

MITTENS—Convincing Arguments Against Neo-Darwinism

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1. Introduction

In *Probability Zero* Vox Day presents arguments for the Mathematical Impossibility of The Theory of Evolution by Natural Selection (MITTENS). The argument in the book is largely based on analyzing whether evolution whereby natural selection acts on mutations (Neo-Darwinism or the Modern Synthesis) can explain the observed 40 million single nucleotide differences between humans and chimpanzees. Day starts with a common ancestry assumption between humans and chimps, with a generous estimate that their lineages merge 9 million years ago,¹ and with 20 million fixations taking place along each lineage. Day's conclusion is that Neo-Darwinism fails to explain the occurrence of 20 million fixations along the human lineage, since the waiting time for their occurrence far exceeds the required 9 million years. The purpose of this post is to review parts of Day's book, and to compare his findings with some of my own waiting time results.

First of all, I want to congratulate Day on a well written book. The mathematical arguments are explained in a pedagogical way, yet they reveal deep insights into population genetics – the mathematical tool for evolutionary theory. It is also courageous to follow the tradition of the Wistar Institute conference 1966 and put forward mathematical challenges to evolutionary theory.

2. Neo-Darwinism and the MITTENS equation(s)

The human and chimpanzee genomes are about 3 billion nucleotides long. They are surprisingly similar, and depending on how one counts, the difference is between 1 and 15 per cent.² If we restrict our attention to nucleotide differences (and ignore insertions, deletions, and other structural variations) the difference is about 1.3%, or 40 million nucleotides. If 20 million of these nucleotides appeared along the assumed human ancestral lineage, Neo-Darwinism predicts that each of these nucleotides first appeared as a mutation in one genome of the human ancestral population and

¹ The most common view among evolutionary biologists today is that humans and chimpanzees have common ancestry, and that their lineages departed about 6–8 million years ago.

² Yoo et al. (2025). Complete sequencing of ape genomes. *Nature* 641, 402–418.

then in subsequent generations spread to the whole population (got fixed). The purpose of *Probability Zero* is to showcase that the number F of fixations that Neo-Darwinism predicts, along the assumed human ancestral lineage, is far less than the required 20 million. This is achieved by introducing an upper bound $F_{\max}$ (the maximum number of fixations) of F , and the empirically based formula

$$F_{\max} = \frac{t_{div} \cdot d}{g_{len} \cdot G_f} \quad (2.1)$$

for calculating it. In this formula t_{div} is the assumed divergence time (9 million years), g_{len} the human generation time (20 years), whereas G_f is the smallest number of generations per fixation observed (=1,600, obtained by Vox Day from data of the well-known multigenerational *E. coli* experiment of Richard Lenski and coworkers). For a population with non-overlapping generations, since $\frac{t_{div}}{g_{len}=450,000}$ is the number of generations since the split, $\frac{t_{div}}{(g_{le} \cdot G_f)}$ would be an upper bound for F along the human ancestral lineage. However, since generations are overlapping, not all individuals are replaced in each generation. For this reason, Day multiplies the upper bound of F with the turnover rate d , i.e. the fraction of individuals in the supposed human ancestral population that is replaced in each generation ($= \frac{g_{len}}{A} = 0.45$, where A is the expected human age). Inserting numbers, one obtains

$$F_{\max} = \frac{9 \cdot 10^6 \cdot 0.45}{20 \cdot 1,600} = 127, \quad (2.2)$$

which is smaller than the required 20 million by more than five orders of magnitude. This leads to the MITTENS conclusion that a Neo-Darwinian explanation of the human-chimp single nucleotide difference is impossible.

