the eukaryotic tree of life (Fedorov, Merican, and Gilbert 2002; Rogozin et al. 2003, 2005; Collins and Penny 2005; Roy and Gilbert 2005; Roy 2006; Carmel et al. 2007a, 2007b; Csuros, Rogozin, and Koonin 2011), with only a few smaller more recent waves of intron expansion in some lineages (e.g., early in the evolution of metazoans, Koonin 2011). Apparently there was an episode of large-scale intron expansion very early in eukaryote evolution.

3. **The nucleus and eukaryogenesis.** The above is fairly well established, but it may be that the role introns played in eukaryote evolution was even larger. It has been suggested that this large-scale intron insertion is what drove the evolution of core features of eukaryotic biology, such as the nucleus itself (Koonin 2006; Martin and Koonin 2006; López-García and Moreira 2006). In prokaryotes, translation of mRNAs is directly coupled to their transcription. However, splicing reactions mediated by *trans*-acting factors are slow relative to translation. The presence of large number of such introns would have led to the production of nonfunctional proteins. The nucleus would have physically separated the two processes eliminating the problem, providing a strong selective pressure toward its evolution.
4. **Complex gene regulatory networks (GRNs) and organismal complexity.** The amazing complexity of gene regulation in multicellular organisms is one of their most striking features, especially when contrasted with the situation in prokaryotes and many single-celled eukaryotes. The typical human gene is associated with multiple regulatory elements (REs) controlling its expression (ENCODE

Project Consortium 2012; Neph et al. 2012). They often act over significant genomic distances, and different REs may drive expression in different cell types. During development, genes are turned on and off by intricate cascades of positively and negatively acting transcription factors; often several layers of regulation are responsible for the expression of each gene (Davidson 2006). It is primarily this complexity of gene regulation that has allowed the increase in organismal complexity in metazoans, as one of the major findings of evolutionary developmental biology has been that the evolution of form and body plans has been driven largely by changes in the timing and location of the expression of a conserved set of genes rather than by changes in the genes themselves (Carroll 2008).

The rewiring of GRNs has been key to this process. However, the molecular changes resulting in GRNs rewiring and expansion are not directly adaptive (Lynch 2006, 2007a). The known mechanisms that create new REs in the genome all involve genomic alterations with slightly negative s (as they increase the size of the mutational target in the genome). These include: (1) the duplication of already existing REs, followed by their divergence, degeneration (so that neither copy can support the normal expression of the gene on its own) and subfunctionalization, with the end result being that the expression of the gene is regulated by and dependent on two different elements in different cell types (Lynch 2006, 2007a) (a similar process unfolds with duplicated genes, Force et al. 1999, 2005); (2) the exaptation of transposon insertions as novel REs (Rebollo et al. 2012); and (3) the *de novo* appearance of REs from noncoding DNA. The dynamics of these processes is a complex function of the mutation patterns of gain and loss of transcription-factor binding sites and of recombination (Lynch 2007a), a full treatment of which cannot be presented here for lack of space. It is sufficient to reiterate that first, the insertion of new noncoding DNA generally has weakly negative effect on fitness, and second, selection will only promote the addition of a new RE to a gene if the net selective advantage $s - \mu_d$ (where s is the advantage of the new RE and μ_d is the disadvantage due to the increased mutational rate to nonfunctional alleles) is greater than the power of genetic drift, on the order of $1/N_e$ (Lynch 2007a). Only highly beneficial increases in regulatory complexity can be expected to be promoted by natural selection in organisms with low N_e . In practice, regulatory and organismal complexity correlates inversely with N_e , therefore it was likely the low- N_e population genetic environment in which metazoans exist that enabled the evolution of their complex body plans, and ultimately the evolution of humans.

A similar line of thinking leads to the concept of constructive neutral evolution (CNE) (Stoltzfus 1999; Lukes et al. 2011; Speijer 2011; Finnigan et al. 2012; Stoltzfus 2012). CNE builds complexity through neutral processes without the action of natural selection, by passing a biological system through a series of intermediate steps, each of which is selectively neutral or nearly neutral. The end result is a new system locked into a complexified irreducibly complex state from which it cannot return, and which need not confer a selective advantage compared to the initial state. The gene or RE duplication and subfunctionalization model described above is a classic example, but others have been described too, such as the evolution of the spliceosome, of RNA editing in certain unicellular organisms, and others (Finnigan et al. 2012; Stoltzfus 2012).

