Gambler's Epistemology vs. Insistence on Impractical Naturalism:

The Unwitting Half-Billion Dollar Wager by the NIH Against Evolutionary Theory

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Abstract

The 2015 Nobel Prize winner in chemistry, Aziz Sancar, may have unwittingly given life to Paley's watch argument when he used the phrase "Rube Goldbergesque designs" to describe the nano-molecular clocks that provide timing to various processes in the human body. Other Rube Goldbergesque designs have been elucidated by National Institutes of Health (NIH) research initiatives such as the ENCODE and RoadmapEpigenomics projects which represent approximately a half-billion dollar total investment.

The success of NIH initiatives and various other projects has drawn a bizarre reaction from some methodological naturalists like evolutionary biologist Dan Graur who said in 2012 "If ENCODE is right, evolution is wrong." Graur's comment is reminiscent of Haeckel who said in 1876: "If we do not accept the hypothesis of spontaneous generation, then at this one point in the history of evolution we must have recourse to the miracle of a supernatural creation."

An unconventional approach called "gambler's epistemology" is introduced as a perspective to clarify why naturalism should not be equated with science. Gambler's epistemology with its reliance on the notion of mathematical expectation shows that the intuitive perception that "life is a miracle" is not rooted in after-the-fact, ad-hoc probabilities, but is consistent with standard practice in science, and thus without formally settling the question whether God or supernatural entities actually exist, Haeckel's unwitting assertion that the emergence of life must be of miraculous origin is at least closer to the truth statistically speaking.

Gambler's epistemology also shows that applying reward-to-risk analysis such as seen in the professional investment and gambling world could be a better practical guide in committing financial and human resources to scientific exploration than enforcement of unspoken creeds of impractical naturalism that may actually be detrimental to scientific discovery.

INTRODUCTION

Though it may be intuitively satisfying to attempt explanations of various phenomena in terms of accessible and repeatable mechanisms such as those deduced via the scientific method, there may be physical phenomena whose explanations may escape such reproducibility. One of the most prominent such examples is the emergence of life. Despite the evidence of Pasteur's 1861 experiments refuting spontaneous generation, it was assumed by Haeckel as late as 1876 that it

was a common and ordinary occurrence for life to emerge spontaneously from non-living matter. This belief was epitomized by his 1876 statement, "If we do not accept the hypothesis of spontaneous generation, then at this one point in the history of evolution we must have recourse to the miracle of a supernatural creation."[1]

The insistence by Haeckel and others that the structure of life could be explained by easily repeatable mechanisms was falsified experimentally. Even the most basic life forms are so complex and exceptional relative to non-living matter that some scientists even now argue the emergence of the first life on Earth may not be subject to ordinary and repeatable mechanisms as a matter of principle and thus outside direct scientific explanation.[2]

There is lasting tribute to Pasteur's experiments against spontaneous generation by the word "Pasteurized" on bottles of milk. The Pasteurization process is testament to the scientifically verified viewpoint that the emergence of life is so exceptional that it is not expected to happen again for all practical purposes. If there is a lesson to be learned from Haeckel's flawed views on the emergence of life it is that insistence on explanations for all phenomena in terms of repeatable mechanisms should not be conflated or equated with scientific understanding.

If science supports the insight that a phenomenon is so exceptional it looks miraculous (if only statistically speaking, not theologically speaking), then this insight should not be suppressed merely because it could conflict with the claims of naturalism. For example, the origin of the universe and the origin of life are events that are scientifically inferred as real, not repeatable and highly exceptional. They can be accepted as such even they it challenges naturalistic viewpoints.

If the strength of naturalism is based on the implicit creed that all phenomenon can be ultimately explained by repeatable and ordinary mechanisms, then when naturalism is confronted with phenomenon not reducible to ordinary and repeatable mechanisms, it would seem naturalism borders on becoming a collection of vague faith-based assertions with no possible formal proof.

Supposing for the sake of argument no God or supernatural forces exist, it would then be still hypothetically possible that a phenomenon could be so exceptional and singular that it cannot be reproduced and hence outside direct scientific verification as a matter of principle. But this raises a philosophical question (that is relevant but unfortunately beyond the scope of this essay), "at what point would a so-called natural phenomenon be so exceptional that it is statistically indistinguishable from a miracle of supernatural origin?"

Extending Pasteur's law of biogenesis that "life comes from life", one might claim on experimental grounds alone that it is quite reasonable to assume animals emerge from animals, plants from plants, eukaryotes emerge from eukaryotes, etc. But these experimental observations would suggest there is immutability of certain forms[3], and that macro evolutionary steps are the result of exceptional rather than typical events. The claim of macro evolution still remains a matter of inference (and some would say imaginative story telling) rather than physical experiment.[4] So in addition to the origin of universe, the origin of life, one might be able to

include the origin of complexity in novel biological forms as the result of unique, exceptional and non-repeatable events. At the very least, if experimental science cannot practically confirm macro-evolutionary transitions, evolutionary biology's status as a scientific discipline might be deemed dubious at least relative to physics and chemistry. As evolutionary biologist Jerry Coyne himself said, "In science's pecking order, evolutionary biology lurks somewhere near the bottom far closer to phrenology than to physics.[5]"

Gambler's Epistemology

An unconventional but hopefully fruitful perspective in framing the issue of naturalism vs. the scientific method is the perspective often adopted by professional gamblers and investors in realms where uncertainty is the norm in decision making. For the purposes of this paper, this informal perspective will be labeled "gambler's epistemology." Gambler's epistemology is neither formally codified nor used as a term explicitly in the gambling and investment world, but coined for the purposes of this essay as a label for a body of principles used by skilled gamblers and investment managers. Rather than offer a strict definition of gambler's epistemology, it suffices to mention some of the elements of this epistemology relevant to the issue of naturalism and the scientific method.

The principles of gambler's epistemology are listed in numerous books (even if the term "gambler's epistemology" is not used). But first, it might helpful to highlight the success of some of the most successful practitioners of this epistemology. Edward O. Thorp was a professor of mathematics at MIT and was author of the books like *The Mathematics of Gambling*,[6] *Beat the Dealer*[7] and *Beat the Market, A Scientific Stock Market System*.[8] He teamed up at MIT with Claude Shannon (the famous pioneer of information theory) during his successful foray into using computer and mathematical analysis to develop techniques to win money from casinos and Wall Street. Thorp, with Shannon's support, published his first work on gambling in the prestigious *Proceedings of the National Academy of Sciences* in 1961.[9,10] Thorp made hundreds of millions of dollars after starting an investment fund that applied his theories and his pupil, Bill Gross went on to manage a trillion dollar hedge fund.[11]

Many decisions in the realm of human affairs are made with far less facts available than the decision makers would like. In the world of successful gambling and hedge fund investment, uncertainty is the order of the day. But uncertainty in one dimension does not necessarily imply uncertainty in another dimension. In fact, maximizing uncertainty of one aspect of a system can lead to near certainty about another aspect of a system. This paradox about reality has been exploited profitably in the business world particularly in skilled casino gambling, casino management, the insurance industry and investment arbitrage.

