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The gene: An appraisal

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abstract

The gene can be described as the foundational concept of modern biology. As such, it has spilled over into daily discourse, yet it is acknowledged among biologists to be ill-defined. Here, following a short history of the gene, I analyse critically its role in inheritance, evolution, development, and morphogenesis. Wilhelm Johannsen's genotype-conception, formulated in 1910, has been adopted as the foundation stone of genetics, giving the gene a higher degree of prominence than is justified by the evidence. An analysis of the results of the Long-Term Evolution Experiment (LTEE) with E. coli bacteria, grown over 60,000 generations, does not support spontaneous gene mutation as the source of variance for natural selection. From this it follows that the gene is not Mendel's unit of inheritance: that must be Johannsen's transmission-conception at the gamete phenotype level, a form of inheritance that Johannsen did not consider. Alternatively, I contend that biology viewed on the bases of thermodynamics, complex system dynamics and self-organisation, provides a new framework for the foundations of biology. In this framework, the gene plays a passive role as a vital information store: it is the phenotype that plays the active role in inheritance, evolution, development, and morphogenesis.

Notice: The originally published version of this paper was corrupted in the proofing process and so far, Elsevier have not produced a corrected version. While they get their act together, I have produced this corrected version. It lacks some of the functionality and correct formating, but it is readable.

1. Introduction

At present, much of biology is regarded as being governed, or regulated, by the genes in the genotype. From the level of the single cell, through organisms and how they develop, evolve, and function, the gene has been assigned a central role. The term is even common in discourse about aspects of human life. It is, in short, considered vital to understanding how life works. The phenotype, on the other hand, plays barely a supporting role in understanding the life process. I am proposing that the evidence demands the reversal of this relationship. In the early 1500s, Nicolaus Copernicus proposed reversing the positions of the Sun and the Earth, yielding the heliocentric solar system. Astronomy was simplified, and 1500 years of Ptolemaic astronomy were consigned to history. Newton's laws of motion were subsequently understood to govern the planets. I propose that the evidence dictates that the phenotype is the governor and regulator of the cell, which is the basic 'building block' of the organism. What can flow from this, I contend, is biology governed by thermodynamics and complex system dynamics and a simpler and more intuitive understanding of what life is.

My metaphor for the cellular phenotype is a brain, and for the gene, a provider of building materials, the gene products. The phenotype 'drives' and regulates the cell and the genes in the nucleus house the information for the phenotype to build and operate the cell (Nijhout 1990). Karl Popper asserts that brains and cells can acquire knowledge (Niemann 2014)[1] and I propose that the seat of that knowledge in the cell is the phenotype located in the cytoplasm.

The need for a re-thinking of biology is urgent. Huge resources are directed to the search for the genes that cause human disease. Rare inherited disease traits are often associated with a specific gene abnormality, but they affect only a few percent of the human disease burden: in this context genetics is clinically useful. Common, or so-called polygenic disease traits, potentially affecting everyone, have not yet yielded, in a clinically useable way. The reason is that genes are not responsible for common disease traits.

[1] See Appendix A for full text of Popper's Medawar Lecture to the Royal Society in 1986.

Explanations in science should be simple, not complicated: in his book, "*Back to Reality*" (Annila 2020), Finnish physicist Arto Annila, constantly emphasises simplicity in explaining even the most apparently intractable aspects of physics[2]. I believe the laws governing biology can be simple too, at least once some counter-intuitive aspects have been grasped[3].

2. A short history of the gene

In February 1865, Gregor Mendel, Abbot of the monastery in Brno, now in the Czech Republic, introduced, in a lecture, what we now know as the gene, calling it an 'element'. He stressed the particulate nature (thingness, or 'Istikeit') of elements,[4] having noted that, in the process of inheritance they retained their unitary nature, rather than blending one with another, as Darwin had assumed.

In 1910, Danish biologist, Wilhelm Johannsen, coined the term 'gene' in a lecture, published as a paper in 1911 (Johannsen 1911)[5]. He also coined the terms genotype and phenotype for what Mendel had called 'characters'. The gene quickly entered the scientific discourse of the time as the 'unit of inheritance' and it 'traded' under this guise for 50 or more years.

In 1944, Austrian physicist Erwin Schrödinger published his 1943 lecture in Dublin, "*What is Life*?", (Schrödinger 1944). His "naïve physicist's ideas about organisms" looked at from a quantum mechanical perspective, yielded the conclusion that the hereditary material must be a solid, he called it an 'aperiodic crystal'.

From around 1960, Petter Portin and Adam Wilkins (Portin and Wilkins 2017), report that the gene started to be viewed as a defined string of nucleobases that coded for a polypeptide: it was a material thing. This transformation was driven by the discovery of the structure of deoxyribonucleic acid (DNA) in 1953 by Francis Crick, James Watson, Rosalind Franklin, and Maurice Wilkins. Crick went on in 1958 to propose how proteins (more properly peptides) which yielded the phenotype, were coded in the gene's DNA sequence (Crick 1958). In 1970, Crick proposed the Central Dogma (which stipulated that information in the DNA flowed to the protein and not the reverse) and the sequence hypothesis, which stipulated that the sequence of the amino acids in a peptide determined the native and biologically active structure of the folded protein (Crick 1970). These developments in the 1950s/60s have determined how the gene has been perceived for the following 50 years: molecular genetics was born.

The prospect of sequencing the whole human genome was on the horizon by the early 1980s. Crick's assertion[6] that the 'secret of life' lay in the DNA that constituted the genes, made in the Eagle pub in Cambridge in February 1953, became increasingly convincing to biologists and the public alike. That 'secret' would be revealed in the sequence of the human genome[7].

The Human Genome Project (HGP), aimed to sequence the 3 billion bases in the human genome, commenced on 1 October 1990[8] with a grant of three billion US$ from the US Congress. Initially headed by James Watson, it was brought to its conclusion in 2003 by Francis Collins, now the Director of the National Institutes of Health in Washington. In 2001, when sequencing was sufficiently advanced to announce preliminary results[9], the human genome turned out to contain far fewer genes than the 'one gene: one polypeptide' hypothesis[10] predicted. Palaeontologist, Stephen Jay Gould, wrote in the New York Times under the heading "*Humbled by the Genome's Mysteries*"[11]:

"*The general estimate [of the number of genes] for Homo sapiens …… had stood at well over 100,000, with a more precise figure of 142,634 widely advertised and considered well within the range of reasonable expectation. Homo sapiens possesses between 30,000 and 40,000 genes, with the final tally almost sure to lie nearer the lower figure*."

Indeed, the final figure lies between 20,000 to 25,000 protein coding genes[12]: the HGP represented a major collision between genetics and reality.

According to Portin and Wilkins (Portin and Wilkins 2017), since the sequencing, several other problems have emerged with the concept of the gene: some gene sequences are not clearly delineated; the sequence of exons[13] in the gene is not necessarily reproduced at translation; a gene sequence may not be contiguous along the chromosome, and a given gene in one cell type may function differently in another. In short, the gene has proved extremely difficult to define concisely. This matters when the aim is to predict the phenotype from the genotype: which was the rationale for the HGP[14]. However, was that even a realistic aim? Take for

[2] For example, the nature of time, t: the energy, E, of a light quantum is Planck's constant, h, divided by the frequency, f, of the light. I.e., E =h/f. Therefore, h = E x t, where f = 1/t. Time is, therefore, embodied in light quanta along with energy. This is unfamiliar because it is historically not how time has been viewed: it is simple but counterintuitive. On the other hand, Newton's laws of motion, formulated in 1687, are both simple and intuitive.

[3] Unfortunately, the concept of the gene is so embedded into biological thought, and even common discourse that it now constitutes intuition. The arguments presented here, thus, appear to be counterintuitive.

[4] Robert Olby in Mendel, Mendelism and Genetics. http://www.mendelweb.org/MWolby.html. (accessed 23.02.2021)

[5] This landmark paper was reprinted in 2014: Johannsen, W. (2014). "The genotype conception of heredity. 1911." Int J Epidemiol **43**(4): 989-1000. In this paper references are made to the original version.

[6] http://news.bbc.co.uk/2/hi/science/nature/2804545.stm (accessed 23.02.2021)

[7] Lewontin says: "…… the great panjandrum of DNA himself, James Dewy Watson, explains in an essay in the collection edited by Kevles and Hood that "he doesn't want to miss out on learning how life works" and Gilbert predicts that there will be a change in our philosophical understanding of ourselves". :Lewontin, R. C. (1992). The doctrine of DNA: Biology as Ideology. London, England, Penguin Books Ltd. p63

[8] https://en.wikipedia.org/wiki/Human_Genome_Project (accessed 23.02.2021)

[9] The official completion date of the HGP was 14 April 2003 but a preliminary report was released in February 2001 to coincide with the birthday of Charles Darwin: Lander, E. S., L. M. Linton, B. Birren, C. Nusbaum, M. C. Zody, et. al. (2001). "Initial sequencing and analysis of the human genome." Nature **409**(6822): 860-921.

[10] By Archibald Garrod around 1900.

[11] https://www.nytimes.com/2001/02/19/opinion/humbled-by-the-genome-s-mysteries.html (accessed 23.02.2021)

[12] https://www.sciencedaily.com/terms/human_genome.htm (accessed 23.02.2021)

[13] The string of bases that comprise a gene is divided into exons, sections which code for gene products and introns, which are non-coding intervening sequences of bases.

[14] See: Lewontin, R. C. (1992). The doctrine of DNA: Biology as Ideology. London, England, Penguin Books Ltd. In the chapter headed "The Dream of the Human Genome" (pp 61-83) Lewontin ridicules the then much heralded idea that the sequence of the genome would tell us about the human condition and "*locate on the human chromosomes all the defective genes that plague us*" noting that some mutant genes (that for cystic fibrosis, for example) had already been located, isolated, and sequenced. A decade ago, Lewontin might have felt entirely vindicated. On 27 July 2010, Craig Venter, the entrepreneur who competed with the HGP to sequence the human genome, was interviewed by Der Spiegel under the title "We have learned nothing from the Genome". Since then, with the development of the technique of genome wide association (GWA), there has been a massive upsurge in genetic studies of common disease and behavioural traits. Despite this, Lewontin remains vindicated: as I will argue, this decade of intense research activity has not advanced our understanding of the causes of common disease and behavioural traits.

example the DSCAM gene found in Drosophila: it can produce 38,016[15] different peptides, (Black 2000), more than the number of genes in the human genome. According to the dogma, each peptide may fold into a different protein performing a discretely different biological function.

