Mutations: evolution's engine becomes evolution's end!

Alex Williams

In neo-Darwinian theory, mutations are uniquely biological events that provide the engine of natural variation for all the diversity of life. However, recent discoveries show that mutation is the purely physical result of the universal mechanical damage that interferes with all molecular machinery. Life's error correction, avoidance and repair mechanisms themselves suffer the same damage and decay. The consequence is that all multicellular life on earth is undergoing inexorable genome decay. Mutation rates are so high that they are clearly evident within a single human lifetime, and all individuals suffer, so natural selection is powerless to weed them out. The effects are mostly so small that natural selection cannot 'see' them anyway, even if it could remove their carriers. Our reproductive cells are not immune, as previously thought, but are just as prone to damage as our body cells. Irrespective of whether creationists or evolutionists do the calculations, somewhere between a few thousand and a few million mutations are enough to drive a human lineage to extinction, and this is likely to occur over a time scale of only tens to hundreds of thousands of years. This is far short of the supposed evolutionary time scales.

Mutations destroy

Ever since Hugo de Vries discovered mutations in the 1890s they have been given a central role in evolutionary theory. De Vries was so enamoured with mutations that he developed an anti-Darwinian saltationist theory of evolution via mutation alone.[1] But as more became known, mutations of large effect were found to be universally lethal, so only mutations of small effect could be credibly considered as of value to evolution, and de Vries' saltationist theory waned. When the Neo-Darwinian Synthesis emerged in the 1930s and 1940s, mutations were said to provide the natural variations that natural selection worked on to produce all new forms of life.

However, directly contradicting mutation's central role in life's diversity, we have seen growing experimental evidence that mutations *destroy* life. In medical circles, mutations are universally regarded as deleterious. They are a fundamental cause of ageing,[2,3] cancer[4,5] and infectious diseases.[6]

Even among evolutionary apologists who search for examples of mutations that are beneficial, the best they can do is to cite *damaging* mutations that have beneficial *side effects* (e.g. sickle-cell trait,[7] a 32-base-pair *deletion* in a human chromosome that confers HIV resistance to homozygotes and delays AIDS onset in heterozygotes,[8] *CCR5–delta32* mutation,[9] animal melanism,[10] and stickleback pelvic spine suppression[11]). Such results are not at all surprising in the light of the discovery that DNA undergoes up to a million damage and repair events per cell per day.[12]

Mutation physics

Neo-Darwinian theory represents mutations as uniquely biological events that constitute the 'engine' of biological variation. However, now that we can see life working in molecular detail, it becomes obvious that mutations are *not* uniquely biological events—they are purely physical events.

Life works via the constant (often lightning-fast) movement of molecular machinery in cells. Cells are totally filled with solids and liquids—there are no free spaces. The molecular machines and the cell architecture and internal structures are made up of long-chain organic polymers (e.g. proteins, DNA, RNA, carbohydrates, lipids) while the liquid is mostly water. All forms of movement are subject to the laws of motion, yet the consequences of this simple physical fact have been almost universally ignored in biology.

Newton's first law of motion says that a physical body will remain at rest, or continue to move at a constant velocity, unless an external force acts upon it. Think of a message molecule that is sent from one part of a cell to another. Since the cell is full of other molecules, with no empty spaces, the message molecule will soon hit other molecules and either slow down or stop altogether. This is the universal problem known as *friction*.

Friction events can result from many causes, but can be crudely divided into two types: one is referred to as *ploughing* and the other is *shearing*. Ploughing involves the physical displacement of materials to facilitate the motion of an object, while shearing arises from the disruption of adhesive interactions between adjacent surfaces.[13]

Molecular machines in cells owe a great deal of their structure to hydrogen bonds, but these are rather weak and fairly easily broken. For example, most proteins are long, strongly-bonded chains of amino acids, but these long chains are coiled up into 3-dimensional machine components, and the 3-dimensional structures are held together by hydrogen bonds.[14] When such structures suffer mechanical impacts, the transfer of momentum can distort or break the hydrogen bonds and critically damage the molecule's function.

Figure 1. A transparent carton of fruit yogurt illustrates how friction in the viscous fluid stopped the motion initiated by mixing the fruit (dark colour) with the yogurt (white colour).