The ability to gain near certainty about one aspect of a system despite uncertainty about another aspect of the same system is easily illustrated by applying the law of large numbers to a system

of 500 fair coins. If we take 500 fair coins, place them in a jar, shake them vigorously and then pour them out on a table, we will induce maximum uncertainty in the heads tails configuration of each coin. But given the binomial distribution, we can be practically certain the coins will not be 100% heads as we examine them on the table.

Fundamental to the law of large numbers is the notion of mathematical expectation (or expected value) that was pioneered by mathematician Blaise Pascal in the middle of the 17th century. Expected value is the expected average of many outcomes or the average behavior of a system of composed of many parts. For example, the expected number of coins that are heads in a large system of coins randomly shaken is 50%, and the law of large numbers constrains that deviations from that expectation would be increasingly exceptional the larger the deviation. For 500 fair coins, 100% heads would be an astronomically large deviation from the expectation of 50% heads from a random (uncertainty maximizing) process. 100% fair coins from a randomizing process (like shaking them in a jar and pouring them on a table) would be a statistical "miracle".

Though it would take some work to rigorously formulate the notions of average vs. exceptional types of outcomes for a deck of cards stirred by a tornado, suffice to say a tornado is not mathematically and physically expected to spontaneously assemble a house of cards. If we happened upon a house of cards, we would expect that it wasn't the result of an uncertainty maximizing process like a tornado. The perception that a house of cards is a special configuration relative to random arrangements of cards is not due to some after-the-fact projection of a pattern by our mind but can be derived from physical and mathematical principles of expectation. If one were to play devil's advocate and argue that "mathematical expectation is itself an imaginary construct" in order to argue that there are not in actuality any special configurations of matter in the universe (like a house of cards or life), but rather "special" is an imaginary construct, one would have to abandon all scientific inferences that are based on the notion of expected results, which would effectively dispose of much of science.

As more is learned about the complexity of life and the high specificity of its components and their connections to each other, it becomes increasingly harder to argue that life is the result of ordinary or typical events in a way that makes mechanical sense. It is much like arguing a 747 can be assembled by a tornado passing through a junkyard.[12] This applies not only to the origin of life problem but also to creating functional biochemical systems that require emergence of numerous well-matched interacting parts.[13]

Finally, the notions of expected value can be applied to decisions involving wagering and investment whereby the best investment is chosen by wagering on a choice that has the highest expected value in terms of payoff. This expected value is calculated by weighting the potential reward on a bet by the probability the bet will win.

For example, if there is a million dollar payoff for being right, but only a 1% probability of being right, the expected value payoff is $1,000,000 x 1% = $10,000. Whereas if there is zero payoff

for being right, and a 99% chance of being right, the expected value payoff is $0.00 x 99% = $0.00. If the cost of placing a wager is a mere $100, over many trials, it is better to wager $100 on the %1 long shot that offers great reward than the 99% certain bet that offers zero reward.

A business executive by the name of Don Johnson was able to win millions from casinos in part by exploiting marketing coupons and rebates that were structured with comparable odds and payoffs as illustrated in the previous paragraph.[14] The trick of course was for Johnson to find and negotiate such absurdly favorable terms for himself against the casinos. Thorp and Gross used similar strategies in construct their highly successful casino and hedge funds strategies. Pascal himself extrapolated his wagering ideas to the realm of the theological in his controversial claim known as "Pascal's Wager" over the existence of the Christian God.[15]

Because of the law of large numbers, an investment strategy based on selecting investments with the highest expected value payoff will yield on average the best return over a large number of trials. This procedure has been highly effective in business contexts and there is abundant literature on the topic and thus will not be covered here in detail except as it applies to the question of investing resources in scientific research into the complexity of life.

Evolutionary Biologists vs. the National Institutes of Health: The Half-Billion Dollar Exploration of the Epigenome

Complexity or the exceptional quality of physical systems is not an artifact of our imagination, but can be derivable from physical and mathematical analysis alone. The origin of life problem is a prime example of how the hope of naturalism to explain all phenomena in terms of ordinary and repeatable mechanisms was dashed. But less well known is the fact in the present day, the discovery of large scale complexity in the epigenome of life is also challenging explanations solely in terms of ordinary and repeatable mechanisms.

A set of projects known as ENCODE and RoadmapEpigenomics (which commands a combined research budget exceeding half a billion dollars) is at the forefront of efforts by the National Institutes of Health (NIH) to explore the genome and epigenome. This research has contributed to development of FDA-approved treatments such as Histone Deacetylase Inhibitors for the diseased epigenomes resulting in rare cancers.[16]

But beyond the benefit to medical science by the ENCODE and RoadmapEpigenomics1 projets, the insights derived from the ENCODE and RoadmapEpigenomics projects led the projects' researchers to go out on a limb and make pronouncements that they believed the genome was 80% or more functional. Their declaration was summarized by the 2012 headline in the prestigious journal *Science*,

> "ENCODE Project Writes Eulogy for Junk DNA -- This week, 30 research papers, including six in Nature and additional papers published online by Science, sound the death knell for the idea that our DNA is mostly littered with useless bases. "[17]

When the researchers declared their strong opinion that the genome was 10 times more functionally complex than previous estimates by certain evolutionary biologists[18], this induced a reaction epitomized by evolutionary biologist Dan Graur who said, "If ENCODE is right, evolution is wrong."[19] Dan Graur also offered these thoughts:

> "the evolution-free philosophy of ENCODE has not started in 2012… the wannabe ignoramuses, self-promoting bureaucrats, and ol' fashion crooks of ENCODE are protected from criticism and penalties for cheating by the person who gives them the money. Thus, they can continue to take as much money from the public as their pockets would hold, and in return they will continue to produce large piles of excrement that are hungrily consumed by gullible journalists who double as Science editors."[20]

Graur is a professor at University of Houston and fellow of the American Association Advancement of Science (AAAS). Graur and several co-authors with the full sanction and cooperation of several fellow evolutionary biologists published the paper, "On the Immortality of Television Sets: 'Function' in the Human Genome According to the Evolution-Free Gospel of ENCODE."[21] The paper passed peer-review by other evolutionary biologists despite its over-the-top tone bordering on name-calling. Several in the scientific community objected to the paper's overtly hostile and trollish tone, ill-suited to science and scholarship[22]. Graur's shrill rhetoric also inspired a reporter for the prestigious journal *Science* to refer to him as "The Vigilante" [23].

Graur's tone might mislead one to think he's an isolated individual, but he has supporters in the community of evolutionary biologists and population geneticists. One of the world's most respected theoretical geneticists, Joseph (Joe) Felsenstein authored the gold standard graduate textbook *Theoretical Evolutionary Genetics*. In the book, Felsenstein explicitly mentions the ENCODE project and why its claims are at variance with the mathematics of evolutionary genetics[24] which would imply that essentially Graur's assertion, "If ENCODE is right, evolution is wrong."

Thus, in the present day we are in a situation where orthodox textbook theory in evolutionary genetics is openly in conflict with the claims of highly respected laboratory researchers commissioned by the NIH. Thus, there would appear to be uncertainty in deciding where research efforts should be focused in the face of unresolved questions over evolution vs. ENCODE, but such situations are tailor made to applying gambler's epistemology.