Despite the lack of clarity over the concept of the gene, and the unexpectedly low number of genes found by the HGP, genetic research has forged ahead in recent decades.

Traits (Mendel's characters and Johannsen's phenotypes) are classified as either monogenic (Mendelian) or polygenic. Monogenic traits, for example, the flower colour that Mendel investigated in pea plants, have been the sole basis for experimental genetics since the time of Mendel, according to American geneticist Richard Lewontin (Lewontin 1974). Rare inherited diseases such as Huntingdon's disease (there are thought to be ~10,000[16]), affecting less than 8% of the population, are often monogenic traits.

Rare diseases have long been diagnosed using classical genetic techniques, but success has been limited. With the benefit of knowing the human genome sequence, improvements were expected. The genomes of 85,000 UK National Health Service (NHS) patients, the majority with undiagnosed rare diseases, have been sequenced in the '100,000 Genomes Project'. Launched in 2012[17], with sequencing completed in 2018[18], few results have been published. The project website[19] says it has provided diagnoses in 20 to 25% of the cases.

Using the genome wide association (GWA) technique[20] and the human genome sequence, polygenic traits (common diseases and behavioural conditions) have allegedly been characterised by tens to hundreds of single nucleotide polymorphisms (SNPs)[21] at nearly as many loci (genes), each of very small effect. This is occurring in populations of thousands to hundreds of thousands of individuals carrying the trait. Furthermore, the total of these effects does not add up to the expected total genetic risks (or variances) of the diseases[22]. The difference is what is known as the 'missing heritability' (Manolio, Collins et al. 2009, Eichler, Flint et al. 2010, Chaufan and Joseph 2013, Blanco-Gomez, Castillo-Lluva et al. 2016): it is currently a major problem at the root of the genetics of common disease and behavioural traits.

GWA data per se are, therefore, of no clinical utility. It is, however, claimed that summing up the SNPs into a so-called polygenic score (PGS)[23] is of diagnostic value (Plomin 2018)[24]: however, this may resolve the problem of many small effects at numerous loci, but it leaves the problem that the PGS can only apply to a small fraction of the total genetic variance. The clinical utility of PGSs has yet to be proven.

Genes have been the 'material currency' of biology for 155 years. They are centrally invoked to explain inheritance, evolution, development, and morphogenesis: they have become icons of biological thought, such that it is heretical that their prominence should be challenged. Yet, they are far from well-defined, and knowing their sequences has not, so far, advanced our understanding of the most important challenge to human health, namely common disease.

3. How Mendel's elements became genes

Now I want to look in more detail at how Johannsen defined the gene. Mendel's 1865 paper lay unrecognised until 1900 when the Dutch biologist, Hugo de Vries, discovered it and re-published it. It could then be integrated with Darwin's ideas on evolution through natural selection, as laid out in "*On the Origin of Species*", which had been published in 1859 (Darwin and Kebler 1859).

The foundation stones of today's biology had been laid.

In the earliest years of the 20th Century, inheritance, or heredity, was the primary problem of the day in biology. Johannsen was opposed to the use of the above terms when applied in biology: he claimed that their everyday use, in terms of the transmission of wealth from one generation to the next, were misleading metaphors

[15] The DSCAM gene has a total length of 61 kb (61,000 base pairs) and is divided into 24 exons. Four of those exons occur with up to 48 alternative sequences. Taking all the viable combinations of alternative splicings of the exons and alternative sequences contributing to the mRNA that can be transcribed from the gene, more than 38,000 peptides, and, therefore, proteins, can be translated.

[16] https://www.who.int/genomics/public/geneticdiseases/en/index2.html (accessed 23.02.2021)

[17] https://www.sciencemag.org/news/2012/12/uk-unveils-plan-sequence-whole-genomes-100000-patients (accessed 23.02.2021)

[18] https://www.genomicsengland.co.uk/the-uk-has-sequenced-100000-whole-genomes-in-the-nhs/ (accessed 23.02.2021)

[19] https://www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project/ (accessed 23.02.2021)

[20] https://en.wikipedia.org/wiki/Genome-wide_association_study (accessed 23.02.2021)

[21] https://en.wikipedia.org/wiki/Single-nucleotide_polymorphism (accessed 23.02.2021)

[22] Typically, common diseases, at the population level, are thought to be between 10 and 70% due to genetic causes. These estimates are determined from family or twin studies. In GWA studies, typically between 5 and 15% of this risk is accounted for. The difference, or 'missing heritability', therefore, ranges up to several 10s of percentage points.

[23] https://en.wikipedia.org/wiki/Polygenic_score (accessed 23.02.2021)

[24] See Chapter 12 "The DNA fortune teller".

for biology[25]. The dominant theory of inheritance was Francis Galton's regression law[26]. Johannsen called it the 'transmission-conception' and regarded it as wrong: it supported Lamarckism[27] and Darwin's pangenesis concept[28], both of which implied the inheritance of acquired characteristics.

Johannsen ran an experiment with self-fertilising bean plants (a so-called 'pure line breeding' programme)[29] and recorded the dimensions of the beans produced over two growing seasons. Bean sizes were distributed according to a normal distribution, but different pure lines differed slightly in the size range of the beans they produced. Johannsen categorised these lines as 'genotypes' and the process of inheritance through the genotype he called the genotype-conception (Johannsen 1911). He found no evidence of ancestral influences in his experiments[30].

Nils Roll-Hansen (Roll-Hansen 2014) says of Johannsen's presentation of his genotype-conception at the lecture in 1910, published in 1911:

"*This lecture summed up his experimental and theoretical achievements, including a sharp analysis of the concepts of 'genotype' and 'gene'. ……. Genotype is the basic concept in Johannsen's 1910 lecture. The stability of the genotype is what makes a science of heredity possible. The concept of 'gene' is derivative. It represents an experimentally identifiable difference between genotypes*"

Thus, Johannsen's work must be credited as the basis for modern genetics and the understanding of inheritance, and the longstanding theory of evolution, the Modern Synthesis (MS)[31], since inheritance is an essential component of evolution.

The American geneticist, T. H. Morgan, writing in 1917 under the title "*The Theory of the Gene*" (Morgan 1917), defended Mendelism and confirmed the location of genes in chromosomes. Mendel's laws of inheritance, based on experiments with pea plants and Johannsen's genotype-concept, were converted into a theory using primarily the concepts of 1) two alleles (versions) per gene, each being capable of being dominant or recessive, and 2) the phenomenon of epistasis[32]. Morgan concedes:

"*It has been said that by assuming enough genetic factors you can explain anything. This is true; and it is the greatest danger of the factorial procedure. If, for example, whenever one fails to account for a result he introduces another factor to take care of what he cannot explain he is not proving anything except that he is ingenious or only naïve*." (Morgan 1917).

Those simple concepts give considerable interpretative latitude and they have been progressively added to over the years in a manner that is perhaps not unlike epicycles in Ptolemaic astronomy. Nevertheless, genetics today is regarded as a successful and sophisticated scientific discipline. Indeed, on the 20th anniversary of the release of the draft human genome sequence in 2001, the journal Nature proclaimed, "*A wealth of discovery built on the Human Genome Project*" (Gates, Gysi et al. 2021). The authors point out that as there is no world without the HGP it is impossible to say how much progress it represents but "*it is nonetheless clear that the HGP's catalogue [of protein-coding genes] catalysed the continuing genetic revolution*".

There are, however, features of genetics that should have given pause for thought.

First, likenesses between siblings, or those between parents and their offspring, which we know empirically to exist, cannot be explained intuitively in terms of the above concepts (see below).

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[25] In his 1911 paper Johannsen writes: "*The view of natural inheritance as realized by an act of transmission, viz., the transmission of the parent's (or ancestor's) personal qualities to the progeny, is the most naive and oldest conception of heredity. We find it clearly developed by Hippocrates, who suggested that the different parts of the body may produce substances which join in the sexual organs, where reproductive matter is formed.*": Johannsen, W. (1911). "The Genotype Cconception of Heredity." American Naturalist **45**: 129-159. Johannsen's main concern appears to be avoiding the inheritance of acquired characteristics. He goes on: "*The personal qualities of any individual organism do not at all cause the qualities of its offspring; but the qualities of both ancestor and descendant are in quite the same manner determined by the nature of the "sexual substances"—i.e., the gametes—from which they have developed. Personal qualities are then the reactions of the gametes joining to form a zygote; but the nature of the gametes is not determined by the personal qualities of the parents or ancestors in question. This is the modern view of heredity*." Further on he says: "*The "genotype-conception," as I have called the modern view of heredity, differs not only from the old "transmission-conception" as above mentioned, but it differs also from the related hypothetical views of Galton, Weismann and others, who with more or less effectiveness tried to expel the transmission-idea, having thus the great merit of breaking the ground for the setting in of more unprejudiced inquiries. Galton, in his admirable little paper of 1875, and Weismann, in his long series of fascinating but dialectic publications, have suggested that the elements responsible for inheritance (the elements of Galton's "stirp" or of Weismann's "Keimplasma") involve the different organs or tissue-groups of the individual developing from the zygote in question. And Weismann has furthermore built up an elaborate hypothesis of heredity, suggesting that discrete particles of the chromosomes are "bearers" of special organizing functions in the mechanism of ontogenesis, a chromatin-particle in the nucleus of a gamete being in some way the representative of an organ or a group of tissues*." Thus, Johannsen was aware of the Weismann barrier whereby the germ cells are 'insulated' from the rest of the organism and that the gametes do not carry 'personal qualities', yet he does not consider the gamete phenotypes, only their genotypes, as Mendel's 'units of inheritance'.