The inside of a cell has a density and viscosity somewhat similar to yogurt (figure 1). The stewed fruit (dark colour) added to the yogurt during manufacture can be seen swirling out into the white yogurt. The fruit has not continued to disperse throughout the yogurt. It was completely stopped by the initial friction. This is like what happens in a cell—any movement is quickly dampened by friction forces of all kinds coming from all directions.

How do cells cope with this friction? In at least five different ways. First, there are motor proteins available all over the cell that attach to mobile molecules and carry them along the filaments and tubules that make up the cytoskeleton of the cell. Second, these motor proteins are continually re-energized after friction collisions by energy inputs packaged in the form of ATP molecules. Third, there are 'address labels' attached to mobile molecules to ensure they are delivered to the correct destination (friction effects continually divert mobile molecules from their course). Fourth, thin films of water cover all the molecular components of cells and provide both a protective layer and a lubricant that reduces the frequency and severity of friction collisions. Fifth, there is a wide range of maintenance and repair mechanisms available to repair the damage that friction causes.

The friction problem—and the damage that results from it—is orders of magnitude greater in cells than it is in larger mechanical systems. Biomolecules are very spiky objects with extremely rough and highly adhesive surfaces. They cannot be manufactured and honed to the smoothness that we achieve in our vehicle engine components such as pistons and flywheel pivots, nor can ball-bearings be inserted to reduce the surface contact area, such as we do in wheel axles. As a biological example, consider the rotary motor that drives the bacterial flagellum. The major wear surfaces are on the rotor (attached to the flagellum) and the stator (the housing for the rotor, attached to the cell wall). The stator consists of 22 molecules, set in 11 pairs. The wear rate is so great that the average residence time for a stator molecule in the stator is only about 30 seconds.[15] The cell's maintenance system keeps a pool of about 200 stator molecules in reserve to cope with this huge turnover rate.

Finding suitable lubricants to overcome friction is a major focus in the nanotechnology industry. A special technique called 'friction force microscopy' has been developed to quantitatively evaluate potential lubricants.[16]

This shows that the laws of physics, operating among the viscous components of the cell, both predict and explain the high rate of molecular damage that we observe in DNA. Between 50% and 80% of the DNA in a cell is continually consulted for the information necessary for everyday metabolism. This consultation requires numerous steps that each involve physical deformation of the DNA—moving around within the nucleus, winding and unwinding of the chromatin structures, unzipping the double-helix, binding and unbinding of the transcription machinery, re-zipping the double-helix, rewinding the chromatin structures and shuffling around within the nucleus. Each step of motion is powered by ATP discharges and inevitably causes mechanical damage among the components. While most of this damage is repaired, the repair mechanisms are not 100% perfect because they suffer mechanical damage themselves.[17]

Mutations rapidly destroy

Within neo-Darwinian theory, natural selection is supposed to be the guardian of our genomes because it weeds out unwanted deleterious mutations and favours beneficial ones. Not so, according to genetics expert Professor John Sanford.[18] Natural selection can only weed out mutations that have a significant negative effect upon fitness (number of offspring produced). But such 'fitness' is affected by a huge variety of factors, and the vast majority of mutations have too small an effect for natural selection to be able to detect and remove them.

Furthermore, if the average mutation rate per person per generation is around 1 or more, then everyone is a mutant and no amount of selection can stop degeneration of the whole population.[19] As it turns out, the mutation rate in the human population is *very much greater than 1*. Sanford estimates at least 100, probably about 300, and possibly more.

All multicellular life suffers

Two recent reviews of the mutation literature not only confirm Sanford's claims, but extend them to *all multicellular life*.

In a review of the distribution of fitness effects (DFE) of mutations,[20] the authors are unable to give any examples of beneficial mutations for humans. In their calculations regarding the rate of deleterious mutations (*MD*) and neutral mutations (*MN*), they use the equalities $MD = 1 - MN$ and $MN = 1 - MD$ which both imply that the rate of beneficial mutations is zero. They do give a few non-zero values for beneficial mutation rates in some experimental organisms, but qualify these results by noting the interference of other variables.

In a review of mutation rate variations in eukaryotes,[21] the authors admit that all multicellular organisms are undergoing inexorable genome decay from mutations because natural selection cannot remove the damage.[22]

Their Box 2 and Table 1 list deleterious mutation rates for a wide range of multicellular organisms, noting they are all *underestimates*, with the possible exception of those for the fruit fly *Drosophila melanogaster* with a value of 1.2. The value given for humans is '~3'.