The above argument is appealing, not least because of its simplicity, and that empirical estimates are available for all quantities involved. However, the formula raises some questions. The most obvious question is whether it is possible to use the fixation rate (the number of fixations per generation) $\frac{1}{G_f}$ of *E. coli* as an upper bound of the human fixation rate. The form and dynamics of the two species' genomes differ in several ways. Firstly, the pointwise mutation rates μ (the expected number of mutations per nucleotide and generation) are different ($1.25 \cdot 10^{-8}$ for humans and about 10^{-10} for *E. coli*). If we account for the different mutation rates of humans and *E. coli*, the first adjustment of the MITTENS equation is

$$F_{\max} = \frac{\mu_{hum}}{\mu_{Ecoli}} \cdot \frac{t_{div} \cdot d}{g_{len} \cdot G_f} = \frac{1.25 \cdot 10^{-8}}{10^{-10}} \cdot 127 = 15,800. \quad (2.3)$$

This is a lot larger than the previous upper bound 127 of F , but still more than three orders of magnitude smaller than 20 million fixations. A second adjustment of the MITTENS equation is to account for the fact that the human genome is 650 times larger than the *E. coli* genome ($3 \cdot 10^9$ versus $4.6 \cdot 10^6$ nucleotides). Intuitively, a larger genome would give more opportunities for fixations. If the number of fixations is proportional to genome length L , this second adjustment of the MITTENS equation would be

$$F_{\max} = \frac{L_{hum}}{L_{Ecoli}} \cdot \frac{\mu_{hum}}{\mu_{Ecoli}} \cdot \frac{t_{div} \cdot d}{g_{len} \cdot G_f} = \frac{3 \cdot 10^9}{4.6 \cdot 10^6} \cdot 15,800 = 10 \text{ million}; \quad (2.4)$$

which still is less than 20 million, but only by a factor of 2.

Does this mean that the MITTENS argument is invalidated when the different mutation rates and genome sizes of the human and *E. coli* genomes are accounted for? Not quite so. Vox Day convincingly argues that if many nucleotides at which fixation takes place have a selective advantage (so that natural selection acts on all these mutations) there is a reproductive cost of having many fixations going on in parallel. Consequently, a larger genome does not necessarily imply a correspondingly larger number of fixations. This cost argument is an instance of Haldane's dilemma, formulated by the well-known population geneticist J.B.S Haldane in 1957.³ In context of the MITTENS equation, it implies that the number of fixations with a selective advantage along the supposed human lineage is far less than what equation (4) predicts, perhaps more in line with equation (3).

Therefore, Vox Day concludes that since Neo-Darwinism relies on natural selection acting on mutations with a selective advantage, Neo-Darwinism cannot explain the observed genetic divergence between humans and chimps by means of common ancestry, within a time frame of 9 million years. I agree with this conclusion, also after adjusting the MITTENS equation for the different mutation rates of humans and *E. coli*. according to equation (3).

3. Neutral theory

Haldane's argument sets a limit on how fast natural selection can act and fix mutations for populations with a limited reproductive ability. To rescue the mathematical theory of evolution, the Japanese population geneticist Motoo Kimura tried to resolve the challenges posed by Haldane's dilemma by formulating the neutral theory of evolution.⁴ According to this theory, most fixation appear at random, with genetic drift rather than natural selection acting on mutations. Vox Day makes a

³ Haldane, J.B.S. (1957). The Cost of Natural Selection. *Journal of Genetics* 55, 511–524.

⁴ Kimura, M. (1968). Evolutionary rate at the molecular level. *Nature* 217 (5129), 626–626.

good point that the neutral theory is a dissent from The Modern Synthesis (Neo-Darwinism), since the impact of natural selection is marginalized. We can, however, still think of the neutral theory as part of the more general Extended Evolutionary Synthesis, whereby many processes and mechanisms are used in attempts to explain common ancestry of all species.⁵

But is the neutral theory more successful than Neo-Darwinism in terms of explaining the observed nucleotide differences between humans and chimps by means of common descent 9 million years ago? If one is trying to explain genome-wide differences between two species through common descent, it is indeed not far-fetched to assume that a majority of nucleotides at which fixation takes place along the two ancestral lineages that supposedly connect the species, are selectively neutral (so that only genetic drift is at work) or at least close to neutral. Let us assume, for simplicity, that ALL nucleotides along the assumed human ancestral lineage are neutral. It is possible then, under certain simplifying assumptions, to get rather simple estimates of F , the number of fixations along the human lineage.