[26] According to Galton, an individual's traits were transmitted from their parents (50%), their grandparents (25%), their great grandparents (12.5%), and so on, with ever diminishing importance, because of the increasing number of ancestors, within whom the traits were distributed.

[27] Jean Baptiste Lamarck was a highly regarded French biologist who died in 1829. He became the professor of Zoology when the Muséum national d'Histoire naturelle opened in Paris in 1793. He advocated the idea that qualities gained during a lifetime could be passed on to future generations. This is called the inheritance of acquired characteristics.

[28] https://en.wikipedia.org/wiki/Pangenesis

[29] The 'pure line' experimental approach differed from that deployed by Mendel with pea plants. Although pea plants are self-fertile, like bean plants, Mendel did not allow self-fertilisation in his experiments. He crossed one plant with another with different characters, such as flower colour, to produce hybrids and not pure lines.

[30] "*Ancestral influence! As to heredity, it is a mystical expression for a fiction. The ancestral influences are the "ghosts" in genetics, but generally the belief in ghosts is still powerful. In pure lines no influence of the special ancestry can be traced; all series of progeny keep the genotype unchanged through long generations*.": Johannsen, W. (1911). "The Genotype Cconception of Heredity." American Naturalist **45**: 129-159.

[31] The Modern Synthesis was proposed by Julian Huxley in 1942: Huxley, J. (1942). Evolution, the modern synthesis. London,, G. Allen & Unwin ltd. It is based on the earlier ideas of neo-Darwinism (see Noble, D. (2017). Dance to the tune of life: biological relativity. Cambridge ; New York, Cambridge University Press pp 131-134) and it remains the backbone of evolutionary theory today. It is criticised, e.g., ibid. but it is also aggressively defended, for example, by Richard Dawkins. It has been extended: Laland, K. N., T. Uller, M. W. Feldman, K. Sterelny, G. B. Muller, A. Moczek, E. Jablonka and J. Odling-Smee (2015). "The extended evolutionary synthesis: its structure, assumptions and predictions." Proc Biol Sci **282**(1813): 20151019. More recent proposals to replace the MS and the Extended Synthesis are: Corning, P. A. (2020). "Beyond the modern synthesis: A framework for a more inclusive biological synthesis." Prog Biophys Mol Biol **153**: 5-12. and Richardson, K. (2020). "In the Light of the Environment: Evolution Through Biogrammars Not Programmers." Biological Theory **15**: 212-222. Critics of the MS are often dismissed by its advocates as Creationists. For this reason the website: https://www.thethirdwayofevolution.com/people (accessed 23.02.2021) features researchers of evolutionary biology who are neither advocates of the MS nor Creationists.

[32] Epistasis, or gene-gene interaction, is where one gene present in a genotype influences the effect of another gene in the same genotype. A gene for baldness over-rides genes for red and blonde hair, for example. This phenomenon was discovered by British biologist William Bateson and colleagues working in Cambridge, England, in 1907

Second, the physicist Max Delbrück defined genetics in 1935 as:
"……. a far-reaching, logically closed, strict science. It is quantitative without making use of the physical measurement system."[33] (Timoféeff-Ressovsky, Zimmer et al. 1935).
Delbrück acknowledges that genetics, unlike chemistry, is not based on a more fundamental physics, from where it would be possible to judge and test hypotheses. Thus, there is no more fundamental level against which to judge the genotype-conception: it is simply a theoretical model for which there is some support.

Third, in 1958 Francis Crick (Crick 1958) published his thoughts on how the information coded in the gene sequences informed the phenotype. Information coded in the base sequence needed to be transformed into information in the form of the molecular structure of a protein, the supposed biologically active molecule in the cell. He proposed the 'sequence hypothesis': which essentially posits that if the biologically inactive product of transcription and translation of a gene, the peptide, folded itself to a native state protein, the information in the gene would be conserved in the protein. There was no underpinning in physics for this hypothesis. However, experiments with the enzyme ribonuclease by American biologist Christian Anfinsen, (Anfinsen, Haber et al. 1961) showed that, in the test tube, denatured enzyme (that had been converted to the peptide) re-folded spontaneously to the active structure, apparently confirming Crick's hypothesis. However, conditions in the test tube[34] are very different from those in the cell (Minton 2006) and the renaturation process took far too long for it to be generally applicable in the cell. Crick reflected on the sequence hypothesis in his Nobel Lecture in 1970: this is what he wrote:
"*Because it was abundantly clear by that time* [1958] *that protein had a well-defined three-dimensional structure, and that its activity depended crucially on this structure, it was necessary to put the folding process to one side, and postulate that by and large the polypeptide chain folded itself up*." (Crick 1970)[35]
Hardly a ringing endorsement of his own hypothesis for such a crucial feature of modern molecular genetics: peptide folding to protein is the process that transforms DNA sequence information into the functional information that informs the phenotype. It is now clear that the sequence hypothesis is invalid (Baverstock 2019a). and, therefore, the genotype-conception, cannot explain how the alleged information coded in the gene sequences informs the phenotype.

Fourth, in 1974, as already noted, Lewontin pointed to a paradox that had been inherent in experimental genetics since Mendel's time: in terms of traits, what is interesting (polygenic traits) is not measurable, and what is measurable (monogenic traits) is not interesting (Lewontin 1974). Has that situation changed? There has been a massive expansion in GWA[36] studies of polygenic traits in the past decade, but these are not leading to theories about how SNPs are related to biological effects: they are largely hypothesis-free 'fishing expeditions' looking for correlations between SNPs/PGSs and complex traits. They have not added anything to the theoretical basis of genetics.

Finally, hypotheses nominating variant genes (so-called candidate genes), as causes of specific common disease traits based on biological considerations, have largely failed. For example, 18 candidate genes have been hypothesised, based on their perceived biological relevance, to account for major depressive disorder. In a highly statistically significant study of a large database of patients, Border et al. (Border, Johnson et al. 2019) reject all 18 genes, some of them having been prominently reported on in the past. This is not an isolated case: the failure of the candidate gene approach (based largely on classical genetics) ought to be a signal that something is very wrong: evidence has comprehensively rejected theory.

Could there be a different way to understand inheritance that fits equally well with Mendel's laws (that were, in any case, based on fudged experimental data (Elston 2018))?

Can we really say that a theory of human inheritance, based on the gene-centric genotype-conception and experimental genetics confined to monogenic traits, is scientifically secure?

Are experiments with self-fertilising pea and bean plants a secure enough foundation to be able to generalise to human heredity? The genotype-conception is a theoretical model: it may be correct, but it is not grounded in science. The pieces of the genetic jigsaw puzzle can be made to fit well enough together, but can we be sure they give us the correct picture of human inheritance?

We will return to genes in inheritance after considering the role of genes in evolution.

4. The gene in evolution

Now we consider the gene's purported role in evolution in providing selectable variation as spontaneous mutations to genes. In 1930 Ronald Fisher published "*The Genetical Theory of Natural Selection*" (Fisher 1930) in which he derives the following law:
"*The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time*."
Fisher, however, does not include the mutations arising during the course of evolution as contributing to variance, stating:
"*The rate at which a mutation increases in numbers at the expense of its allelomorph will indeed depend on the selective advantage it confers, but the rate at which a species responds to selection in favour of any increase or decrease of parts depends on the total heritable variance available, and not on whether this is supplied by large or small mutations. There is no limen of appreciable selection value to be considered*." (Fisher 1930)[37].
Given the prominence that Fisher's theory holds in the MS and the importance in that attached to new variation arising from mutations, it is perhaps surprising that Fisher's theory is still considered important. According to evolutionary biologist, Ernst Mayr, (Mayr 2001)[38] mutations are the principal source of new variation for natural selection to act on.

The reason for this apparent anomaly is the way Fisher frames his theory: his law only applies to an instant in time and includes other processes that advance evolution (Grafen 2003). Basener and Sandford (Basener and Sanford 2018) have set out to correct this deficit by modifying Fisher's model to include mutations

[33] *"… eine weitgebend in sich logisch geschlossene, strenge Wissenschaft. Sie ist quantitaiv, ohne vom physicalischen Maßsystem Gebrauch zu* machen.": Timoféeff-Ressovsky, N. W., K. G. Zimmer and M. Delbrück (1935). "Über die Natur der Genmutation und der Genstruktur." Nachrichten der Biologischen Gesellschaft für Wissenschaft, Göttingen **1**: 189 - 241.
[34] As a dilute solution in aqueous buffer, in contrast to the highly molecularly crowded environment of the cell cytoplasm: Fonin, A. V., A. L. Darling, I. M. Kuznetsova, K. K. Turoverov and V. N. Uversky (2018). "Intrinsically disordered proteins in crowded milieu: when chaos prevails within the cellular gumbo." Cell Mol Life Sci **75**(21): 3907-3929. Up to 30% of the cell cytoplasm can be occupied by peptides and proteins.
[35] Interestingly, Crick does not mention Anfinsen's supportive experiment in this paper and neither does Anfinsen reference Crick's papers. Arguably, in his Nobel lecture, Anfinsen backs away from the idea that his work on ribonuclease is relevant to the cell: Anfinsen, C. B. (1973). "Principles that govern the folding of protein chains." Science **181**(4096): 223-230.
[36] A search on PubMed on the terms 'GWA' OR 'genome-wide association' in the 'Title/Abstract' search field returned nearly 31,000 publications since 2003.
[37] pp 15-16.
[38] p 279

that occur during the evolutionary process. Empirical evidence of how evolution occurs over a significant number of generations is needed to test their models and that is in short supply.