Thus, all multicellular life on earth is undergoing inexorable genome decay because the deleterious mutation rates are so high, the effects of the most individual mutations are so small, there are no compensatory beneficial mutations, and natural selection is ineffective in removing the damage.

The wheels have come off the neo-Darwinian juggernaut!

How long to extinction?

How long could multicellular life survive in the face of universal genetic degradation? This is a very important question, and I will attempt to answer it by using several different lines of evidence.

Human ageing and cancer

We have recently discovered that there is a common biology in cancer and ageing—both are the result of accumulating molecular damage in cells.[23] This confirms the arguments outlined above, that for purely physical reasons molecular machinery suffers extremely high damage rates, clearly evident within the lifespan of a single human. Every cell has a built-in time clock to limit this damage and minimize the chance of it becoming cancerous. At every cell division, each *telomere* (the caps on both ends of a chromosome that stop the double-helix from unravelling) is shortened by a small amount, until they reach the *Hayflick Limit*—discovered in 1965 to be a little over 50 cell divisions. The cells then stop dividing and they are dismantled and their parts are recycled.

By adding the enzyme *telomerase*, the telomere shortening problem can be circumvented, but that then exposes the cell to a greater risk of becoming cancerous because of accumulating damage elsewhere in the cell. The overall balance between protection from damage and the need for longevity determines fitness (reproductive success) and life span.[24] The body's normal reaction to increasing genome damage is to kill off the damaged cells via programmed senescence (of which the telomere clock with its Hayflick limit is but one part). But cells become malignant (cancerous) when mutation disables the senescence mechanism itself, which then enables the damaged cells to proliferate without limit.[23] The Hayflick limit of around 50 cell divisions for humans seems to provide the optimum balance.

Fifty human generations of 20 years each gives us only 1,000 years as a timescale over which a human lineage would begin to experience a significant mutation load in its genome. This is alarmingly rapid compared with the supposed evolutionary time scale of millions and billions of years.

Reproductive cells

Ever since August Weismann published *The Germ-Plasm: A Theory of Heredity*[25] in 1893, a discrete separation has been shown to exist between body cells (the *soma*) and germ-line cells (*germplasm*). Germ-line cells were thought to be more protected from mutation than other body cells. However, another recently discovered cause of ageing is that our stem cells grow old as a result of heritable DNA damage and degeneration of their supporting *niches* (the special 'nest' areas in most organs and tissues of the body where stem cells grow and are nurtured and protected). The telomere shortening mechanism—intended to reduce cancer incidence—appears to also induce the unwanted side-effect of a decline in the replicative capacity of certain stem-cell types with advancing age. This decreased regenerative capacity has led to a 'stem-cell hypothesis' for human age-associated degenerative conditions.[26]

Human fertility problems suggest that the decline in niche protection of stem cells also applies to our gametes (eggs and sperm). For males, fertility—as measured by sperm count, sperm vigor and chance of conception—begins to decline significantly by age 40 and the rate of certain paternal-associated birth defects increases rapidly during the 30s (figure 2).[27] For females, the chance of birth defects increases rapidly from around the mid-30s, particularly because of chromosome abnormalities (figure 2). In the middle of the most productive part of our lives, our bodies are therefore showing clear evidence of decline through accumulation of molecular damage in our genomes.

Do germ-line cells really suffer less damage?

When DNA was discovered to be the carrier of inheritance, Weissman's germ-plasm theory gave rise to the 'immortal strand hypothesis.' When the DNA of an embryonic stem cell replicates itself, it was thought that the

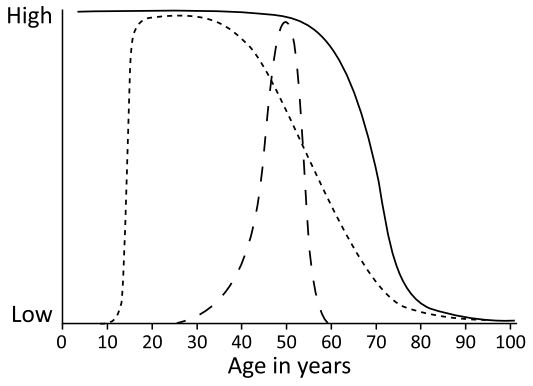

Figure 2. Schematic representation of human life expectancy (—), male fertility (···), and risk of fetal abnormality with mother's age (---). Despite the protective Hayflick limit on cell divisions and life expectancy, very significant molecular damage accumulates in humans even during the most productive years of life. Mutations do even more damage than the Hayflick limit and associated cancer rates suggest.