IMPLICATIONS FOR THEISTIC EVOLUTION

These and many other ideas and observations mandate a shift in our view of evolution and its mechanisms (Koonin 2011) in which nonadaptive evolutionary forces play a prominent role. The outcome of evolution is not determined solely by the selective forces operating on a population. Instead natural selection is a “stochastic sieve” constrained by N_e , acting not on an infinite space of variations but on material shaped by the patterns and dynamics of mutational processes (Stoltzfus 2012).

It turns out that, because the human lineage has existed in a low- N_e state for hundreds of millions of years, our genomes and biology are full of maladaptive features that selection has not been able to eliminate. The view of humans as the pinnacle of evolution, representing its most advanced and sophisticated product, is not a viable position anymore (Koonin 2009); in fact the opposite is true. The most adapted and fit organisms on the planet are bacteria thanks to their enormous N_e and the corresponding strength of natural selection in their lineages. Yet it seems that this very same reduction of N_e is also what has enabled the evolution of organismal complexity that eventually produced organisms capable of pondering their own origins and evolution. This path is not open to prokaryotes as the genomic embellishments that eventually generate organismal complexification are quickly weeded out by purifying selection.

A full appreciation of the role that nonadaptive processes have likely played in human evolution poses challenges to the various versions of TE that, in the opinion of the author, have not been given the necessary attention. I say this while heavily stressing that, as is usually the case at the cutting edge of science, what I have discussed so far is not truth set in stone, but instead represents a shift in our estimates of the probability distribution of what is likely to be correct. Still, a version of TE that is fully compatible with evolutionary theory needs to provide a mechanistic explanation for the way a God could have created humans, and it has to

account for what we have learned so far about the process, even if our knowledge is still imperfect. So what are the options?

The central issue is whether the evolution of humans was inevitable. This is, of course, not a new debate (McMullin 1998). Jacques Monod emphasized the contingency of mutations and the role it plays in evolution (Monod 1972), and Stephen Jay Gould famously argued that if the tape of life was to be replayed humans would not evolve again (Gould 1989), while the most common TE position has viewed the evolution of humans as inevitable and/or planned by God. The contingency of mutations occupied a central place in Monod's arguments, while Gould focused on macroscopic events. These are indeed sources of significant unpredictability, but they do not tell the whole story as we have seen above. The role that the population genetic environment has played in shaping the biology of different lineages adds another major component of contingency to the process.

It is, of course, possible that the appearance of humans or something very close to them would not be a strict requirement from God's perspective and any species with an equivalent level of intelligence would fulfill his purpose (although the specific details of real-world religions impose certain constraints—for example, Christianity would not work well with a species practicing external fertilization as the concept of the virgin birth would make very little sense in such a case, and Christian symbolism is in many ways a derivative of the fact that we are bipedal humanoids), but the reasoning that follows will apply either way as this is primarily a difference of a degree, not of a kind. This is because the arguments mainly concern the evolution of eukaryotes as a whole rather than the specific details of very recent human evolution (in which culture and behavior have also played a significant role). There have clearly been quite strong selective pressures toward the evolution of enhanced cognitive capabilities in the hominid lineage; however, these pressures both arose and were realized in practice because the capacity to evolve complex intelligence had already been present, capacity that was the result of the long multibillion-year history of the lineage up to that point, and that was not guaranteed to evolve in a lineage that would be later subjected to them. It is also possible that a deity is responsible for the existence and evolution of the world without having any specific outcome in mind in the beginning.

There are three main strands of TE thought with respect to how God used evolution to produce present-day life. The first one involves God setting up the initial conditions of the Universe in a way that ensures the appearance of humans. In the second, the process of evolution is guided by God toward a particular outcome. The third one has God being part of the process of development of the world and influencing it without having complete control over it.