[The appendix will lay out a simplified description of Felsenstein's and Graur's arguments which are (ironically and for totally different reasons) supported by creationists like respected Cornell geneticist John Sanford.]

ENCODE, RoadmapEpigenomics, E4

Subsequent to the success of the multibillion dollar Human Genome Project which enumerated the DNA sequences in the human genome and which was completed in 2003, the question remained as to how the individual parts of the genome worked. The head of the Human Genome project and now current director of the NIH, Francis Collins predicted it would take centuries to understand how each part of the genome works[25]. Among the first steps into this exploration was the NIH ENCODE project whose mission was to start cataloging the parts of the genome and the role of the individual parts.

The ENCODE project commanded a budget of 288 million dollars[26] and began in 2003. The RoadmapEpigenomics project has a budget of 300 million dollars[27] and began in 2008. There is a peripherally related project that is in the planning stages called E4 (Enabling Exploration of the Eukaryotic Epitranscriptome) which has a projected budget of 205 million.[28]

The ENCODE project developed many experimental techniques and established databases which are now being continued in the follow-on RoadmapEpigenomics project. There are about 40 classes of experiments performed by ENCODE[29], some of which are depicted in figure 1 below:

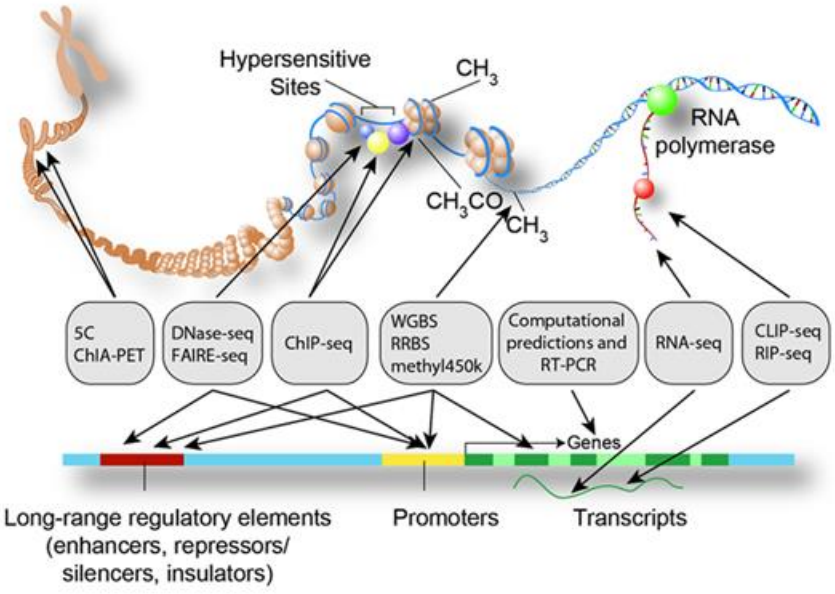


Figure 1.[30] A small sampling of the experiments conducted by ENCODE on a stretch of DNA (the multi-colored bar toward the bottom). The gray bubbles represent classes of experiments. Many of the experiments such as WGBS (whole genome bisulfate sequencing), RRBS, methyl450k, ChiP-seq, RNA-seq are relevant to exploring the human epigenome.

The experimental findings of the ENCODE project startled the researchers since it suggested substantially more of the genome was functional (80% or more) than predicted by evolutionary theorists (less than 10%).[31] This functionality includes DNA's involvement in a conceptual entity known as the epigenome.

DNA is widely viewed as read only memory (ROM), but the ENCODE project furthered the emerging view that DNA also acts as a component of cellular random access memory (RAM). Figure 2 and 3 shows an amusing coincidence of a "beads on a string" structure that appears in man-made RAM as well as biological RAM.

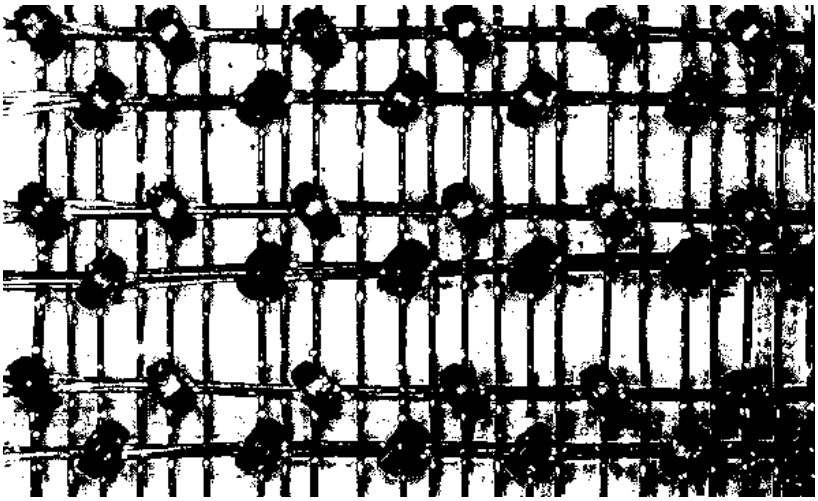
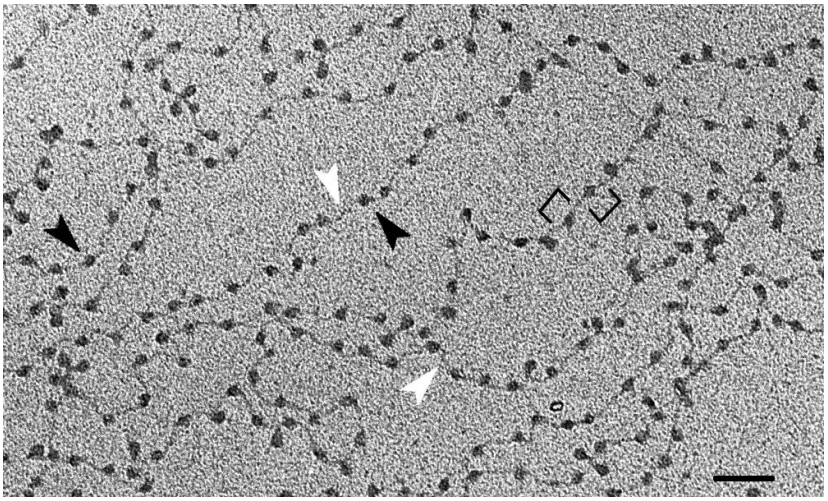


Figure 2. Primitive man-made random access memory (RAM). Notice the "beads on a string" like structure. Each "bead" is where a single bit of memory is stored.[32]