However, the Long-term Evolution Experiment (LTEE), which has been running since 1988 under the direction of Richard Lenski and colleagues, has racked up over 66,000 generations of a population of E. coli bacteria (Lenski 2017). An initial 12 cultures, drawn from a single source of starved genetically pure E. coli, have been grown in medium containing a limiting concentration[39] of glucose as the only readily accessible carbon source to bacteria grown under aerobic conditions. A single aliquot of each culture is inoculated into a new flask of medium every 24 hours: by that time the bacteria will have used up the glucose. Periodically, the fitness, in terms of the rate of growth of the bacteria compared to that of the founder bacteria, and the body size/cell volume of the bacteria, are assessed. Mutations are measured by gene sequencing less frequently.

This is by no means a 'natural experiment': it is adaptation to life in the inside of a laboratory flask, in a medium with a single accessible carbon source, in an incubator. However, the overwhelmingly most likely source of new variation arising in the cultures is new mutations (Lenski 2017) resulting from errors in replication. It has been proposed that epimutations[40] have a role in evolution (Jablonka 2017) but these are generally induced by stress from the environment. The environment of the bacteria in the LTEE is constant across the generations. Therefore, there should be few complications in interpreting the results in the context of expectations based on the MS. The LTEE has, however, been started without any prior hypothesis: rather a set of questions such as, 'is there a limit to extent of adaptation?' and 'how repeatable is adaptation?' (Lenski 2017).

When 10,000 generations had accrued, it was clear that all 12 samples were evolving similarly with respect to fitness but not with respect to cell volume. Both showed initially rapidly increasing trajectories that tailed off and could be fitted by hyperbolic curves (Lenski and Travisano 1994).

In 2009, one of the 12 samples which had accrued 40,000 generations, was analysed in detail. Fitness followed a hyperbolic growth curve up to 20,000 generations and mutations were accrued linearly (Barrick, Yu et al. 2009)[41]. See Figure 1. When extended to 50,000 generations it was clear that the fitness curve was better fitted by a power, rather than a hyperbolic, law (Wiser, Ribeck et al. 2013). See Figure 2

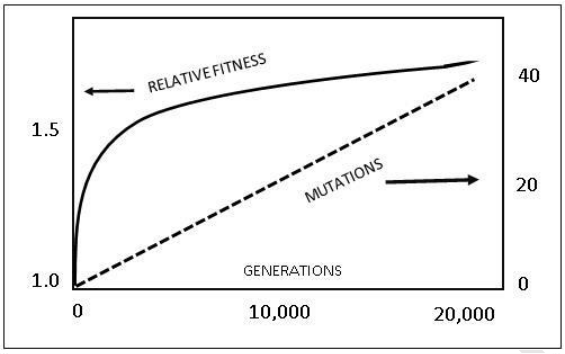

Fig. 1. A cartoon illustrating the evolution of relative fitness (solid line) and mutations (dashed line) in the first 20,000 generations of the LTEE. The evolution curves of fitness in all 12 independent experiments are superimposable. This contrasts with the curves of evolution of cell volume (not shown), which, although of similar form are not superimposable. By 10,000 generations cell volumes range from 1.5 to 2.5 times the original cell volume (Lenski and Travisano 1994) See Fig. 2 therein.

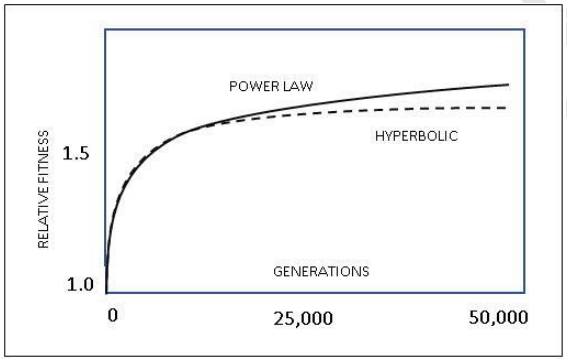

Fig. 2. A cartoon to illustrate the fitting of a power law and a hyperbolic curve to the data for the evolution of relative fitness in 10 of the 12 independent experiments of the LTEE (two experiments are excluded because they became hypermutable after about 30,000 generations). Fitting the data up to 20,000 generations to the two models and then extrapolating both models to 50,000 generations confirms the fit to the power law (Wiser et al., 2013) See Fig. 2B therein.

The primary results from the LTEE are:

1) an identical, initially steep, evolution of fitness in the 12 experiments with a linear evolution of mutations. See Figure 1.
2) 12 non-identical, but increasing profiles for cell volume, (see legend to Figure 1) and
3) evolution of fitness up to 50,000 generations according to a power law. See Figure 2.

At around 30,000 generations, one of the 12 samples acquired the ability to metabolise citrate. Citrate is a component of the medium but is inaccessible under aerobic, but not in anaerobic, conditions. Since the E. coli have a citrate transport system and so can metabolise citrate (Hall 1982, Van Hofwegen, Hovde et al. 2016), the LTEE has not yielded a novel capability for the bacteria, as has been claimed (Dawkins 2009)[42].

What is to be made of this experiment? How can these results be explained at an intuitive level? Judging from the report on a single sample in 2009 (Barrick, Yu et al. 2009), the results seem to have been a conundrum for Lenski and colleagues:

"*The simplest hypothesis that could explain the discrepancy between the nearly constant rate of genomic change and the sharply decelerating fitness trajectory posits that only a small fraction of all substitutions are beneficial, whereas most are neutral or nearly so. Accordingly, the beneficial substitutions would be concentrated in the early phase of rapid adaptation to the conditions of the experiment, but over time that initial burst would be swamped by the constant accumulation of neutral mutations by drift. However, four lines of evidence allow us to reject this explanation.*"

[39] The concentration of glucose is limited such that the bacteria will have consumed it within the 24 hours and returned to the starving state.
[40] For example, methylation of DNA.
[41] after which fitness increased dramatically and the population was deemed to be hypermutable.
[42] See pp 127-130

There was no ready explanation for the non-correspondence between the genomic evolution and the evolution of adaptation, or of the initial steep increase in fitness. What would be the probability of 12 samples (Galapagos Islands?) following identical fitness trajectories if the cause was randomly acquired mutations? This feature seems to rule out an effect from acquired mutations on fitness.

According to Fisher's theorem (with no mutations acquired during the evolutionary process) any increase in fitness would be due to the selection of beneficial alleles already in the founder population. This might account for the 12 experiments having the same initial slopes but why would not the same argument apply to cell volume, and is it feasible that it would apply to fitness over as many as 50,000 generations?

Richard Dawkins is one of the foremost advocates of Darwinian evolution and the MS today. He devotes about 15 pages to the LTEE in his book "*The Greatest Show on Earth: the evidence for evolution*", which was published in 2009 (Dawkins 2009). At the state of the LTEE when Dawkins was writing, 45,000 generations had accrued, and he was aware that all 12 samples were evolving in a similar way in terms of fitness[43]. In the conclusion of his discussion of the experiment, he writes this:

"*Lenski's research shows, in microcosm and in the lab, massively speeded up so that it happened before our very eyes, many of the essential components of evolution by natural selection, random mutation followed by non-random natural selection; adaptation to the same environment by separate groups independently; the way successive mutations build on their predecessors to produce evolutionary change; the way genes rely for effects on the presence of other genes. It all happened in a tiny fraction of the time evolution normally takes*."

Dawkins apparently has no qualms about the rapid increase in fitness in the early stages of the experiment when few mutations have arisen[44] and most of those would be deleterious, not beneficial (see below). He sees no problem with all 12 experiments being in lockstep as far as their gain in fitness is concerned. In connection with the increase in cell volume, he evidently expects that each tribe, as he calls each experiment, will take a different course[45].

Can Dawkins have it both ways: evolution of fitness is identical in all 12 experiments, while in terms of cell volume, each of the samples evolves independently of the others and both are dependent only on randomly acquired mutations during the evolutionary process?

Dawkins' enthusiasm for the LTEE leads him to take a stab at creationists[46] as the experiment offers no support for intelligent design. However, the LTEE does not, at face value, offer support for the MS and evolution driven by genetic variation provided by mutations.

For the naive observer one thing stands out in this experiment: the power law governing the identical increases in fitness in all 12 experiments for over 50,000 generations (Wiser, Ribeck et al. 2013). Intuitively, randomly acquired mutations arising during the experiment cannot account for this. It is a very significant result, and I will return to it after seeing whether modifications of Fisher's theorem (mentioned above) can explain the LTEE results.

Lenski and his colleagues have modelled an explanation of their experiment (Good, McDonald et al. 2017) and they have considerable leeway in terms of the number of variables with an unknown effect that they can exploit. They can surely concoct a jigsaw puzzle where the available evidence fits relatively well. As I noted earlier, there was no prior hypothesis for the LTEE to test, only a list of questions. Constructing hypotheses after the results of the experiment are known, as Lenski and colleagues have done, is called 'harking' (Kerr 1998) and it is exactly what the Ptolemaic astronomers did for 1,500 years.

4a. Does Fisher's theory of natural selection help explain the LTEE results?

Basener and Sanford modify Fisher's law of natural selection to include the new mutations arising during the evolutionary process saying:

"*Our goal is to correct and re-apply Fisher's Theorem, such that it is consistent with real biology*." (Basener and Sanford 2018)[47]

But first, they consider Fisher's condition of no new mutations arising. That would be the situation in the LTEE at the very earliest times, where there is a steep rise in fitness in all 12 samples. Over a relatively short period (Fisher's law is for an instantaneous relationship between variance and change in fitness) fitness increases linearly at a rate proportional to the variance, which remains constant. That is Fisher's law of natural selection and it is not consistent with a power law.

Next, they show that extending Fisher's model to long times, still with no mutations occurring, results in a population initially increasing linearly in fitness but levelling off at maximum fitness with zero variance, i.e., no further scope for increase in fitness. This is not consistent with a power law either.

Basener and Sanford then consider two different distributions for beneficial and deleterious mutations acquired during the evolutionary process. The first model assumes an initial distribution of beneficial and deleterious mutations in equal measure, normally distributed in terms of effect size. Under this model, fitness increases initially slowly, gradually increasing in rate over time. That is not consistent with a power law observed. As Basener points out[48], their simulations give the average response to the distribution of mutations; individual experiments could vary due to the random mutational events that may happen at various times (during evolution). Maddamsetti et al. confirm that:

"….. the replicate populations of the LTEE have largely diverged in their mutation rates and biases, even though they have adapted to identical abiotic conditions" (Maddamsetti and Grant 2020).