One argument presented in support of human inevitability is convergent evolution (Conway Morris 2003). Based on the well-known observation

that evolution often converges onto the same solutions to similar problems, it is argued that the evolution of intelligence was inevitable given the conditions in the universe we live in. While it is indeed true that certain ecological niches have been repeatedly filled by distantly related but phenotypically similar organisms, there is a fundamental flaw with this argument and it is that evidence for convergent evolution only exists when an adaptive solution has been arrived at independently by different lineages. This is not the case for all adaptations. Human-like intelligence is, as far as we know, an unique development, at least on our planet, and all this is without going into the theological issues that would arise had it in fact appeared more than once, issues, which become even more problematic once we consider the universe as a whole (if the evolution of humans was inevitable on our planet, starting from the formation of the solar system, given the unimaginable vastness of the universe an argument can be made that it would also be almost inevitable that humans would not be the only intelligent species in the universe, something which poses a challenge for those religions a core component of which is the central position of humans in the cosmological order).

We also know of even more critical events in the evolution of life that to the best of our knowledge were unique. The origin of eukaryotes is one. It was a one-time event with, as far as we can tell, no analog. Endosymbiosis between a eukaryote and a prokaryote and between two eukaryote cells (Cavalier-Smith 2002) has evolved multiple times, and we even have examples of what appear to be ongoing such events in present-day life (Okamoto and Inouye 2006), but no successful endosymbiosis between archaea and bacteria has ever been observed. This strongly indicates that eukaryogenesis was a unique and highly improbable event. As we saw above, this was probably the single most important event in human evolution after the origin of life itself—it allowed the evolution of multicellularity and organismal complexity. As far as we know, no prokaryote ever evolved multicellularity, even though there are no obvious biological limitations to it except that this particular evolutionary path might be closed to them due to the population genetic environment in which they exist (this observation also goes against the view of evolution as having a direction toward increasing complexity—in the lineages, in which natural selection is strongest, the dominant mode of evolution is genomic reduction and streamlining).

We now also know that many traits fundamental to our biology are largely the result of stochastic neutral processes. This necessitates a significant shift further in the direction of the view that the evolution of humans was a chance event, not hardwired in the fabric of the universe. It is a lot easier to see how it could be inevitable had it been driven only by natural selection and macroscopic environmental factors (even with all the geological cataclysms that affected it). Once introns and transposons have colonized a genome and N_e has become sufficiently low, it is almost certain

that the genome will expand (in the absence of other evolutionary pressures), introns will be maintained, and so on. However, this only concerns the trait of presence of introns and TEs, not each particular insertion, and it is those particular genomic changes, evolving effectively neutrally most of the time, that eventually affect phenotypes by providing material for alternative splicing, for the appearance of new REs, and for the rewiring of GRNs. For example, we saw earlier that the position of many introns is conserved across all eukaryotes and they trace all the way back to their last common ancestor and the initial invasion of its genome by Group II introns. Therefore what alternative splicing products can be generated from these genes today is still constrained by an ancient random transposable element insertion that happened at a time when no mechanisms of adaptively important and regulated alternative splicing had developed. Here is perhaps the place to note that the origin of life itself was likely a more predictable (even if highly improbable, as often pointed out) event than its subsequent evolution—it was driven by the chemical properties of organic molecules while nucleic-acid-based evolution involves the exploration of an astronomically large space of possibilities.

While not built-in in the process of evolution, the emergence of humans could still be knowable in advance to a deity—God could have predetermined the outcome of evolution in the initial conditions of the universe. This view is best illustrated by the metaphor of God as an amazingly skillful billiard player on the grand scale of the whole universe, who sinks all balls in the correct order with the breaking stroke (Johnson and Lamoureux 1999; Lamoureux 2010), that is, God set the Universe in motion and human evolution was already determined at that moment. There is no way to reject such a hypothesis as it is fundamentally untestable. It has, however, in the light of what we know about the process of evolution, a number of undesirable properties.