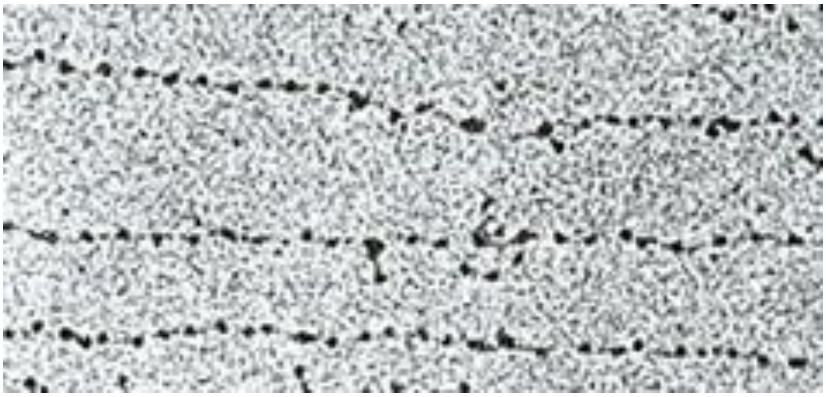


Figure 3.[33,34] Biological RAM. Actual electron micrographs of histone/nucleosome complexes of DNA. Its structure is referred to as "beads on a string" where the "beads" are the histone/nucleosomes and the "string" is the DNA connecting the beads. *The Stem Cell Handbook* refers to this complex as part of the "random access memory" of the cell. Amazingly, even though the chemical and physical mechanisms of memory in this biological RAM are different than the man-made RAM depicted in figure 2, they coincidentally conform to a "beads on a string" architecture.

The term "epigenome" is unfortunately and disparagingly used in association with Larmarkian and Lysenkoist ideas, but means something almost totally different to those who view the epigenome as complex entity that is necessary for the development of somatic cells in a multicellular organism. Roughly speaking, there may be one genome, but as many epigenomes in an adult human as there are cells.

Though the definition of the epigenome is in constant flux and dispute, a segment of researchers generally define the epigenome as including methyl modifications to the DNA itself, chemical modifications to the histones which the DNA wraps around, and even the non-coding RNAs that are involved in cellular operation.[35] The word "epigenetic" refers to isolated parts of the epigenome, and the epigenome refers to the sum total of epigenetic parts. The ENCODE and RoadmapEpigenomics project are generally sympathetic to the definition of the epigenome that emphasizes methyl modifications to DNA and chemical modifications to histones.

Furthermore, the *Stem Cells Handbook* considers the genome as an analogy to ROM and the epigenome as an analogy to RAM.[36] Whatever the labels, epigenomic research commands a large amount of financial interest in the medical community with an estimated therapeutic market of 8 billion dollars in 2017 and much more in the future.[37] A more accurate term instead of "epigenome" might be "chromatin modifications". At least for the purposes of this paper, unless otherwise stated, "epigenome" will mean "chromatin modifications". Each cell has a different set of chromatin modifications than another cell. Thus there is the potential for an adult with 100 trillion cells to have 100 trillion epigenomes.

As an academic exercise, one can attempt to count the hypothetical possible number of chemical states in the combined collection of 100 trillion epigenomes in an adult human. One way to state the number of states, since it is astronomically large, is to express the number of states in terms of Shannon information bits. Given there are about 100 trillion cells in the adult human, 16.5 million nucleosomes per cell, and at least 40 bits of information per nucleosome (see figure 4

and 5)[38], a back-of-the envelope calculation yields an approximate total RAM in an adult human on the order of sextillion (10^{21}) bits. Some of this RAM is believed to be utilized in the brain for learning and cognition, for the body in self-healing and development, and many yet-to-be discovered functions required to implement the various organs and systems in the body. The discoveries by the ENCODE and RoadmapEpigenomics projects contributed to the understanding of how this enormous amount of epigenetic RAM is utilized.

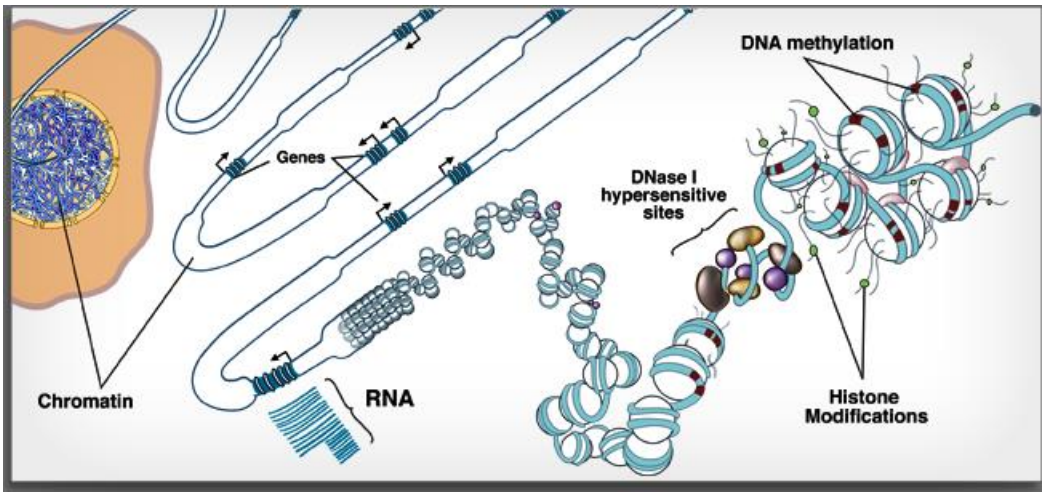


Figure 4. From the RoadmapEpigenomics project. A depiction of DNA conceptually uncoiled from the cell nucleus (left) to reveal the "beads on a string" architecture of chromatin. Chromatin is composed of DNA and histones around which the DNA wraps. The "bead" is called a nucleosome and consists of DNA wrapped around 8 histones. The nucleosomes occur at a frequency of about every 200 base pairs of DNA.