Consider a human population of size N . Since each individual carries two copies of the human genome (one inherited from the father and one from the mother), the population carries $2N$ genome copies, of which $2Nd$ are replaced in each generation because of overlapping generations. The expected number of mutations per nucleotide and generation is therefore $2Nd\mu$. The probability that a new mutation gets fixed (i.e. spreads to the whole population) is $\frac{1}{(2N)}$ at a nucleotide that experiences a selectively neutral mutation. This gives a nucleotide-wise rate of fixation $2Nd\mu \cdot \frac{1}{(2N)} = d\mu$ per generation that only involves the turnover rate d and the mutation rate μ , not the population size N .⁶ If fixations take place independently at all nucleotides,⁷ the total number of fixations along the human ancestral lineage is

$$\begin{aligned} F_{hum} &= L_{hum} \cdot d \cdot \mu_{hum} \cdot t_{div} \\ &= 3 \cdot 10^9 \cdot 0.45 \cdot 1.25 \cdot 10^{-8} \cdot 450,000 \\ &= 7.6 \text{ million} \end{aligned} \tag{3.1}$$

very close to the second extended MITTENS equation (4). Can we explain the similar values of F obtained from equations (4) and (5)? Both equations assume

⁵ Pigliucci, M. and Müller, G.B. (eds.) (2010). *Evolution, The Extended Synthesis*. MIT Press, Cambridge Massachusetts. The Royal Society. (2016). *New trends in evolutionary biology: Biological, philosophical, and social science perspectives*. November 7–9, 2016. <https://royalsociety.org/science-events-and-lectures/2016/11/evolutionary-biology/>

⁶ For populations with non-overlapping generations ($d = 1$), this result originally goes back to Wright, S. (1938). The distribution of gene frequencies under irreversible mutation. *Proc. Natl. Acad. Sci. USA* 24, 253–259.

⁷ This is a simplified assumption that ignores so called linkage disequilibrium between nucleotides. It is still quite a good approximation for a selectively neutral model, since Haldane's cost restrictions for parallel fixations are not in force.

parallel fixation between loci. Whereas equation (4) makes use of Vox Day's empirical estimate of the fixation rate of *E. coli*, equation (5) is based on the neutral theory of evolution. Therefore, the similar output of the two equations indicates that the empirically determined fixation rate of *E. coli* agrees quite well with what the neutral theory would predict. Indeed, if non-overlapping generations and a turnover rate $d = 1$ of *E. coli* are assumed, the neutral theory predicts a genome-wide fixation rate $L_{Ecoli} \cdot \mu_{Ecoli}$ per generation, so that the expected number

$$G_{neutral} = \frac{1}{L_{Ecoli} \cdot \mu_{Ecoli}} = \frac{1}{4.6 \cdot 10^6 \cdot 10^{-10}} = 2,170 \quad (3.2)$$

of generations between fixations for *E. coli* is quite close to Vox Day's empirical estimate $G_f = 1,600$.

The conclusion is that the neutral theory of evolution matches quite well both the empirically determined fixation rate of *E. coli* and the number of fixations along the ancestral human lineage that supposedly connects us with chimps. Whereas the first conclusion is an empirical verification that the neutral theory predicts *E. coli* fixations quite well, the second conclusion is only a verification of evolutionary *assumptions* about common descent of humans and chimps. Indeed, early estimates of the human mutation rate μ_{hum} were obtained in order match the observed genetic divergence between humans and chimps, and the assumed time of split between the two species, obtained from unreliable radiometric dating of fossil records.⁸ More recent and reliable estimates of μ_{hum} are empirical and based on comparing the genomes of parents and children. This so-called pedigree method gave lower estimates of μ_{hum} and therefore evolutionary biologists pushed back the assumed time of divergence between humans and chimps, so that the neutral theory still predicts the genetic divergence between the two species quite well.⁹

To summarize, the neutral theory of evolution cannot explain common ancestry between humans and chimps at all based on genome-wide nucleotide differences between the two species, since the neutral theory is used in the first place to date the assumed time of divergence. Although this point is not addressed in Vox Day's book, we will see that it resonates well with another critique of the neutral theory that Day puts forward.