First, such a scenario is once again significantly more plausible if the outcome of evolution depended primarily on macroscopic parameters acting through natural selection. Accounting for the role of neutral processes mandates an incredibly precise and micromanaged fine tuning of initial conditions, on the level of molecules, atoms and subatomic particles. God must have encoded in the early universe the appearance of a very long string of particular point mutations, transposon insertions, and so forth, their clearance of the barrier of the initial stochastic phase of establishment in populations (recall that most mutations, even when beneficial are rapidly eliminated through drift), and the fixation of the right alleles by drift. It is hard to see how this can be anything but equivalent to God having predetermined the trajectories of pretty much all particles in the universe. This happens to contradict our current understanding of the physical world as being indeterministic on that level (because of quantum mechanics), but it also presents a theological problem: extrapolating to the present, it would

mean that our own actions are predetermined by the initial conditions of the universe too. This problem can be made to go away if one proposes that evolution was fully predetermined up to a point at which hominids were sufficiently developed to be endowed by God with souls. From then on they had free will. However, while a full discussion of this issue is beyond the scope of this essay, the concept of an immaterial soul as traditionally understood is in direct contradiction with modern physics, and any propositions involving such entities have to find a way to reconcile their existence with the Standard Model of particle physics before being considered as viable. Briefly, in order to influence the physical actions of the human body, souls must somehow interact with the physical world. This would be happening at energies far lower than the limits to which the Standard Model has been tested. It follows first, that they would be detectable and likely detected a long time ago, which is not the case, and second, that the particles of ordinary matter can interact with whatever new particle or a force souls are made of. But all properties of these particles are fully explained and very tightly constrained by the Standard Model and observations. Therefore, while it is impossible to reject the existence of souls after death, completely separate from ordinary matter (as this is also an untestable hypothesis), that such entities play a role during the biological life of a human is extremely unlikely.

Second, it is not clear what differences of substance exist between the idea of God setting up the universe with a particular outcome of evolution predetermined at such level of detail and ID. While ID proponents often argue strongly against TE, including this particular class of versions of it (from their perspective, TE does not feature a sufficient level of involvement on the part of God; Kojonen 2013), a number of them accept common descent (Behe 1996). Acceptance of common descent while rejecting the undirectedness of evolution on the molecular level unites the two views to an extent that makes them almost indistinguishable. The sequence of the human genome and its historical trajectory through the sequence space are largely directly engineered by God according to each.

The same objection (equivalence to ID) applies to the second class of TE propositions, the one invoking repeated divine intervention to guide the process of evolution. The more sophisticated versions of this set of ideas involve divine guidance happening on the quantum level in a hidden and unobservable way (Miller 1999; Russell 2003; Polkinghorne 2008) though the precise details on how this might be physically happening are unknown. There is a plausible scientific basis for this assertion and it is that point mutations (mutations changing individual base pairs in DNA) happen, from our perspective, randomly in the genome and are due to physical and chemical processes at the level of individual atoms and subatomic particles. It certainly does seem possible that God could be influencing them purposefully in a way that, due to quantum indeterminacy, does

not apparently violate the laws of nature. This is a seemingly appealing solution, but one that is still unsatisfactory. First, it only really works well for point mutations, and point mutations are far from sufficient to explain the history of life. Random genetic drift, transposable element insertions, horizontal gene transfer and endosymbiosis all played critical roles and it is much more difficult to make the same argument for such events, because of the large size and/or number of molecules involved. The endosymbiotic event that resulted in the origin of eukaryotes is not the same thing as an electron being ejected from an atom. Second, the mere appearance of point mutations is on its own far from sufficient to ensure that they will have any effect on evolution. They need to become fixed in populations first, and no matter how beneficial they are, most mutations are eliminated by random genetic drift before they get a chance to reach fixation. In order for God to have directly engineered the genome through purposeful guidance of mutations, he would have had to intervene pretty much constantly, in a far less subtle way, in order to insert mutations and then ensure the fixation of some of them and the elimination of others, with a large fraction of this action having to happen at levels at which the quantum indeterminacy explanation would be difficult to invoke. There is also a more general problem with such a position, which is that it is even closer to ID than the view that God set the universe in motion and then observed without intervening due to the amount of intervention that would be necessary. Even if it can avoid proposing the repeated violation of the physical laws of nature, it still constitutes essentially a rejection of the modern theory of evolution. The foundation of the theory is population genetics, which describes the changes in gene frequencies in populations based on basic sampling and probability theory principles. If changes in allele frequencies are not the result of random processes and selection, but are in fact directly guided by God, then population genetics is false (at the very least, it is false in the human lineage although even such a restricted version is problematic as humans do not exist in a vacuum but as part of a much larger ecosystem, with the evolution of other species affecting ours). It is, of course, possible that this is how the world indeed is, as we have no way to test such a hypothesis. A world in which changes in allele frequencies are not governed by random sampling processes but by a God might be indistinguishable from our point of view from one in which they are. Nevertheless, it remains true that this class of TE views represents only a reconciliation of theology with the fact of evolution (common descent) but not with the theory, which is implicitly rejected.