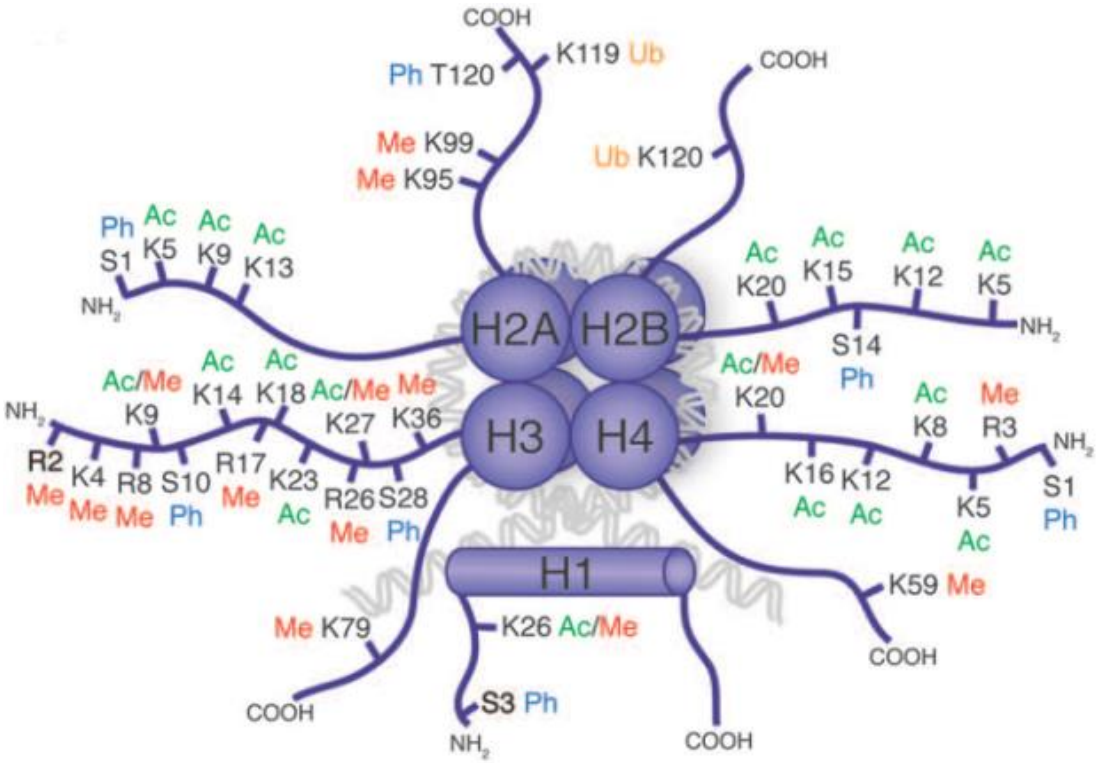


Figure 5.[39][40] A tabulation of the known chemical modifications to histone tails in the DNA nucleosome complexes. Each nucleosome occurs regularly for about every 200 base pairs of DNA. This figure shows 42 possible chemical modifications to the histone core of a nucleosome, but there are likely more modifications to be discovered. "Me" means methylation, "Ac" acetylation, "Ph" phosphorylation, "Ub" ubiquitination. Each modification can be approximated as representing 1 bit of information. In truth, a chemical modification shown in the above diagram can sometimes represent more than one bit of information because in cases such a methylation, there are up to 3 different degrees of methylation.

In addition to the epigenome, in the last few years, there has emerged the notion of the epitranscriptome which represent chemical modifications to RNA transcripts[41]. For a eukaryotic organism to manage such a vast amount of information suggests a degree of complexity that is incompatible with current evolutionary genetics. The appendix will go into some of the technical details of this inference. But suffice to say, if evolutionary genetics cannot explain the complexity of epigenome and epistranscriptome, it is not currently (perhaps not even in the future) feasible to explain the certain complexities in biology in terms of repeatable and ordinary mechanisms, and thus it weakens the claims of naturalism to the extent that naturalism denies the existence of highly exceptional processes that would qualify as statistical miracles.

CONCLUSION

Although it is a philosophical question as to what point a phenomenon passes a threshold of being either natural or supernatural, a sufficiently extraordinary set of events might be perceived as indistinguishable from a supernatural miracle even if hypothetically there were no God or gods to speak of. The exceptional property of life is illustrated by Haeckel's claim that if the doctrine of spontaneous generation were false, then the emergence of life would have to be of miraculous supernatural origin. Questions of God and the existence of the supernatural are outside the scope of this paper, but the resolution of the question of God and the supernatural are not needed to realize that naturalism is not to be equated with science.

The case for naturalism is weakened if a phenomenon exists that would hint that astronomically exceptional circumstances were involved in its emergence. It would appear life is one such phenomenon. If specialness of life doesn't challenges naturalism, at the very least, it challenges the ability to explain it in terms of ordinary and repeatable processes.

It is understandable that some methodological naturalists find the idea of miraculous-looking complexity in life as incompatible with a naturalistic narrative that insists miraculous events had no role in the emergence of life and its complex features. But such sentiments are speculations, and though superficially sounding like scientific explanations, such assertions should not be conflated or equated with actual science, and hence investment decisions in committing resources to scientific exploration should not be constrained merely because such explorations have the potential to discover facts that are unfavorable to naturalistic philosophy.

If ENCODE is right and the genome is more functional than evolutionary biologists have argued, but no money is invested in research friendly to ENCODE's claims, medical science and the chance to alleviate human suffering risks being permanently compromised. On the other hand, if money is invested to prove that Dan Graur and the evolutionary biologists he represents are right, there will be no benefit to the human medical condition even if they are right. Thus, according to Pascal's wagering theories, in light of these payoffs, and providing there is some small probability that ENCODE is right, money should be wagered on ENCODE, and indeed that is where the money is being wagered by the NIH on behalf of US taxpayers.

Insisting on the truth of naturalism in the disguise of evolutionary theory could impede scientific progress in the medical sciences if the whims of some evolutionary biologists like Dan Graur are realized. The National Science Foundation (NSF) has invested 170 million dollars in unresolvable evolutionary phylogenies of little or no utility to medical science.[42] To date, no therapies based on the 170 million dollar phylogeny project have come to market. By way of contrast, with the help of research like ENCODE, epigenetic therapies are already being delivered to patients with more such therapies in the pipeline. Therefore, a gambler's epistemology that seeks to maximize reward in the face of uncertainty would seem a superior approach versus blind insistence on impractical naturalism.

Appendix 1

Simplified Explanation of Genetic Entropy and Reasons for Dan Graur's Complaint Against ENCODE

A population can tolerate a certain number of mutations per individual per generation. The tolerable load of mutations is also known as "mutational load". Graur's complaint against ENCODE can be summarized as the problem of mutational load.

Calculations of mutational load for humans was prominently put forward by Hermann Muller who estimated the human genome can tolerate at most 1 bad mutation per individual per generation. [43] Muller won the Nobel Prize for his research into genetic deterioration due to radiation.

If ENCODE is right, the functional genome would be on the order of 3 giga base pairs, and given accepted mutation rates, the size of the functional genome would imply on the order of 50-100 function-compromising mutations per generation per individual.[44] Graur himself explicitly said:

> *If 80% of the genome is functional, as trumpeted by ENCODE Project Consortium (2012), then 45-82 deleterious mutations arise per generation. For the human population to maintain its current population size under these conditions, each of us should have on average 3×10^{19} to 5×10^{35} (30,000,000,000,000,000,000 to 500,000,000,000,000,000,000,000,000,000,000,000) children.* ***This is clearly bonkers.*** *If the human genome consists mostly of junk and indifferent DNA, i.e., if the vast majority of point mutations are neutral, this absurd situation would not arise. [emphasis mine]*

Darwin and Spencer asserted "survival of the fittest" as an axiom of nature. But survival of the fittest occurs between siblings and cousins (figuratively speaking) of a generation, not between ancestors and descendants across generations. If the children are substantially more damaged than their parents on average, no amount of selecting the best kids among their peers will result in genetic advancement over time, but rather deterioration even though the axiom of "survival of the fittest" was true. A simplified conception of this problem is illustrated in figure 6.

The problems posed by mutational load and other aspects leading to genetic deterioration has been summarized in a book by genetic engineer John Sanford at Cornell.[45] Curiously, though Sanford is a creationist, he would likely agree with Graur and the evolutionary biologists, "If ENCODE is right, evolution is wrong."