'old' strand would remain with the self-renewing 'mother' stem cell, while the newly constructed daughter strand proceeds down the path of differentiation into a body cell. In this way, the 'old' strand would remain error free—because it has not suffered any copying errors—and thus becomes effectively immortal.

However, a research team at the Howard Hughes Memorial Institute recently tested this theory using the stem cells that produce blood, and found that they segregate their chromosomes randomly.[28] That is, the 'immortal strand hypothesis' is wrong. If stem cells are not given this kind of preferential treatment then it is reasonable to conclude that germ-line cells are also subject to the same molecular damage as somatic cells. This is confirmed by the observation that human fertility exhibits damage long before age-related diseases take over.

A single human lifetime is enough to show very significant mutation damage, even in our reproductive cells.

Haldane's dilemma

The severe contradictions that these findings pose for neo-Darwinian theory corroborate what has become known as *Haldane's dilemma*. J.B.S. Haldane was one of the architects of neo-Darwinism who pioneered its application to population biology. He realized that it would take a long time for natural selection to fix an advantageous mutation in a population—fixation is when every member has two copies of an allele, having inherited it from both mother and father. He estimated that for vertebrates, about 300 generations would be required, on average, where the selective advantage is 10%. In humans, with a 20-year generation time and about 6 million years since our last common ancestor with the chimpanzee, only about 1,000 such advantageous mutations could have been fixed. Haldane believed that substitution of about 1,000 alleles would be enough to create a new species, but it is not nearly enough to explain the observed differences between us and our closest supposed relatives.

The measured difference between the human and chimpanzee genomes amounts to about 125 million nucleotides, which are thought to have arisen from about 40 million mutation events.[29] If only 1000 of these mutations could have been naturally selected to produce the new (human) species, it means the other 39,999,000 mutations were deleterious, which is completely consistent with the reviews showing that the vast majority of mutations are deleterious. Consequently, we must have *degenerated* from the apes, which is an absurd conclusion.

According to Kirschner and Gerhart's facilitated variation theory,[30] life consists of two main components —*conserved core processes* (the structure and machinery in cells) and *modular regulatory processes* (the signalling circuits and switches that operate the machinery and provide a built-in source of natural variation). The 40 million 'mutation' differences between humans and chimps are therefore much more reasonably explained as 40 million *modular differences* between the *design* of chimps and the *design* of humans.

Quantitative estimates of time to extinction

There are a number of different ways to estimate the time it would take for relentlessly accumulating mutations to send our species to extinction.

Binomial estimates

Some very rough estimates can be derived from the Binomial distribution, which can predict the likelihood of multiple mutations accumulating in an essential genetic functional module. A binomial model of a mutating genome could consist of the cell's DNA being divided into N functional modules, of which N_e are essential; that is, the lineage fails to reproduce if any of the essential modules are disabled. For any given mutational event, $p = 1/N$ is the probability of being 'hit', q is the probability of being 'missed', and $p + q = 1$.

What is the likely value of N? We can derive two estimates from the knowledge that there are about 25,000 genes, plus the discovery from the pilot study report of the ENCODE project that virtually the whole human genome is functional.[31]

For the first estimate, the average protein contains a few hundred amino acids and each amino acid requires three nucleotides of code, so the average gene would take up about 1,000 nucleotides of exon space (an *exon* is the protein-coding part of a gene). There are about 3 billion nucleotides in the whole human genome, so if we assume that the average protein represents an average functional unit then $N = 3$ million.

The second estimate comes from the ENCODE report that gene regions produce on average 5 RNA transcripts per nucleotide, and the untranslated regions produce on average 7 RNA transcripts per nucleotide. There are about 33 times as many nucleotides in the untranslated regions as in the genic regions. Assuming that transcript size is approximately equal in each region, then there are 25,000 x 5 = 125,000 gene transcripts and 25,000 x 33 x 7 = 5,775,000 untranslated transcripts, making $N = 5{,}900{,}000$ in total. Our two estimates of N are therefore 3 to 6 million in round figures.