The third major group of TE ideas is perhaps best represented by (though not limited to) process theology. It features God influencing but not fully controlling events as they unfold in the process of cosmic and biological evolution. In the words of Howard Van Till:

Process theology has invested a great deal of effort in developing a language for speaking of divine action that is effective but non-coercive. Its vision of *naturalistic theism* rejects all forms of supernatural intervention that interrupts or overpowers the system of creaturely causes and effects. At the same time, it postulates that divine action is an essential aspect of every process and event that occurs. Divine action is not confined to occasional episodes of irruptive intervention; divine activity permeates the world of our daily experience. Yet this ubiquitous divine activity is never coercive; it does not force any creature to do anything. Like the human action of *persuasion*, divine action (within limits that follow from the character of God and of the God/world relationship) can be effective in stimulating the desired outcome without forcibly violating the object of its influence. (Van Till 2002, 68)

From an evolutionary theory perspective, there is an appealing aspect to these ideas. It is the absence of the direct engineering of DNA sequences that is a necessity in other TE proposals. However, compatibility with evolutionary theory is only achieved by process theology if the evolution of humans was not in fact inevitable. Otherwise divine “persuasion” would have to be strong enough to essentially reduce to the interventionism discussed above (McMullin 1998). It is doubtful that humans not being inevitable is what process theologians mean. It is difficult to understand how exactly process theologians view the role of God in evolution in the light of a proper understanding of the population-genetic environment of the human lineage, and the theological implications of it, as the question simply has not been discussed sufficiently. In fact, a general issue with process theology is that it has not engaged with the most current understanding of evolution. Implicit in a lot of writings on the subject seems to be the understanding of evolution as having an inherent direction toward greater complexity and eventually intelligence (e.g., Peacocke 1999). This view was historically the result of humanity’s phylogenetic chauvinism and is no longer tenable in the twenty-first century (as extensively discussed above, life on Earth could very well still be limited to prokaryotes destined to remain single-celled by purifying selection, if it wasn’t for some extraordinary events around 2 billion years ago; we can by no means consider complexification as a primary mode of evolution). Nevertheless, with some modifications process theology can be reconciled with evolutionary theory.

These TE propositions are all developed starting with the supposition that God is temporal being. However, an atemporal God would be subject to different constraints, which significantly affect the way in which his role in the evolutionary process could be reconciled with our current understanding of it. An atemporal God is usually described as existing outside of the Universe, and being aware of its past, present and future development. The views that God had the course of events predetermined or that he intervened numerous times to steer them in a particular direction face the same criticism discussed above even under this understanding of God’s nature. However, there is an attractive aspect of God’s atemporality

and it is that it largely eliminates the necessity for the evolution of the universe and life in it to be planned or guided by God. Within that framework, it is possible for God to be responsible for the creation of the universe and its continued existence but without having specifically created humans in their present form, with the evolution of the latter being known to him due to his atemporal nature. This, of course, presents some well-known theological problems on its own, in particular with respect to human free will, but it potentially resolves many of the contradictions with the science.