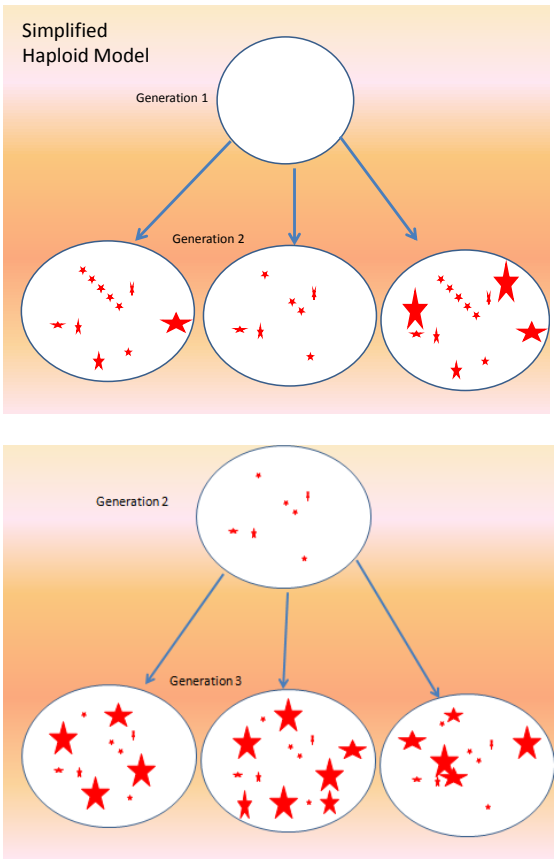


Figure 6.[46] Conceptual diagram of inevitable genetic deterioration. The Bubbles represent individuals in a generation and the red stars are detrimental mutations. The parent from generation 1 has hypothetically no mutations. Each of the kids in generation 2 has lots of mutations the parent didn't have. Even supposing the kid in generation 2 with the least mutations is selected to spawn the kids in generation 3, it will pass on its defects to its children in addition to adding new bad mutations to kids in generation 3. The number of detrimental mutations increases with each generation. Granted this is a simplified single parent (haploid) model, but it is provided for conceptual purposes. The more complex models (such as developed by Muller and others afterwards which leverage the Poisson distribution) arrive at the same essential conclusion, furthermore their calculations yield a estimate that 1 bad mutation per individual per generation on average cannot be tolerated by the human species.

Appendix 2

Life as a Rube Goldberg Machine

A Rube Goldberg machine is customarily defined as a contraption, invention, device or apparatus that performs a simple task in an indirect, convoluted and complicated fashion. It is named after American cartoonist and inventor Reuben Garrett Lucius "Rube" Goldberg (1883–1970).

In 1996 Michael Behe in his book *Darwin's Black Box* used notion of Rube Goldberg Machines to describe complex biochemical systems (like blood clotting and vision). However, the term "Rube Goldberg Machine" was overshadowed by his idea of "Irreducible Complexity".[47]

Behe's ideas have had influence on other biologists even though they disagree with his claims of Intelligent Design and his criticisms of Darwinism. A possible hint of Behe's influence on scientific culture is suggested by a description and diagram in the 2010 *Cell and Molecular Biology* Textbook by Gerald Karp which showed a picture of a Rube Goldberg machine with the following caption[48]:

> "Cellular activities are often analogous to this Rube Goldberg machine in which one event automatically triggers the next event in a reaction sequence."

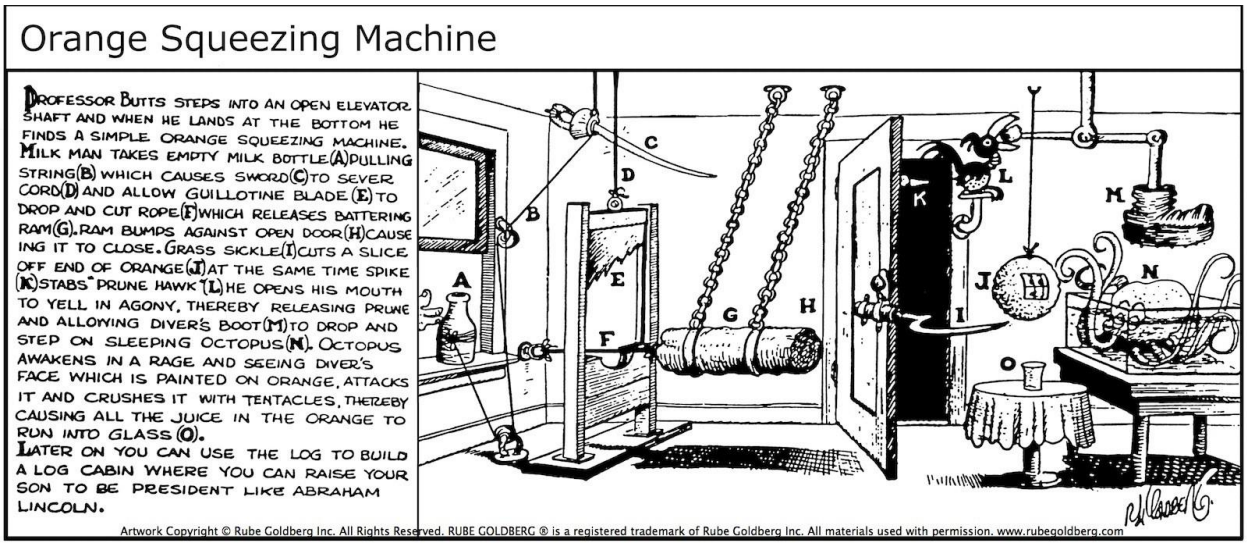


Figure 7.[49] An orange squeezing Rube Goldberg machine which was featured in Gerald Karp's 2010 book *Cell and Molecular Biology Textbook* to illustrate cellular activities.

Additionally, the 2015 Nobel Prize winner in Chemistry, Aziz Sancar, wrote the 2008 paper "The Intelligent Clock and the Rube Goldberg Clock".[50] In that paper, Sancar uses the phrase "Rube

Goldbergesque Designs" to describe Eukaryotic biological clock. Intelligent Design advocates might be tempted to argue Paley's watch is a molecular Rube Goldberg Machine.[51]

The phrase "Rube Goldberg" has been used both as a term of derision but also of praise for the way biological systems are constructed. Sancar used it as a term of derision, but Behe as a term of praise. Rube Goldberg machines transcend characterization as "good design" and "bad design" since Rube Goldberg machines are "bad designs" in the sense that they have excessive complexity which increases the fragility of the system but "good designs" in the sense that they showcase the creativity and ability of the designer to balance a design on the edge between functionality and disaster (like a house of cards).

Evolutionary biologists assume that natural selection has sufficient tendency to select toward the greater complexity we see in life.[52] This has never been theoretically nor empirically established. No formal computation has been offered as to what the mathematical expectation is toward selection of complexity from simpler systems in general. At best the question is unanswered, at worst the assumption that selection frequently selects for complexity is completely wrong.

The peacock's tail and problem of Rube Goldberg extravagance made Darwin sick since he reasoned natural selection should select against the extravagance of such complexity rather than for it since such extravagant complexity makes the species more vulnerable and fragile and thus less survivable. He reasoned therefore a mechanism other than natural selection created the peacock's tail. But since he rejected special creation, he suggested a theory of sexual selection (whereby mates select for complexity), but then that leaves open the question of what created the extravagance of sexual reproduction in the first place, not to mention if sexual selection created extravagance that reduced survivability for the species as a whole, then such extravagance would still be selected against.