4. Nearly neutral theory

We have found so far that neither Neo-Darwinism nor the neutral theory of evolution can be used to conclude common ancestry between humans and chimps

⁸ This is referred to as the phylogenetic method of estimating mutation rates.

⁹ Keightley, P.D. (2012). Rates and fitness consequences of new mutations in humans. *Genetics* 190, 295–304.

based on the genome-wide nucleotide difference between the two species. Vox Day points out another drawback of using the neutral theory, and its assumption that all mutations are either neutral or very harmful (so that individuals carrying the latter mutations die). He reminds us that the neutral theory is only approximately correct, in the sense that most mutations are not in fact neutral but rather slightly deleterious, with such a small selective disadvantage that they essentially have the same probability of becoming fixed as the neutral mutations. This is Tomoka Ohta's extension of the neutral theory, referred to as the nearly neutral theory of evolution.¹⁰

If we are using the neutral theory in an attempt explain common ancestry between humans and chimps, by estimating the number of fixations along an assumed human ancestral lineage, we must accept that most of these supposedly neutral mutations are in fact not neutral but rather slightly deleterious. Although the fixation rate of slightly deleterious mutations is essentially the same as for neutral mutations, the problem is that these slightly deleterious mutations accumulate when parents pass on their DNA to children, so that the overall fitness of the population declines over time and the population eventually (and quite rapidly) dies. Therefore, if one attempts to use the neutral theory of evolution to estimate the number of fixations along a human ancestral lineage that supposedly connects us with chimps, we must also take the cumulative declining fitness effect of the slightly deleterious mutations into account, with a conclusion that humanity is a lot younger than what evolutionary biologists predict.

Although Vox Day does not cite John Sanford, this is essentially Sanford's genetic entropy argument, that all species (not only humans) acquire an increasing amount of genetic garbage over time (increased genetic entropy through accumulated slightly deleterious mutations) so that none of them can be old.¹¹

5. Guided evolution

I agree with Vox Day that neither Neo-Darwinism, the neutral theory of evolution nor the nearly neutral theory of evolution can be used to confirm common ancestry between humans and chimps within the stipulated time frame of 9 million years. With Neo-Darwinian mechanisms the waiting time for 20 million nucleotides to fix is a lot larger than 9 million years, whereas a waiting time of the order 9 million years for the neutral theory simply confirms that the neutral theory was used in the

¹⁰ Ohta, T. (1973). Slightly deleterious mutant substitutions in evolution. *Nature* 246 (5428), 96–98.

¹¹ Sanford, J. (2008). *Genetic Entropy and the Mystery of the Genome*. Feed My Sheep Foundation, Inc. Basener, W.F. and Sanford, J.C. (2018). The fundamental theorem of natural selection with mutations. *Journal of Mathematical Biology* 76(7), 1589–1622. Basener W., Cordova S., Hössjer O. and Sanford J. (2021). Dynamical Systems and Fitness Maximization in Evolutionary Biology. In: Sriraman B. (ed.) *Handbook of the Mathematics of the Arts and Sciences*. Springer, Cham. See also Muller, H.J. (1950). Our load of mutations. *American Journal of Human Genetics* 2, 111–176.

first place to date the time of divergence between humans and chimps. The nearly neutral theory, on the other hand, leads to the conclusion that humanity must be young, regardless of whether we have common ancestry with chimps or not.