Another interesting proposal, related to the idea of an atemporal God (but not necessarily limited to it) and also not in an open conflict with the theory of evolution, is the one that God created the world by simulating/creating a wide variety of possible worlds and then picking the one(s) that suited his goals (Wilkins 2012). Under such a scenario, there is no need for direct divine intervention in evolution and no need for the evolution of humans to be inevitable. It just had to happen in one of the very large number of universes God simulated. Such a proposal dispenses with the notion of divine omnipotence (but so does process theology) as an omnipotent God would presumably be capable of directly creating whatever universe he wishes without having to resort to random sampling of the possibilities, but there are unresolved theological issues raised by all TE proposals and it is up to theologians to sort them out.

CONCLUDING REMARKS

Most work on the relationship between theology and evolutionary theory has focused solely on the panadaptationist view that has dominated popular representations of evolution. However, modern evolutionary theory identifies multiple main forces of evolution (natural selection, mutation, genetic drift, migration), with only one of them (natural selection) being adaptive, and developments in the last few decades have firmly established that the nonadaptive forces have played a major role in shaping the biology of eukaryotes, and especially of multicellular organisms, due to their lowered long-term effective population size.

This has major implications for TE propositions through its impacts on the question of whether human beings are an inevitable product of the evolutionary process. The outcome of evolution is not just the result of environmental factors acting through natural selection but of stochastic events happening at the level of DNA molecules inside the cell. The views one can adopt that I am aware of and that still retain God in the picture while not being outright creationist are therefore the following:

1. God directly engineered the human genome, whether through a very large number of direct interventions to insert mutations and

ensure their fixations or through incredible fine tuning of the initial conditions of a universe that was fully deterministic from then on. Such a position, however, only reconciles the fact of evolution with belief in God. From the perspective of modern evolutionary theory it is equivalent to ID, and this is probably a more proper label for it than TE.

2. The satisfactory outcome of evolution from the perspective of a deity includes a much larger portion of the genotype/phenotype space than seems plausible to us, and such an outcome was sufficiently certain without having to directly engineer it.
3. God's role in evolution was roughly what is described by the process theology framework but human beings were not an inevitable outcome of the process.
4. God created the universe and sustains it but had no direct involvement in the evolution of humans, which was known to him due to his atemporal nature.
5. God simulated a very large number of universes and picked the one(s) which developed according to his purposes.

The last four propositions are generally compatible with evolutionary theory (although the third one may not be compatible with modern physics—objections analogous to the ones regarding the existence of souls can be raised with respect to the role of God in the universe). They probably do not, however, fit within most traditional theological frameworks but I do not claim or even aim to provide final solutions of all these problems. They are issues to be resolved by theologians in the future.

I would in the end like to once again mention that the reasoning laid out above is based on what is most likely to be true given our best current scientific understanding of evolution rather than absolute unchangeable truth. As with everything concerning the real world we live in, complete certainty is impossible to achieve. It could be that human evolution was in fact predictable and inevitable given the initial conditions of the universe. This is a question the answer of which we will likely never know—we certainly do not have a good detailed understanding of the evolutionary forces that acted on the human lineage in more recent times or how they interacted with its population genetic environment, and figuring out the precise details may require detailed data about the past that we have no hope of ever collecting. However, we have learned a lot about the deep general patterns and forces behind evolution of life on Earth and it is this knowledge that makes human inevitability seem unlikely. It is also possible that any of the TE versions I consider to be incompatible with the most up-to-date science in fact does describe how the world is, provided the additional constraint that such a universe be indistinguishable from one in

which purely material forces were behind the process. It could be that God indeed intervened constantly during evolution in a way that was completely invisible and undetectable by us (Sober 2011). The problem is that at the end of this continuum of views lies the idea that the Earth is really less than 10,000 years old and only appears old to us because God made it look so, something most respected voices in this debate would consider highly unlikely to be true, but which nevertheless shares with those more benign views the unifying feature of representing an *ad hoc* explanation specifically put together to escape all possibility of direct testing. Such propositions cannot be rejected and there will always be room for belief in them, but it is still preferable that, when discussing the compatibility of certain ideas with the science, the best current understanding of it is openly and honestly taken into account, and any dividing lines are clearly delineated, to which I hope this essay will contribute.

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