What is the likely value of *Ne*? Experiments with mice indicate that 85% of genes can be knocked out one at a time without lethal effects.[31] This is due to the robustness and failure-tolerance through fallback processes built into the genomic designs. That means any one of those remaining 15% genes will be fatal if disabled. Multiple mutations occur however, so the likely value of *Ne* when exposed to multiple mutations will be much higher than 15%. The maximum possible value is 100%. In a study of 2,823 human metabolic pathways, 96% produced disease conditions when disrupted by mutation,[32] so if we take an average between this value and the minimum 15% then we get about 60% of functional units being essential.

How many random mutations are required on average to disable an essential functional module? In rare cases, a single mutation is enough to disable a person's ability to reproduce. A two-hit model is common in cancer. In a study of cell signalling networks, these two hits usually knocked out: (i) the programmed death system for dealing with damaged (cancerous) cells, and (ii) the normal controls on cell proliferation—so the damaged cancer cells can proliferate without limit. The proportion of cancer-associated genes was also found to increase with the number of linkages between genes. When a healthy gene is linked to more than 6 mutated genes, ~80% of all genes in the network are cancerous. Extrapolating from this, we find that by the time a normal gene is linked to about 10 mutated genes, then the whole network has become cancerous.[34]

Almost 70% of known human genes can be causal agents of cancer when mutated.[35] Cancers can result from as little as a single mutation in a stem cell, or multiple mutations in somatic cells.[36] The minimum possible value of 1 is known to be rare, so the more common occurrence of the 2-hit model makes it a reasonable best-estimate minimum. But it may require 10 modules to receive two hits each for the whole network to become dysfunctional.

The maximum number of hits required to disable a single module may be 100 or more, but if the average functional module only contains 1,000 nucleotides then this figure, at 10% of the whole, seems rather large. An order-of-magnitude average is perhaps more likely to be 10 random mutations per functional module.

To provide some context for these estimates, recent work shows that the cell-cycle checkpoint damage repair system is activated when 10 to 20 double-strand breaks accumulate in a cell undergoing division.[37] That is, life will tolerate only 10 to 20 DNA breaks per cell before it starts repair work, whereas we are examining scenarios in which there are thousands and millions of damage events per cell. Our numbers are clearly up in a region where the cell's repair mechanisms are working at their hardest.

What then is the likelihood of accumulating either 2 hits in 10 modules, or 10 hits in one module, in any one of either 15% or 60% of the 3 to 6 million functional modules? The binomial distribution in Microsoft Excel was used to make the following calculations, making the further assumption that the likelihood of the unit being a critical one must exceed 50% for extinction to be more likely than not in the next generation.

Assuming 60% essentiality, only one functional module needs to be disabled for the probability of its essential status to exceed 50%. For the 2-hit model, about 6,000 to 12,000 mutations are required to disable ten of the 3 to 6 million functional modules. For the 10-hit model, 3 to 6 million mutations are required to disable one functional module.

Assuming 15% essentiality, four modules need to be disabled before the probability of at least one of them being essential exceeds 50%. For the 2-hit model, 250,000 to 500,000 mutations are required to disable ten modules with four mutations each among the 3 to 6 million functional modules. For the 10-hit model, 3.7 to 7.5 million mutations are required to disable four functional modules.

If every individual produces 100 new mutations every generation (assuming a generation time of 20 years) and these mutations are spread among 3 to 6 million functional modules across the whole genome, then the average time to extinction is:

- 1,200 to 2,400 years for the 2-hits in 10 modules model and 60% essentiality
- 50,000 to 100,000 years for the 2-hits in 10 modules model and 15% essentiality
- 600,000 to 1,200,000 years for the 10-hit model and 60% essentiality
- 740,000 to 1,500,000 years for the 10-hit model and 15% essentiality.