Therefore, we should not expect all 12 experiments to have identical fitness profiles.

This first distribution of acquired mutations, however, is not a realistic model: there is a strong consensus that deleterious mutations outnumber beneficial mutations. The second distribution Basener and Sanford modelled assumes that detrimental mutations (small in individual effectiveness) will out-number beneficial ones by a margin of a thousand to one. This is, in fact, conservative, as other estimates including by the Japanese geneticist, Kimura and by Lenski, suggest a margin

[43] Dawkins seems to have based his assessment of the experiment on: Lenski, R. E. and M. Travisano (1994). "Dynamics of adaptation and diversification: a 10,000-generation experiment with bacterial populations." Proc Natl Acad Sci U S A **91**(15): 6808-6814.

[44] At approximately 2,000 generations in one experiment, relative fitness had increased to 1.4, just under half the gain at 50,000 generations but only 5 mutations had accrued: Interpolated from Figure 2 in: Barrick, J. E., D. S. Yu, S. H. Yoon, H. Jeong, T. K. Oh, D. Schneider, R. E. Lenski and J. F. Kim (2009). "Genome evolution and adaptation in a long-term experiment with Escherichia coli." Nature **461**(7268): 1243-1247.

[45] "*You can see* [referring to a graph on p. 123, which shows similarly shaped profiles to that for fitness] *that most of the increase in body size occurred in the first 2000 or so generations. The next interesting question is this. Given that all 12 tribes increase in body size over evolutionary time did they all increase in the same way by the same genetic route? No, they didn't. And that is the second interesting result. The graph at the top of page 123 is for one of the 12 tribes. Now look at the equivalent hyperbolic best fits for all 12. Look how spread out they are. They all seem to be approaching a plateau but the highest of the 12 plateaus is almost twice as high as the lowest. And the curves have different shapes: the curve that reaches the highest by generation 10,000 starts by growing more slowly than some of the others and then overtakes them before generation 7000.":* Dawkins, R. (2009). The greatest show on Earth : the evidence for evolution. New York, Free Press.

[46] Ibid pp 133/4.

[47] p1596.

[48] Private communication: William Basener.

of one million to one. This model shows an initial reduction in fitness, which decelerates with time, again quite contrary to observation and the observed power law relationship.

Thus, neither Fisher's longstanding and widely accepted theorem of natural selection unmodified, nor the two distributions of mutations that Basener and Sanford used to modify the theorem, fit the observations derived from the LTEE.

Now we consider the significance of the power law and the evolution in lockstep of fitness of the 12 independent experiments. Wiser et al. write:
"*The power law describes the fitness trajectories well, but it is not explanatory*." (Wiser, Ribeck et al. 2013).
This is not necessarily so: natural processes, which inevitably involve energy dissipation, are described by power laws (Makela and Annila 2010), and evolution is one such natural process requiring nothing more than an energy input (in terms of nutrients). Evolution of fitness is an expression of the principle of least action, synonymous with the 2nd law of thermodynamics (hereinafter, the 2nd law), i.e., physics, not biology. Whatever it is in the processes in the functioning of the cell that leads to the increases in fitness is qualitatively different from that which leads to cell volume increases. Unlike fitness, being fat is not directly related to survival and is not, therefore, under the control of the principle of least action. So, the case for mutations in genes being the source of new variation to drive evolution is unsupported by the LTEE.

Thus, based on the LTEE, there is no influence on the evolution of fitness from mutations acquired during the process: Fisher was correct when he wrote of mutations: "*There is no limen of appreciable selection value to be considered*", but for the wrong reason. In terms of the MS, new variation needs to be created if evolution is to lead to the nearly infinite range of diversity we see.

However, the LTEE is not the only example of a failure to observe the expected response to a selective pressure in the presence of what is assumed to be genetic variation. For example, Pujol et al. note:
"….. evidence for responses to selection that match predictions are often missing in quantitative genetic studies of wild populations." (Pujol, Blanchet et al. 2018)
They propose that multiple biological mechanisms can unlink genetic variation from the response to selection, but equally, it may be that what they take to be genetic variation is not that, and another process (the principle of least action) is driving evolution.

If it is not the selection of genetic variance by natural selection that is driving evolution, we must accept that the gene is not Mendel's unit of inheritance: this must be the cellular phenotype.

5. History has neglected the phenotype

My argument is that the cellular phenotype, not the gene/genotype, plays the leading role in both inheritance and evolution. I will demonstrate (in the next section) that the cellular phenotype has the essential character of 'thingness' which is needed to be Mendel's unit of inheritance and, that the direct inheritance of the phenotype is viable. Further, I will argue that the cellular phenotype has independent agency in the process of evolution and is its biological component.

The cellular phenotype emerges from a process fuelled by the interaction of the products of transcription and translation of genes: it is represented by a quasi-stable attractor state[49]. This is the consequence of the cell being a thermodynamically open complex dissipative system. Quasi-stability means that up to a point, the attractor is robust to internal and external (environmental) stresses but beyond that point makes randomly determined transitions to variant attractor states/phenotypes. (Baverstock and Rönkkö 2008, Baverstock and Karotki 2011). In such a transition, phenotypic properties may be lost or gained. Empirical support for the instability of the phenotype (more commonly termed 'genomic instability') being initiated by low doses of ionising radiation (and other environmental stresses) is robust (Morgan 2003a, Morgan 2003b). Genomic/phenotypic instability is a biological phenomenon, unrecognised until the early 1990s (Kadhim, Macdonald et al. 1992), which cannot be incorporated into the Mendelian molecular genetic paradigm (Baverstock 2000, Karotki and Baverstock 2012). Furthermore, phenotypic instability in vivo acts over several generations as demonstrated by Huumonen et al with C. elegans (Huumonen, Immonen et al. 2012). A founder population of the 2nd generation offspring of irradiated worms (i.e., not directly irradiated) showed a highly significantly greater diversity of gene expression (in 400 probes) after several generations of culture, compared to sham irradiated worms. Quasi-stability is a crucially important physical property of the cellular phenotype.

The cellular phenotype is governed by rules of engagement (RoE) (Baverstock and Rönkkö 2008)[50] which determine the evolution in time of the gene product composition of the interactional process from which the phenotype emerges. The phenotype is its own regulator: a metaphor for its role in the cell is a brain, as already noted. As pointed out by the philosopher Karl Popper in his 1986 lecture to the Royal Society in London (Niemann 2014), cells and brains can acquire knowledge, both by trial and error and from stored information. As early as the early 1900s learning behaviour was observed in single-celled organisms such as the Stentor. As Dennis Bray points out, that, and much other evidence, has been systematically ignored in mainstream biology (Bray 2009). Over the last two decades, things are changing and, for example, the mechanism of learning in single cells is being explored (Csermely, Kunsic et al. 2020).

[49] Attractor states are emergent properties of complex dissipative, or non-equilibrium, systems. They are the product of self-organisation and involve dynamic steady states, where two or more counteracting processes are balanced one against the other. A simple example is the soliton: https://en.wikipedia.org/wiki/Soliton. I
As a wave in water, the soliton is a dynamic steady state between the wave's tendency to dissipate, or break up into smaller waves, and to 'break' in shallow water (as seen on the shoreline). When these two processes are balanced, the soliton is formed. Such solitons were discovered by naval architect, John Scott Russell, on the Union Canal in Edinburgh in 1834. Solitons have highly counterintuitive emergent properties, for example, the velocity of the wave is proportional to its amplitude. Such non-equilibrium states are described as quasi-stable because they have what is called a boundary of attraction within which they are stable and outside of which they cease to exist. The concept of the boundary of attraction is better seen in another attractor state, the 'bicycle/rider' system. The rider keeps the bicycle in the upright position by shifting the centre of gravity of the system to the right or the left and turning the front wheel to the left or right. The system is only stable if all four 'dynamic dimensions' are within certain limits (the boundary of attraction), and freely accessible within those limits. It is true that the stability of this system is aided by the gyroscopic effect of the rotating wheels but it is possible to maintain the upright position while stationary and it is impossible to ride a bicycle with the front wheel in a tram track. The quasi-stability of the cellular phenotype is critical to the functioning of the cell.

[50] The dynamic state of the cell (the phenotype it is expressing) is governed by ongoing 'rules of engagement' (RoE) applicable to the gene products resident in the cell. The RoE form a nonholonomic record of the history of the species to which the cells belong. If, at a particular time, the RoE require a gene product that is available, the attractor state (phenotype) is stable: if it is not available a transition to a variant attractor and, therefore, phenotype, can occur – a direct transition between phenotypes (that is without modifying the genotype, as is the case in cell differentiation). This is possible because of the physically quasi-stable nature of the phenotype. The RoE constitute the *syntax* of the cell/system. See also: Baverstock, K. (2016). "Genes without prominence." Inference: International Review of Science **2(2)**.; specifically, under "Gradualism is not an option".

The cellular phenotype, seen as an emergent quasi-stable state of a complex dissipative system, is, therefore, quite a different entity from that traditionally envisaged: it endows responsiveness to the environment and is a seat of 'knowledge' that gives independent agency to the cell, including in its own evolution. (We will see later that it also harbours the information that determines morphological features of multicellular organisms.)

By seeking, even in primitive ways, to improve its adaptation to its environment, an organism can modify both itself and its environment. One of the most important aspects of such modifications is improved access to nutrients. This was noted in 1835, by the British selective breeder, Edward Blyth, nearly 20 years before Darwin published, On the Origin of Species". Blyth wrote:

"[A]*mong animals which procure their food by means of their agility, strength, or delicacy of sense, the one best organized must always obtain the greatest quantity; and must, therefore, become physically the strongest, and be thus enabled, by routing its opponents, to transmit its superior qualities to a greater number of offspring*." (Blyth 1835).