According to the PBS documentary on evolution, prior to Darwin's theory, the prevailing view was that biological organisms were created to attest of the Creator's ingenuity to men who studied these organisms, not to provide for primarily for the creature's survival.[53] The peacock's tail remains problematic for explaining biology purely in terms of survival since such excessively complex systems would increase fragility and thus decrease survivability in a competitive environment.

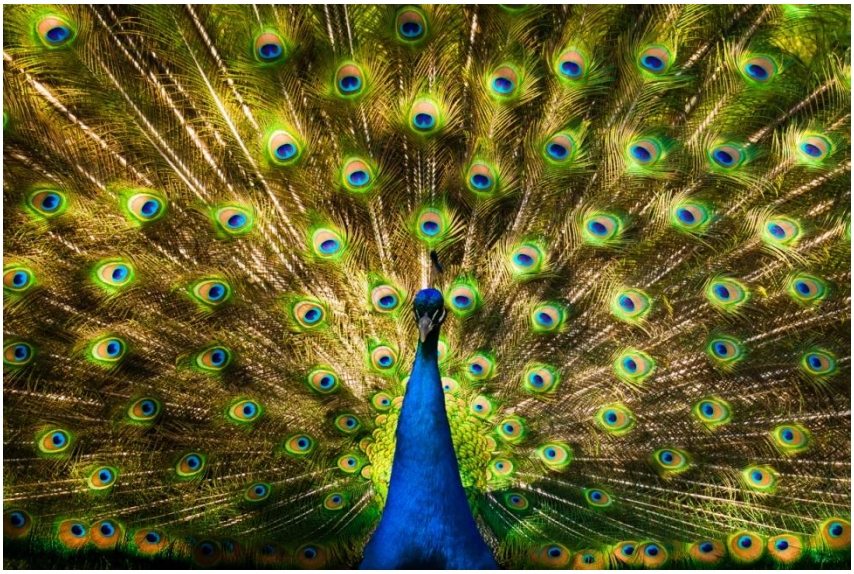


Figure 8.[54] Peacock's tail.

Darwin's theory equivocates the notion of "selectively favored". Selectively favored in present does not imply selectively favored in past. Nevertheless, this equivocation seems to be a staple in "proving" selection theory as a credible theory whereby selection evolves toward non-existent traits[55].

For example, in mammals a functioning insulin-regulated metabolism is a requisite for life but a dysfunctional one results in death. Population geneticists model selection mathematically by attaching an S-coefficient to a trait. Superficially it would seem selection would favor evolution of an insulin-regulated metabolism and hence a favorable S-coefficient should be attached to that trait in population genetic models. But if an ancestral species does not have an existing insulin-regulated metabolism and if it is life critical, then the species goes extinct in one generation. Affixing S-coefficients in mathematical models of the past based on life criticality of traits in the present is thus completely illegitimate. Nevertheless, models of utilizing such illegitimate reasoning are put forward as proof of Darwinian theory with phrases in peer-reviewed literature such as "this trait evolved in order to…." These statements are made while failing to recognize that selection cannot select toward non-existent traits and that Darwinian evolution cannot have the foresight to evolve toward some goal.

On the other hand if the insulin-regulated metabolism is not life-critical, on what basis can it be argued it was selectively favored in the past since creatures with insulin-regulated metabolisms in the present might be nothing like creatures without insulin regulated metabolisms in the past. For such an insulin regulated metabolism to evolve, it would require numerous parts to appear simultaneously such as the insulin molecule itself, a means of manufacturing insulin (like emergence of new beta cell types), a means of regulating insulin (feedback mechanisms), and a means of responding to insulin (appropriate tyrosine kinase receptors).

Since simultaneous appearance of requisite parts seems astronomically remote, evolutionary biologists postulate co-option (exaptation) whereby these parts are used for some other purpose first. But this is purely speculative, and even supposing the parts were available there is the further problem of actually evolving instructions to assemble and utilize the parts.

Supposing someone is given all the necessary characters to solve a 40 character password where each character is unique, it would be still challenging to solve the password even though all the available characters are known (analogous to a co-option scenario) -- the chances of solving such a password in one try would be 1 out of 40 factorial (or 8×10^{47}). An evolutionary algorithm cannot solve a complex password without knowing the actual password in advance. There is no feedback that one is getting closer to a solution with each trial. In like manner, for complex all-or-nothing Rube Goldberg type systems, selection can't select toward the individual parts since there will be no feedback that one variation is closer to success than another.

In fact, sometimes a half formed organ or system is worse for the creature than no organ at all and hence selection would in general select against formation of novel Rube Goldberg complexities. As paleontologist Stephen J. Gould said, "what good is half a wing?"[56]

Darwin's claim of natural selection might be argued to be rhetorical false advertising to the extent it is contrary to experimental and observational evidence, and hence his proposed mechanism is in actuality un-natural selection. Darwin's views are certainly not what happens naturally in the present day as evidenced by the fact that increased selection pressure on ecological systems leads on average to extinction of complex multicellular forms rather than emergence of them. For example, it is widely acknowledged that birds and other complex species are going extinct faster than they are being replaced by new complex forms under the increased selection pressure induced by human ecological intrusion.[57]

Appendix 3

Rube Goldbergesque Designs, Specificity and Complexity

Figure 9.[58] A small house of cards behind dominos standing on a small wooden box behind a lock and key. The house of cards and dominoes illustrate systems of objects that cannot be produced by an uncertainty maximizing process such as a tornado or similar process that affixes random orientations and positions to the objects. The lock and key combination is included in the photo since it is important to understanding that even though there are an infinite number of ways to make lock and key combinations, it doesn't imply the probability is high that a working lock and key will emerge from random processes – the probability is not high, it is remote.

A typical objection to the probability arguments put forward by Intelligent Design proponents is that the probability calculations they advocate are after-the-fact calculations, therefore illegitimate. For example, any random shuffle of a deck of cards will yield an astronomically rare sequence that occurs 1 out of 52 factorial (approximately 8×10^{67}) times. So each random possible sequence of cards is astronomically remote, hence opponents of Intelligent Design would argue any probability calculation about a sequence of cards cannot be used to argue one sequence is more special than any other. They would extend the same sort of objections to the emergence and complexity of life.

However the specialness of one sequence is not due to the improbability of a sequence, but how far from mathematical expectation a sequence is. Earlier it was mentioned that 100% fair coins heads is maximally far from the expectation of 50% fair coins heads. Additionally, suppose we found all the cards belonging to the red suits at the top of the deck and all cards belonging to the black suits at the bottom. The expected value for the first 26 cards at the top of the deck is approximately 50% red cards and 50% black cards, whereas 100% red cards at the top of the deck is farthest from expectation with odds of 1 out of 5×10^{14}. [the calculation is $26/52 \times 25/51 \ldots. 1/27 = 26!/(52!/26!) = 5 \times 10^{14}$]. Based on textbook math, the "all red-suited cards at

the top" configuration is an exceptional configuration. The symbolic properties (red and black suits) are decoupled from the physical properties which leads the possibility that certain special symbolic sequences are not practically explainable by random physical processes but rather by processes that defy natural randomizing tendencies.