Truncation selection

Evolutionary geneticist Dr James Crow argued that humans are probably protected by 'truncation selection'.[27] Truncation occurs when natural selection preferentially deletes individuals with the highest mutation loads. Plant geneticist John Sanford put Crow's claims to the test by developing a computer simulation of truncation. His assumptions were: 100 individuals in the population, 100 mutations per person per generation, 4 offspring per female, 25% non-genetic random deaths per generation, and 50% selection against the most mutant offspring per generation. He assumed an average fitness loss per mutation of 1 in 10,000. His species became extinct in only 300 generations. With a generation time of 20 years this corresponds to 6,000 years.[38]

Sanford's assumptions are somewhat unrealistic, but there are other ways to approach the problem. Mutations are pure chance events that follow a Poisson distribution, and this behaves like the normal curve when the average expected value is greater than about 30.[39] In a Poisson distribution, the variance is equal to the average expected value, and the standard deviation is the square root of the variance. When the expected average value is 100, the standard deviation will be 10. The normal curve now tells us the following:

- Half the people will suffer about 100 mutations or more, and half the people will suffer about 100 mutations or less.
- About 84% of people will suffer 110 mutations or less, and so the remaining 16% of people will suffer 110 or more mutations. Alternatively, about 16% of people will suffer 90 or less.
- About 97.7% of the population will experience 120 mutations or less, and the remaining 2.3% will suffer 120 mutations or more. Alternatively, 2.3% will suffer 80 or less.
- About 99.9% of the population will suffer 130 mutations or less, and the remaining 0.1% will suffer 130 or more mutations. Alternatively, 0.1% will suffer 70 or less.

Table 1. Estimated number of generations and years to extinction for populations of various sizes, when fitness declines by 1.5% in each generation.

Population size N	Generations to extinction	Years to extinction
10	110	2,200
100	260	5,200
1,000	420	8,400
10,000	570	11,400
100,000	720	14,400
1,000,000	870	17,400
10,000,000	1030	20,600
100,000,000	1180	23,600
1,000,000,000	1330	26,600
10,000,000,000	1480	29,600
100,000,000,000	1640	32,800

If we remove the most mutant—those above 130 mutations per person per generation—then we will only remove 0.1% of the population and it will make virtually no difference. If we removed the most mutant 50% of the population that would not solve the problem either, for two reasons. First, the great majority of the remaining people still suffer between 70 and 100 mutations per person per generation, far above the value of 1 that ensures inexorable decline. Second, removing half the population each generation would send it extinct in a few dozen generations.

Synergistic epistasis and population size

None of the above models include the effect of *synergistic epistasis* (if one gene is mutated, its impact is ameliorated by the coordinated activity of other genes) or of population size. We can include these by using Crow's estimate that the fitness of the human race is currently degenerating at a rate of about 1 to 2% per generation. If we use an average value of 1.5% then only 98.5% of the next generation will produce reproductively viable offspring. The next generation after that will only have 98.5% of those survivors able to produce reproductively viable offspring, and so on.

For any given stable population size N, the size of the next generation that can produce reproductively viable offspring will be 98.5% of N, and for any given number of generations G, the number of survivors able to produce reproductively viable offspring will be $(98.5\%)^G$ of N.

Table 1 shows the approximate numbers of generations after which the population degenerates to extinction (only one individual is left, so breeding cannot continue). No population can sustain a continual loss of viability of 1.5%.

The above model assumes that right from the beginning there will be 1.5% loss of fitness each generation. However, the binomial simulations earlier showed that individuals can tolerate somewhere between a few thousand to a few million mutations before the damage critically interferes with their ability to reproduce. This means that *synergistic epistasis* is a real phenomenon—life is robust in the face of mutational assault. Instead of the immediate loss of 1.5% every generation, the general population would remain apparently healthy for a much longer time before the damage became apparent.

However, the rate at which mutations accumulate will remain the same because the cause remains the same—mechanical damage. This means that most people will be apparently healthy, but then approach the threshold of dysfunction over a much shorter period, creating a population crash rather than a slow decline.

Either way, however, the time scales will be approximately the same because the rate of damage accumulation remains approximately the same.

Summary

Mutations are not uniquely biological events that provide an engine of natural variation for natural selection to work upon and produce all the variety of life. Mutation is the purely physical result of the all-pervading mechanical damage that accompanies all molecular machinery. As a consequence, *all multicellular life on earth* is undergoing inexorable genome decay because the deleterious mutation rates are so high, the effects of the individual mutations are so small, there are no compensatory beneficial mutations and natural selection is ineffective in removing the damage.