Both the ability of an organism to modify its environment (e.g., find new nutrient sources, or through niche construction) and for its phenotype to be modified directly by its environment (e.g., through phenotypic instability), are necessary conditions for evolution to produce the infinite variety of species it clearly has (Waddington 2008). In evolution, everything affects everything else except in the case of organisms that live in unchanging and unchangeable environments, e.g., E. coli in the LTEE and, the naked mole-rat that lives only in caves.

Having independent agency means being able to choose or decide to influence the future. Humans, of course, believe that they can do that with their brains. Many will agree that other species can also do that but often a line is drawn below which this will not be the case. However, empirical evidence should lead us to expect that independent agency is an essential part of all life (Baluska and Levin 2016). For example, Darwin proposed that the tip of a plant root functioned like a brain (Baluska and Mancuso 2009). Intelligence is found in plants (Calvo, Gagliano et al. 2020), and many primitive organisms[51], including single-celled microbes (Bray 2009). Brains are ubiquitous in biology.

Agency can be viewed on two levels, the macroscopic and the microscopic. The former is the actual action of the agent on its environment and the latter has to do with the processes that enable agency, within the agent. The action of choosing, being an irreversible action, entails an increase in entropy[52] to be in accordance with the 2nd law. The implications for the microstate of the organism will be addressed below.

To return to the issue of inheritance: Johannsen writes exclusively of the genotypical constitution of the gametes as the basis for heredity. He states: "*Particular resemblances between an ancestor and one or more of his descendants depend—so far as heredity is responsible—on corresponding particular identities in the genotypical constitution, and, as we have urged here, perhaps to excess, the genotype is not a function of the personal character of any ancestor. …… The genotype-conception is thus an 'ahistoric' view of the reactions of living beings—of course only as far as true heredity is concerned*." (Johannsen 1911) But neither do the phenotypes of the gametes reflect the personal character of ancestors. So, why cannot the phenotypical constitution of the gametes be the basis for inheritance? I am proposing that the zygote is the product of the fusion of the two parental gamete phenotypes.

The genotypes and the phenotypes of both parents are present in the zygote, so can their roles be separated from one another? Yes, if mutations are not responsible for the variance that drives natural selection in evolution, then it cannot be the genotype/gene that is the unit of inheritance. If agency is what is moving evolution forward the phenotype must be responsible. We will come back to discuss the implications of this in the Discussion.

In the animal kingdom inheritance involves the fusion of the sperm and egg. Human genetics is the concern here so I will pursue the argument further in the context of human, rather than plant or other organism reproduction.

6. Human inheritance

A first point to make is that there are ancestral similarities in the lines of inheritance of humans: an example is the chin and nose in the Hapsburg line, which have been obvious over many generations. However, the Norwegian geneticist, Stig Omholt, wrote in 2013:

"*There is no a priori reason why an offspring, arising from the random sorting of chromosome pairs plus genetic recombination and the subsequent immense number of highly complex and nonlinear processes making the individual, should on average resemble its parents more than a randomly drawn couple from the population. We have no theory that tells us why this would not give rise to a quite unpredictable parent-offspring relationship*." (Omholt 2013)

This view sharply contradicts that advanced in the very influential and still highly regarded paper on heredity based on pure Mendelian inheritance by Fisher in 1918 (Fisher 1918). So, who is correct?

Ken Richardson in his book "*Genes, Brains and Human Potential: the science and ideology of intelligence*", (Richardson 2017) heavily criticises Fisher's approach of applying the principles of Mendelian inheritance to continuously varying traits. That inherited factors that vary continuously, like human height, were likely to involve several genes, was recognised by Fisher. His solution was to treat these additively as if they were independent of one another. Richardson points out that it is extremely unlikely that several genes acting together to produce a trait, would do so independently of one another, i.e., without gene-gene or gene-environment interactions. This view is confirmed by Rice and Borecki who write:

"*Resolving the various sources of familial resemblance entails other issues [than additive variance]. For example, there may be major gene effects that are largely or entirely nonadditive, temporal or developmental trends, and gene-gene (epistasis) and gene-environment interactions*." (Rice and Borecki 2001).

Genes acting independently underlies Fisher's approach: he notes:

"…throughout this work it has been necessary not to introduce any avoidable complications" (Fisher 1918).

One such was interaction between genes, i.e., epistasis, which was, in Fisher's mind, an avoidable complication. Furthermore, Fisher's approach predicted very little impact of the environment on inheritance, but we know that cannot be true. For example, a study of birth cohorts from 1886 to 1994 in 143,390 twin pairs estimates heritability to be between 0.69 and 0.84 for men and between 0.54 and 0.78 for women (Jelenkovic, Hur et al. 2016). Fisher's view that Mendelian inheritance is sufficient to account for human inheritance can, thus, be rejected.

Omholt and his colleagues were able to construct a complex mathematical model introducing some new concepts, for example, monotonicity (Gjuvsland, Wang et al. 2013) to get out of this inconvenient hole but is it not simpler and more intuitive to say that inheritance is direct phenotype to phenotype inheritance, i.e., Johannsen's transmission-conception at the level of the phenotypes of the gametes?

[51] For example, there is extensive interest in amoeba, where the ability to solve mazes has been demonstrated: Nakagaki, T., H. Yamada and A. Toth (2000). "Maze-solving by an amoeboid organism." Nature 407(6803): 470. Amoeba also exhibit memory in relation to nutrient sources: Kramar, M. and K. Alim (2021). "Encoding memory in tube diameter hierarchy of living flow network." Proc Natl Acad Sci U S A **118**(10) and a continuous spectrum of behvioural states: Fleig, P. et al (2020) "Emergence of behaviour in a self-organised living matter network" ; https://doi.org/10.1101/2020.09.06.285080

[52] https://arxiv.org/abs/2007.05300 (accessed 20.02.2021)

To see how this will work we need to address first the processes of development and morphogenesis from the formation of the zygote to adulthood.

In the male and female gametes, complex changes occur in the genotypes before fertilisation of the egg by the sperm. However, sperm and egg are both functioning cells with phenotypes represented by attractor states. The sperm, although in partially suspended animation through protamine condensation of much of its chromosome content, contains gene products essential for successful fertilisation, as does, of course, the egg (Krawetz 2005). Thus, when the sperm head enters the egg, two functional complex systems occupy the egg cytoplasm. As attractor states they are discrete (behave like particles due to their boundaries of attraction) and do not blend one with the other.

As already noted, one of the simplest examples of an attractor state is a soliton or solitary wave. They are a useful metaphor for the physical aspect of the cellular phenotype albeit infinitely simpler. The soliton can be described thus: a non-equilibrium dissipative dynamic steady state that adopts (self-organises into) an attractor state. As waves in water, the dynamic steady state is between dispersion and breaking of the wave. These counteracting processes effectively trap the excess energy in the wave. The environment is important if the wave is not infinitely broad as is the case for a tsunami. In a canal, river, or long water tank, the energy in the wave is prevented from escaping laterally by the banks or walls of the containment. The environment thus plays a crucial role in the stability of the soliton and indeed any self-organised state, including the cellular phenotype.

Solitons are discrete states in whatever medium they occur, and they exhibit counter-intuitive emergent properties. For example, if two solitons collide, they simply pass through one another without exchanging material: they do not blend. Like solitons, attractor states (representing the phenotypes) have the properties that Mendel stipulated for the units of inheritance, i.e., particle- or thing-like and unitary[53].

Where two dynamical systems co-exist in proximity, they tend to synchronise (Yang 1999). This behaviour was observed in the mid-1600s by the Dutch physicist, Christian Huygens, when he was experimenting with pairs of pendulum clocks to measure time (fix longitude) on ships at sea in relation to that at their home ports (Oliveira and Melo 2015). A situation that is more relevant to zygote formation arises in artificial intelligence, where two (or more) artificial neural networks (attractor states) can be merged, retaining the properties of both. Another more intuitive example might be the merging of two companies manufacturing related products. The two could become one, operating from a combined manufacturing base: the full range of products from both companies could continue to be produced. Synchronisation in natural systems is a natural process because it minimises the energy of the coupled system.

Thus, the production of the zygote from two cellular attractors, without losing or diluting the individual characters of each (i.e., not blending), is certainly not ruled out as the basis of inheritance.

The human zygote is a single cell and, in the process of development, must be able to differentiate and proliferate into at least some 230 tissue or organ-specific cell types in the human body: almost all[54] will have the same genome sequence. Today, it is believed that these different cell types derive their tissue identity from so-called 'marking' on the chromatin[55], primarily methylation of DNA. These marks serve to allow the expression/repression of specific genes that characterise the cells of specific organs or tissues. Either before, or immediately after fertilisation, the participating genomes are 'cleaned' of their marks[56], and, after fertilisation reprogramming of the marking starts (Reik, Dean et al. 2001). The problem is: what is the source of the information that re-programmes the genome? That information cannot be coded in the DNA[57]. This is a major problem for the conventional theory of development.

The so-called epigenome, the specific patterns of marks on specific genes, is crucial at the zygote stage: the zygote cannot be pluripotent unless all marks that influence cell fate have been erased. As the genome sequences for several species, e.g., human, mouse, bonobo, etc. are remarkably similar, the question: "how does the zygote know 'I am a mouse', or 'I am a human', or 'I am a bonobo?" is a valid question if it is to rely on the gene sequences alone. The origin of the information that places the vital 'marks' is a major open question for conventional biology, even in respect of mitosis of somatic cells, when the marks have to be replicated on the daughter cells:

"*Cellular specialization during development is based on the ability to establish, maintain, and execute different gene expression programs. How transcriptional programs are established during development and maintained in cycling cells is a fundamental question in biology. Chromatin organization plays a fundamental role in this process, but it remains unclear how specific chromatin states are stably inherited from a mother cell to its daughters*." (Alabert, Loos et al. 2020)

The ignorance here is fundamental and critical to any theory of development that involves genes as the unit of inheritance.