To argue that "we just made all-red special in our minds, but it really isn't" would seem a last resort attempt to argue the all-red-suited-cards-at-the-top-of-the-deck configuration is not special. But to argue there is ultimately nothing exceptional in the universe, that "special" or "exceptional" is rooted in our imagination, would be to undo the foundations of probability theory and much of science that depends on it.

Independent of the question of Intelligent Design, the question of the existence of exceptional configurations can still be asserted. Living organisms are exceptional chemical configurations based on theory and experiment (such as Pasteur's experiments). Our perception of the specialness of life is not consequence of after-the-fact probabilities nor seeing faces in clouds.

Another objection to the specialness of life is that "there are many ways to make chemical replicators, hence our perception that life is special is based on after-the-fact probabilities that don't consider the fact there are an infinite number of ways to make life." But the counter-objection is that even though there are an infinite number of ways to make lock-and-key systems or complex replicating chemical systems (aka life), this does not make them highly probable. And if the replicator demands high specificity of the parts and connections (like a house of cards), it is exceptional as a matter of principle.

Various system parts can be said to have high specificity if they cannot tolerate much change or perturbation without the salient nature of the system breaking down. In figure 8, systems with high specificity are illustrated by the highly specific orientation and position of cards required to put them into a house configuration (vs. just lying flat), by dominoes being able to stand on their edges, and by the matching of a key to a lock. Randomly picked orientations and positions (non-specific configurations) of cards will not result in systems such as a house of cards even though there might be an infinite number of ways to make a house or village of cards. Similar considerations apply for the dominoes and lock-and-key systems and the origin of life.

A system composed of many parts can be said to be complex. Some might call a system possessing both large amounts of specificity and complexity as possessing "specified complexity", but because the phrase "specified complexity" has so many conflicting definitions (some involving information theory)[59] the term is de-emphasized in this paper.

Instead, the notion of "Rube Goldberesque Design" is suggested as more descriptive of the nature of biological complexity that is in a highly specified state. It is this class of extravagant complexity that bothered both Darwin in the past and evolutionary biologists in the present because such designs would be selected against rather than for owing to the fact greater specificity and complexity (like a greater house of cards) is more vulnerable to failure.

Darwin argued his theory of natural selection explains the emergence of high complexity in biology, but his theory is not what is observed in nature, and even by his own admission as symbolized by the peackock's tail, extravagant Rube Goldberg complexity present in life would actually be selected against rather than for.

Framing the spontaneous generation debate in terms of Natural vs. Supernatural or in terms of Intelligent Designs vs. Mindless Design muddles the more basic scientific question. The basic scientific question is whether life is a typical or exceptional chemical configuration. Life is an exceptional chemical configuration, astronomically so. Impractical naturalism is not comfortable with phenomenon that hints of events so singular they would be indistinguishable from miracles. Thus when faced with the fact of an exceptional phenomenon like the mechanical complexities of life, proponents of naturalism often try to argue something isn't that complex after all.

It is no surprise therefore that evolutionary biologists who are also naturalists are often inclined to insist biological systems are not that complex after all, that the complexity is an illusion. They argue the convoluted apparently clumsy ways living things go about their business is evidence against the intelligent design and in favor of natural evolution. But convoluted mechanisms could just as well be interpreted as Rube Goldbergesque designs, and Rube Goldbergesque designs in nature, like the peacock's tail, could just as easily argue for intelligent design as against it. But in any case, it is very hard to argue any Rube Goldbergesque design, be it God-made or nature made, would be a phenomenon consistent with natural mathematical and physical expectation.

ENCODE and research into epigenomics has uncovered several biological Rube Goldberg machines that epitomize specificity and complexity. One example such a Rube Goldberg machine is described in the Appendix 4.

Appendix 4

Example of a Biological Rube Goldberg Machine Involiving non-Coding RNA

Non-Coding RNAs were widely viewed as mostly junk. Though the matter junk DNA has not been totally settled, one example of an RNA that was thought to be junk and then discovered to be functional was the HOTAIR lincRNA . The HOTAIR lincRNA was given that name since the researchers joked that if the lincRNA molecule they were studying turned out to be junk, then their hypothesis would be a bunch of "hotair".[60]

John Rinn discovered the HOTAIR lincRNA originates from Chromosome 12 and by the winds of Brownian motion sails to Chromosome 2. HOTAIR writes modifications to Chromosome 2 on the Histone Random Access Memory (RAM) by recruiting the PRC2 polycomb repression complex (depicted below).[61] This marking on the RAM of each skin cell causes skin at the sole of the feet to be different from skin on the eyelids. Since Rinn's discovery, HOTAIR was discovered to interact with DNA in other chromosomes. HOTAIR's discovery has inspired research into the roles of other such non coding RNAs.

The system involving HOTAIR can be said to be a Rube Goldbergesque design in that a very complex ritual of tightly specified parts is involved in carrying out a task of gene regulation whereby DNA from one chromosome regulates DNA on another chromosome which regulates the differential development of skin cells.

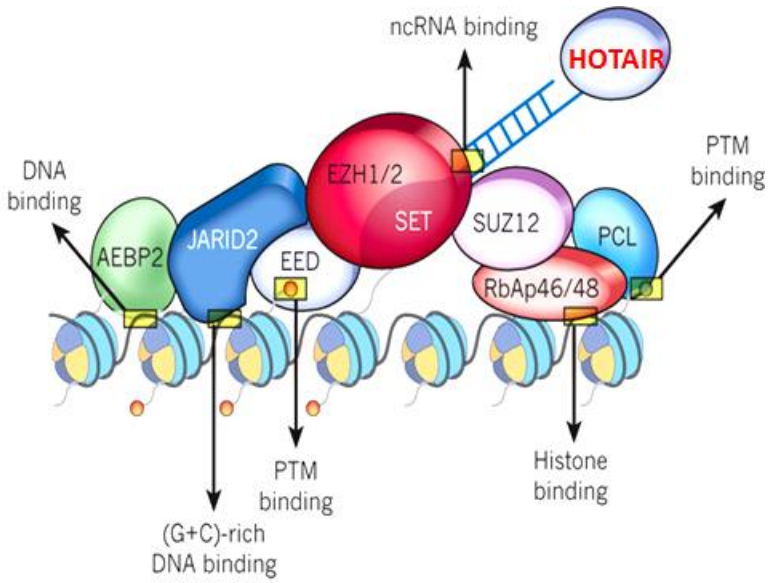


Figure 10.[62] PRC2 Polycomb Repression complex modifies the histone tails after being recruited by the HOTAIR lincRNA. The PRC2 complex has complex connections both to the DNA and the histones and histone tails as well as the protein components and the RNA. The Rube Goldberg interaction entails at least 7 protein complexes in the PRC2 complex attaching to the DNA, the histone proteins in the nucleosome, and a lincRNA coming from another chromosome.

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