So much damage occurs that it is clearly evident within a single human lifetime. Our reproductive cells are *not* immune, as previously thought, but are just as prone to mechanical damage as our body cells. Somewhere between a few thousand and a few million mutations are enough to drive a human lineage to extinction, and this is likely to occur over a time scale of only tens to hundreds of thousands of years. This is far short of the supposed evolutionary time scales. Like rust eating away the steel in a bridge, mutations are eating away our genomes and there is nothing we can do to stop them.

Evolution's engine, when properly understood, becomes evolution's end.

References

1. De Vries, H., *The Mutation Theory*, German edition 1900–03, English

edition 1910–11; De Vries, H., *Species and Varieties: Their Origin by Mutation,* 1905, <en.wikipedia.org/wiki/Hugo_de_Vries>, 11 August 2007.

2. Niedernhofer, L.J. *et al*., A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis, *Nature* **444:**1038–1043, 2006.
3. Kudlow, B.A., Kennedy, B.K. and Monnat, R.J. Jr, Werner and Hutchinson–Gilford progeria syndromes: mechanistic basis of human progeroid diseases, *Nature Reviews Molecular Cell Biology* **8**:394–404, 2007.
4. Eccleston, A. and Dhand, R., Signaling in cancer, *Nature* **441**(7092):423, 2006.
5. He, X.C. *et al*., PTEN-deficient intestinal stem cells initiate intestinal polyposis, *Nature Genetics* **39**:189–198, 2007.
6. Casanova, J-L. and Abel, L., Human genetics of infectious diseases: a unified theory, *The EMBO Journal* **26**:915–922, 2007.
7. Carroll, S.B., *The Making of the Fittest: DNA and the ultimate forensic record of evolution*, Norton, New York, pp. 174–179, 2006.
8. Guilherme, A. and Pacheco, F., CCR5 receptor gene and HIV infection, <www.cdc.gov/genomics/hugenet/factsheets/FS_CCR5.htm>, 11 August 2007.
9. Lamb, A., CCR5–delta32: a very beneficial mutation, *Journal of Creation* **20**(1):15, 2006; <www.creationontheweb.com/content/view/5390/>.
10. Carroll, S.B., *Endless Forms Most Beautiful: The new science of evo devo*, Norton, New York, Ch. 9, 2005.
11. Carroll, S.B., *The Making of the Fittest: DNA and the ultimate forensic record of evolution*, Norton, New York, Ch. 8, 2006.
12. <en.wikipedia.org/wiki/DNA_repair>, January 29, 2008.
13. Leggett, G.J., Brewer, N.J and Chong, K.S.L., Friction force microscopy: towards quantitative analysis of molecular organisation with nanometre spatial resolution, *Phys. Chem. Chem. Phys.* **7**:1107–1120, 2005.
14. Most organic macromolecules contain numerous hydrogen atoms bonded to carbon atoms. Because hydrogen has only one (negative) electron and one (positive) proton, the 'cloud' of electron trajectories tends to be easily skewed towards the stronger electromagnetic fields in the core of the carbon chain, thus giving the hydrogen atom a small net positive force, which is then available to form a 'hydrogen bond' with electron-rich (negative) sites on other nearby molecules, or on adjacent folds in its own chain.
15. Leake, M.C. *et. al*., Stoichiometry and turnover in single functioning membrane protein complexes, *Nature* **443**:355–358, 2006.
16. Leggett, G.J., Brewer, N.J. and Chong, K.S.L., Friction force microscopy: towards quantitative analysis of molecular organisation with nanometre spatial resolution, *Phys. Chem. Chem. Phys.* **7**:1107–1120, 2005.
17. Copy fidelity varies with the different DNA copying systems that are present in all eukaryote cells, with the different kinds of errors that can occur, and with the different stages at which errors can occur. A couple of errors in ten million is fairly typical, but mutant cells may produce a hundred to ten thousand times this value. E.g. Pursell, Z.F., Isoz, I., Landström, E-.L., Johansson, E. and Kunkel, T.A. Regulation of B family DNA polymerase fidelity by a conserved active site residue: characterization of M644W, M644L and M644F mutants of yeast DNA polymerase ε, *Nucleic Acids Research* **35**(9):3076–3086, 2007.
18. Sanford, J.C., *Genetic Entropy & The Mystery of the Genome*, Elim Publishing, New York, 2005.