Artificial life studies, however, point the way to an alternative way of looking at development and morphogenesis. Mauno Rönkkö, a Finnish computer scientist has developed an artificial ecosystem based on a deterministic particle system. The ecosystem consists of soil, grass, water pools, rain, worms, beetles etc. (Ronkko 2007). When the programme is run, the grass grows when it rains and releases a scent that the worms are attracted to: they eat the grass, and the beetles hunt them. All these 'components' of the ecosystem are composed of individual particles each with information relating to how they interact with other particles immediately adjacent to them. The remarkable thing is that, out of what is a fully deterministic system, emergent and lifelike properties are realised. Rönkkö writes:

"*We analyzed the dynamics of six nontrivial scenarios: formation of rivers and ponds, grass growing in rain, worms finding edible grass, a beetle jumping and correcting its orientation, beetles hunting worms, and the environment affecting the global dynamics. Each of these scenarios exhibited distinct emergent dynamics, and in each scenario the dynamics showed nonmechanistic, unpredictable, and sometimes even spontaneous characteristics*." (Ronkko 2007).

The point is that the information that enables these dynamic features to emerge is distributed across the whole ecosystem attached to the numerous individual particles. There is a very interesting parallel here with the most recent understanding of the process of cellular metabolism. According to De la Fuente et al. the numerous enzymes responsible for metabolism, self-organise into a global 'metabolic network attractor'. The authors say:

"*The self-organization of cooperating enzymes into multienzyme complexes, seem to be central features of cellular metabolism, crucial for the functional activity, regulation and efficiency of biomolecular processes and fundamental for understanding the molecular architecture of cell life*." (De la Fuente, Cortes et al. 2013).

Enzymes/proteins are, of course, information-carrying molecules hence the parallel with Rönkkö's ecosystem is close.

[53] Robert Olby in Mendel, Mendelism and Genetics: http://www.mendelweb.org/MWolby.html. (accessed 24:07:2020)

[54] Some exceptions are some cells in the immune system, and red blood cells that have no nucleus, and thus no genomic DNA.

[55] Acetylation of chromatin, methylation of DNA and structural features of the histones comprising chromatin.

[56] The zygote starts life as a single, so called, pluripotent stem cell capable of differentiating into any other more specialised and functional, cell type. Therefore, all inherited marks from the parental genomes must have been removed.

[57] If the DNA carried the instructions to apply the marking, it would have to carry at least 230 variants for the ~230 cell types in the human but how could it know, in any specific instance, which one of those to express? It could not. So, another source of information, independent of the DNA, is required. This is the fallacy that underpins the current paradigm for biology, based on a genetic regulatory network (GRN): Baverstock, K. (2011). "A comparison of two cell regulatory models entailing high dimensional attractors representing phenotype." Prog Biophys Mol Biol **106**(2): 443-449.

The life-like character of the artificial ecosystem led us to propose that the individual cells in the body of a multicellular organism harbour the necessary information, embedded in their phenotypes, to construct, at all stages of development, the bodily structure of an organism (Baverstock and Ronkko 2014). All the spatiotemporal complexity of the process is bound up in what is essentially self-organisation based on knowledge[58], individual cells being informed by the RoE[59].

The flocking of birds and the shoaling of fish are two very simple metaphors for this phenomenon. Individuals (the equivalent of the cells) are obeying local rules about their position in relation to their immediate neighbours. This alone leads to a coherence in dynamical emergent behaviour across the flock or shoal. The information in Rönkkö's artificial ecosystem is of exactly this character. It elicits a coherence in the dynamical behaviour across the ecosystem, which gives the emergent quality of 'life-like': it is, of course, not 'life'; it just has that character, but it shares with 'life' the phenomenon of emergence despite its deterministic origin.

The conventional explanation for morphogenesis is a 'toolkit' of homologous hox genes which:

"….. being highly conserved among phyla; …… generate the patterns in time and space which shape the embryo, and ultimately form the body plan of the organism"[60].

It is difficult to imagine how genes, composed of DNA, a passive molecule, can generate "*patterns in space and time*".

The British scientist Alan Turing (Turing 1990) proposed a mechanism for self-organised morphogenesis, (described in detail (Schweisguth and Corson 2019)) which is essentially self-organisation based on a reaction-diffusion mechanism. Schweisguth and Corson, reviewing the evidence for self-organisation in morphogenesis, conclude that there is:

"….. unambiguous evidence for self-organisation in tissue patterning". (Schweisguth and Corson 2019).

It is, therefore, reasonable to postulate that, following the transmission of the phenotypes of the gametes of two parents to their offspring, that an offspring develops into an adult in such a way that is not driven by the transferred parental genes but rather, is properly seen in terms of self-organisation based on local 'knowledge' retained in individual cells and deriving from the RoE. (Baverstock and Ronkko 2014). The zygote 'knows' what it will develop into quite independently of its genotype. However, the cell can only know that if the genotype can provide the appropriate materials in the form of gene products (Nijhout 1990). Genes, as 'builder's merchants', must provide gene products of the highest integrity, hence the lengths the cell goes to, to preserve the integrity of its DNA[61].

That self-organisation commences at a very early stage in human embryogenesis has been empirically established (Deglincerti, Croft et al. 2016, Shahbazi, Jedrusik et al. 2016, Shahbazi, Siggia et al. 2019). In the period of 7 to 14 days after fertilisation, the period following implantation, critical re-modelling of the embryo occurs. Sharbazi et al. report:

"*… events at this stage of human development are embryo-autonomous highlighting the remarkable and unanticipated self-organising properties of human embryos*." (Shahbazi, Jedrusik et al. 2016)

These results were obtained with an in vitro implantation system; there was, therefore, no input from the mother at this critical stage. This is the clearest possible evidence that development and morphogenesis are processes of self-organisation and are not dependent on genes except for the required gene products.

There are, therefore, two sources of information that specify the organism: 1) the RoE, which are species specific and inform all cells in the organism, and 2) the genomic DNA sequence. The former acts as the formal system syntax and the latter provides the gene products upon which the system draws to yield the phenotype. This means that the nucleus of the cell housing the genes is placed outside the system: it is treated as an organelle: a 'planet' in the cell's 'solar system' with the cytoplasm as the 'sun'.

What is described above is a system view of life based on a hierarchical self-organised structure out of which life emerges. This is very different from the prevailing view, even when that is presented as 'system biology'. Writing in 2011 in the journal Cell, under the title, "*The Cell in an Era of Systems Biology*", Paul Nurse[62] , wrote:

"*Our view is that scientific explanations and methodologies are essentially reductionist in nature. However, although it is difficult to imagine a scientific enquiry or explanation that is not reductionist, it is important to keep a focus on the behavior of whole systems in biology and to understand how the interactions and processes brought about by component parts acting at lower levels in a system are constrained by overall functions acting at higher levels*." (Nurse and Hayles 2011).

Reductionism might be viable for simple systems (machines) but it is totally inappropriate for complex systems. Nobelist and physicist, the late P. W. Anderson, warned in1972 that while it is possible to reduce a system to the basic laws that govern it:

"…. in general, the relationship between the system and its parts is intellectually a 'one-way street'. Synthesis [from underlying laws] *is expected to be all but impossible; analysis, on the other hand may be not only possible but fruitful in all kinds of ways.*" (Anderson 1972).

7. Discussion

In this paper, I have analysed how, under the appropriate branches of physics, cells would function at the single and multicellular organism levels. Two branches of physics are involved, namely, thermodynamics and complex dissipative system dynamics. The cell, the basic building block of organisms, is self-evidently a thermodynamically open, complex dissipative system. I have called the model of the cell based on this foundation in physics, the "Independent Attractor", or IA model, the term 'independent' representing the model's relative independence from the gene as an active functional element.

The analysis reveals several features that are at odds with the prevailing view of biology, most notably:

1. No empirical support for gene mutations providing selectable variance to drive evolution,
2. Therefore, cellular phenotypes, not genes, must be Mendel's units of inheritance,

[58] The philosopher Karl Popper draws a distinction between knowledge and information *per se*: knowledge is either derived through trial, error, and elimination, or derived *from* stored information. Information without a contextual framework within which to evaluate it is valueless: Niemann, H.-J. (2014). Karl Popper and the two new secrets of life : including Karl Popper's Medawar lecture 1986 and three related texts. Tübingen, Mohr Siebeck. In this case 'knowledge' is the more appropriate term because it derives from information held in the gene sequences that specify the gene products.

[59] Consider the development of a ball and socket joint. Throughout the development process these two separate components must match one another very closely. This requires that both components share complementary spatial and temporal knowledge from which to build the joint.

[60] https://en.wikipedia.org/wiki/Evolutionary_developmental_biology (accessed 23.02.2021)

[61] DNA, under physiological conditions is subject to continual degradation due to hydrolysis and oxidation. Baverstock, K. (1991). "DNA instability, paternal irradiation and leukaemia in children around Sellafield." Int J Radiat Biol **60**(4): 581-595. Considerable resources of the cell are devoted to detecting and repairing this damage to maintain the integrity of the gene products that the cell requires to function correctly.

[62] Formerly President of the UK Royal Society and now Chief Executive and Director of the Francis Crick Institute, London

3. Environmental stress can trigger unscheduled direct phenotype to phenotype transitions (phenotypic instability),
4. The LTEE proves that natural selection is a physical manifestation of the 2nd law,
5. Development and morphogenesis in multicellular organisms are processes of self-organisation based on knowledge carried by the cellular phenotype.