A common feature of Neo-Darwinism, the neutral theory of evolution and the nearly neutral theory of evolution, is that mutations are completely random. This is to say that evolution is blind, without foresight. Vox Day also believes in common ancestry between humans and chimps but following the tradition of the American 19th century botanist Asa Gray he argues for a version of evolutionary theory whereby mutations are not completely random but rather guided towards a goal. This leads to evolution directed by an Intelligent Mind. Whereas Gray believed that this Intelligent Mind is God (theistic evolution), Vox Day remains agnostic about the identity of the Mind.

6. Functional differences and uncommon descent

I agree with Vox Day that there are large genetic differences between some species that neither Neo-Darwinism nor the (nearly) neutral theory of evolution can explain. However, I do not explain such differences through guided evolution and common ancestry, but rather through uncommon ancestry. In particular, I believe there are strong genetic arguments for humans and chimps not having common ancestry. These arguments are not based on *genome-wide* single nucleotide differences between humans and chimps, but rather on other *localized* functional differences between the genomes of the two species. Two striking differences between the genomes of humans and chimps are 1) that many genes shared by the two species are expressed very differently,¹² and 2) that humans have several hundred orphan genes, not present among chimps nor in any other species.¹³ Together, these two features explain some of the large phenotypic differences between humans and chimps, such as larger brain size, larger linguistic capacity and upright walking of humans.

One mechanism for explaining gene activity is that certain proteins (transcription factors) attach to short stretches of DNA (so-called binding sites) in the vicinity of genes to control how much these genes are expressed. In collaboration with the late Günter Bechly and Ann Gauger, in 2021 I developed a mathematical model for the time it would take for several genes to change expression through coordinated mutations, when new binding sites appear and transcription factors can recognize

¹² Gauger, A.K., Hössjer, O. and Reeves, C. (2017). Evidence for human uniqueness. Chapter 15 of *Theistic evolution. A scientific, philosophical, and theological critique*, Moreland J.P., Meyer, S.C., Shaw, C., Gauger, A.K. and Grudem, W. (eds.). Crossway, Wheaton, Illinois.

¹³ Ruiz-Orera et al. (2015). Origins of de novo genes in humans and chimpanzee. *PLoS Genetics* 11(12), e1005721.

and attach to these new binding sites.¹⁴ Although this mathematical model has not yet been applied to humans and chimps, my prediction is that the waiting time for several genes to change expression (so that their expressions match that of humans rather than chimps) far exceeds 9 million years.

Since the proteins that genes code for cooperate in regulatory networks, some traits require changed activity of many genes for the whole network to function. If the target is changed expression of all the genes of such a network, the network is often (close to) irreducibly complex, since a functioning regulatory network must have many of its proteins in place. Since (guided or unguided) evolution typically proceeds in small incremental steps, the intermediate steps of the evolutionary trajectory towards such an irreducibly complex (or close to irreducibly complex) target would most likely have low fitness. For this reason, uncommon descent is in my view a more credible explanation for the different gene activity of humans and chimps.

Common descent is even harder to defend as an explanation of human orphan genes. Genes are several thousand nucleotides long, each with a unique combination of exons, introns, start and stop codons. These genes are clearly irreducibly complex, and the waiting time for evolution (guided or not) to produce an orphan gene is most likely many orders of magnitude larger than 9 million years.

7. Summary

Vox Day has written an excellent book, where mathematical tools are used to showcase that unguided evolution (Neo-Darwinism or the neutral theory of evolution) cannot be used as an argument for common ancestry between humans and chimpanzees. In my view these conclusions remain even after some adjustments to the MITTENS equations.

Whereas Vox Day believes in guided evolution and common descent as a way of explaining nucleotide differences between humans and chimps, I rather advocate uncommon descent between the two species. This view of mine is (among other things) based on a waiting time argument, i.e. that very long periods of time are required to explain localized differences (such as very different expressions of genes and many human and chimpanzee orphan genes) between the human and chimpanzee genomes.

¹⁴ Hössjer, O., Bechly, G. and Gauger, A. (2021). On the waiting time until coordinated mutations get fixed in regulatory sequences. *Journal of Theoretical Biology* 524 (2021), 110657.