19. Humans have lived on earth for about 6,000 years and about 250 generations. For a population size of 1 million people, an average rate of one mutation per 20 people per generation is sufficient to ensure that everyone today is a mutant. I.e. $(0.054)^{250}$ x 1 million people < 1. If the supposed 300,000 generations since the split with apes is assumed, then a rate of only 1 mutation in 21,000 people per generation is enough to ensure that everyone today is a mutant.
20. Eyre.-Walker, A. and Keightley, P.D., The distribution of fitness effects of new mutations, *Nature Reviews Genetics* **8**:610–618, 2007.
21. Baer, C.F., Miyamoto, M.M. and Denver, D.R., Mutation rate variation in multicellular eukaryotes: causes and consequences, *Nature Reviews Genetics* **8**:619–631, 2007.
22. Two important difference between multicellular organisms and bacteria and viruses in this regard are: (a) effective population size (trillions in the latter); (b) the latter have higher tolerance for mutations and are able to actively use them to their own advantage when required. E.g. Wagner, J. and Nohmi, T., *Escherichia coli* DNA Polymerase IV mutator activity: genetic requirements and mutational specificity, *Journal of Bacteriology* **182**(16): 4587–4595, 2000.
23. Finkel, T., Serrano, M. and Blasco, M.A., The common biology of cancer and ageing, *Nature* **448**:767–774, 2007.
24. Serrano, M. and Blasco, M.A., Cancer and ageing: convergent and divergent mechanisms, *Nature Reviews Molecular Cell Biology* **8**:715–722, 2007.
25. Weismann, A., *The Germ-Plasm: A Theory of Heredity*, Charles Scribner's Sons, 1893. On-line version: <www.esp.org/books/weismann/germ-plasm/facsimile/>.
26 Sharpless, N.E. and DePinho, R.A., How stem cells age and why this makes us grow old, *Nature Reviews Molecular Cell Biology* **8**:703–713, 2007.
27. Crow, J.F., The high spontaneous mutation rate: is it a health risk? *Proceedings of the National Academy of Science* **94**:8380–8386, 1997.
28. Kiel, M.J. *et al.*, Haematopoietic stem cells do not asymmetrically segregate chromosomes or retain BrdU, *Nature* **449**:238–242, 2007.
29. DeWitt, D.A., Chimp genome sequence very different from man, *Journal of Creation* **19**(3):4–5, 2005.
30. Kirschner, M.W. and Gerhart, J.C., *The Plausibility of Life: Resolving Darwin's Dilemma,* Yale University Press, New Haven, CT, 2005.
31. Williams, A., Astonishing DNA complexity uncovered, <www.creationontheweb.com/content/view/5158>.
32. <en.wikipedia.org/wiki/Knockout_mouse>, 14 August 2007.
33. Ma, H., *et al.*, The Edinburgh human metabolic network reconstruction and its functional analysis, *Molecular Systems Biology* **3**, Article number 135; published online, 2007, <www.molecularsystemsbiology.com>.
34. Cui, O. *et al.*, A map of human cancer signaling, *Molecular Systems Biology* **3,** Article number 152, 2007.
35. Kim, L., Accumulation of mutations: cancer or molecule-to-man evolution? *Journal of Creation* **21**(2):77–81, 2007.
36. He, X.C. *et al*., PTEN-deficient intestinal stem cells initiate intestinal polyposis, *Nature Genetics* **39**(2):189–198, 2007.
37. Löbrich, M. and Jeggo, P.A., The impact of a negligent G2/M checkpoint on genomic instability and cancer induction, *Nature Reviews Cancer* **7**:861–869, 2007.
38. Sanford, ref. 18, p. 113.
39. Arnold, S.F., *Mathematical Statistics*, Prentice Hall, NJ, Table 6, 1990.

Alex Williams received a B.Sc. in botany from the University of New England, an M.Sc.(Hons.) in radioecology from Macquarie University, and is an elected member of the Australian Institute of Biology. He has diplomas in Christian studies from Tabor College and Bible College of South Australia (in missiology), and a Licentiate in Theology (with distinction) from the Australian College of Theology. During 20 years in environmental research, he became the Australian representative to the United Nations in his field, and produced for them a two-volume multi-authored monograph on the environmental behaviour of radium. He then spent seven years in mission work and is now an honorary botanist at the Western Australian Herbarium in Perth. He is a regular contributor to *Creation* and *Journal of Creation* and co-author of *Dismantling the Big Bang*.