Relying on a decision, which, among other things, might have been influenced by a specific plant breeding technique (Johannsen 1911) and two highly influential, but flawed, works by Fisher (Fisher 1918, Fisher 1930) but with no compelling biological or physical insight, the genetic community has adopted Johannsen's genotype-conception and the role of the gene in that, as the functional basis for the four main elements of biology, namely, inheritance, evolution, development, and morphogenesis. The gene is, therefore, fundamental to biology as it is viewed today. There is a famous and widely accepted statement made in 1964 by the evolutionary biologist and founding influence on the MS, Theodosius Dobzhansky: "*nothing in biology makes sense except in the light of evolution*". (Dobzhansky 1964). If Lenski's LTEE is anything to go by, evolution does not make sense in terms of genes, so then, neither does biology. Evolution has undoubtedly taken place (Dawkins 2009) and mutations to the genomic DNA have undoubtedly been accrued (Lynch 2010) but the two, based on the results of the LTEE, are apparently not connected. Had Lenski adopted a more conventional approach and set-up the LTEE to test a clear hypothesis[63], Fisher's 1930 theory of natural selection would have been rejected by evidence as early as the mid-1990s.

If genetic variance does not drive evolution, then genes are not the units of inheritance. The alternative is the gamete phenotype which, being an attractor state with a boundary of attraction, has the 'particle-like' character that Mendel demanded[64]. The inheritance of likenesses based on genes being the units of inheritance, as claimed in Fisher's 1918 paper, based on purely additive Mendelian inheritance (Fisher 1918), is not credible but is uncritically lauded as the basis of the modern genetic technology of GWA (Visscher and Walsh 2019, Visscher and Goddard 2019). Additionally, Crick's crucial 'sequence hypothesis' (governing the transfer of information from the DNA sequence to the gene products which generate the phenotype) is invalid (Baverstock 2019a), even apparently in the view of Crick himself in 1970 (Crick 1970) [see above]. Omholt maintains that the genotype-to-phenotype map for complex traits is far from straightforward. He writes:

"*It should be noted that …… there is no direct causal arrow from genotype to phenotype in the sense that DNA is responsible for exerting a direct effect as a sub-system on the system dynamics*." (Omholt 2013)[65].

That absent causal connection between alleles (or mutations), and the phenotype is essential if the currently extremely active technology of GWA is to measure traits. However, GWA does measure something. Typically, as already noted, a large population, bearing a common disease or behavioural trait, will exhibit hundreds to thousands of SNPs, at almost as many loci, each contributing a very small effect to the genetic risk, when compared with a control population of similar size. Even though mostly there is no biological rationale as to why these SNP/loci would be associated with the trait, the small contributions from each SNP are added up into a PGS, from which it is claimed diagnoses of the trait can be made (Plomin 2018). Population stratification, geographical and social, could confound associations between SNPs and traits, (Sanderson, Richardson et al. 2021) if those existed. As it appears that they don't, the effect of stratification is to produce false positive results, thus, falsely increasing confidence in PGSs as diagnostic tools. For example, in a study in Finland, PGSs for five common diseases and three complex traits were calculated for 2,376 individuals whose parents had lived in a known specific geographical location. Within Finland, there is a well-defined genetic population structure, with an east-to-west divide (Kerminen, Havulinna et al. 2017). For all but one of the five disease traits and one of the three complex traits, the PGSs detected the geographic structure (indicating where the individual was born) and not the distribution of the trait (Kerminen, Martin et al. 2019). In most studies the background genetic structure is not as well-known as it is in Finland: it is, therefore, in most cases, not possible to discriminate between measurements of genetic background and false positives (Richardson and Jones 2019).

Since 1983 at least, when Barbara McClintock presented her Nobel Prize lecture entitled "*The Significance of Responses of the Genome to Challenge*", it has been known that environmental stress or shocks, can induce phenotypic changes in terms of karyotypic rearrangements in the genomes of maize (McClintock 1984). This same phenomenon has been established in many other experimental systems with diverse endpoints, initially in radiobiology, as radiation-induced genomic instability (Morgan 2003, Morgan 2003, Kadhim, Salomaa et al. 2013), or simply, genomic instability, as it can also be induced by other environmental stresses (Karotki and Baverstock 2012). Genomic, more appropriately, phenotypic, instability, a direct (without involving the genotype) transition from one cell phenotype to another, is in effect unscheduled and undirected cell differentiation. There is, therefore, no rational basis for GWA studies, or, therefore, for PGSs.(Baverstock 2019b).

Therefore, an important implication of the phenomenon of phenotypic instability is that common disease and behavioural traits are not genetic, but rather are caused solely by environmental stress. The justification for assuming a substantial genetic component in such traits derives from studies of twins (Plomin 2018), which are, in any case, compromised by the flawed 'equal environments assumption' (Joseph, 2015). However, if genes are not the units of inheritance, then estimates of heritability based on genotypes are meaningless.

That the fitness profiles of the 12 independent experiments of the LTEE are not compatible with Fisher's law of natural selection, even when the impact of ongoing mutation, modelled by (Basener and Sanford 2018), is incorporated, and the fact that the 12 fitness profiles are identical, although each experiment is acquiring different mutations (Maddamsetti and Grant 2020), shows that gene mutation is not the source of variance that is being selected to improve fitness. On the other hand, the fit to a power law of the evolution of fitness in 12 independent experiments over more than 50,000 generations indicates that natural selection is driven by physics, as proposed by Sharma and Annila (Sharma and Annila 2007). The physics is the principle of least action (De Maupertuis 1746), which is synonymous with the 2nd law, with nutrient the driving source of free energy. Blyth's remark (see above) in 1835, drawing attention to the importance of nutrient for the survival of organisms (Blyth 1835), taken together with Maupertuis' principle would seem to be a sufficient explanation for evolution in the LTEE and likely

[63] Such as: "fitness will evolve according to the theory of natural selection proposed by Fisher, with due modification to allow for the influence of mutations occurring during the evolutionary process".
[64] Robert Olby in Mendel, Mendelism and Genetics: http://www.mendelweb.org/MWolby.html. (accessed 24:07:2020)
[65] Omholt's paper is highly innovative, building on ideas going back a few decades. He acknowledges that thermodynamically open systems can include both living and non-living systems: "*Living systems do not have exclusive ownership to phenomena like self-assembly, self-organization, emergence, two-way causation between lower- and higher-level system dynamics features, and order creation through local reduction of entropy.*" (p76). However, it is a misapprehension that the creation of order requires a local reduction in entropy: see Annila, A. and K. Baverstock (2016). "Discourse on order vs. disorder." Commun Integr Biol **9**(4): e1187348. It does not. Secondly, the genotype, the DNA, is invoked as being what makes the difference between the living and the non-living, in that it enables the living system to self-transcend its morphological constraints. However, Rönkkö demonstrated that artificial life beetles, embedded in their artificial life ecosystem, transcended their morphological constraints as deterministic objects, comprised of information bearing particles: Ronkko, M. (2007). "An artificial ecosystem: emergent dynamics and lifelike properties." Artif Life **13**(2): 159-187. There is no distinction between the animate and the inanimate. To claim such is vitalism: Annila, A. (2020). Back to Reality. New York, Privus Press. See p. 237.

in evolution generally. That cell volume in the LTEE bacteria does not increase identically in all colonies should not be a surprise. It has been clearly demonstrated that individual bacteria in a genetically pure colony differ significantly in their chemotactic behaviour (Salek, Carrara et al. 2019, Salek, Carrara et al. 2019). The heterogeneity in behaviour is said to derive from variation in gene expression. It can be assumed that cell volume, unlike fitness, is not governed by the principle of least action and is not, therefore, a selectable property.

Maupertuis' principle dictates that a free energy disequilibrium (in this case between environment or ecosystem and an organism) will be levelled as efficiently as local conditions permit. In the LTEE, at the start, the 12 experimental flasks contain equal numbers of genetically identical bacteria, provide identical environments, and identical quantities of available nutrient, specifically the same limiting concentration of glucose. In each succeeding 24 hours the glucose is exhausted more rapidly, at least up to 60000 generations, but that difference diminishes every day, and unless the governing power law is truncated at some point that pattern of behaviour will continue indefinitely. The LTEE is an evolving system that has 'nowhere to go' because the environment is unchanging, and unchangeable by the bacteria. In the real world, as noted above, organisms modify their environment through, for example, niche construction, and the environment modifies phenotypes through stress and phenotypic instability. The former is the exercise of agency by organisms, which push back on the local conditions to maximise, as much as possible, the flow of free energy from the environment: this is the biological component of evolution.

The evidence of autonomous self-organisation at the earliest stages of embryogenesis (Shahbazi, Jedrusik et al. 2016, Shahbazi, Siggia et al. 2019) is a compelling indication that the whole process of development and morphogenesis is based on self-organisation. The information for that process derives from the RoE and is stored in the cellular phenotype but is contingent on the environment in which it takes place. The life-like behaviour of Rönkkö's fully deterministic virtual ecosystem (Ronkko 2007), when considered holistically, provides a powerful argument for the proposed role of self-organisation in development (Baverstock and Ronkko 2014).

Thus, starting with the self-organised metabolic network that extracts energy from nutrient (De la Fuente, Cortes et al. 2013), through the self-organised gene-product network from which cellular phenotype emerges (Baverstock and Rönkkö 2008), to the self-organised structure of cells that is the organism (Baverstock and Ronkko 2014); a self-similar 'matryoshka' on three hierarchical levels is revealed. Being alive, including consciousness, independent agency, and what they entail, is rooted at the cellular level and is an emergent property of interacting gene products. This is the system/cell microstate that allows agency. Free energy is dissipated, and the entropy in the system is increased, appearing in the system as growth and information (Annila and Baverstock 2016). Recall that Boltzmann said that organisms sought entropy first and foremost (Boltzmann 1974)[66].

Ken Richardson points out that it is not the case that evolution is taking place in the stable environment envisaged by the MS, or according to genetic programmes but rather to inducible covariation grammars ('biogrammars') (Richardson 2020)[67]. This is what Conrad Waddington foresaw in his "*Paradigm for an* [open ended] *Evolutionary Process*" published originally in 1969 (Waddington 2008). This is also what Fisher sought, based on genetics, in 1930 (Fisher 1930) but failed to achieve (Basener and Sanford 2018). Richardson's ideas on biogrammars are in tune with Robert Rosen's theory of organisms as anticipatory systems where: "*an anticipatory system is a natural system that contains an internal predictive model of itself and of its environment, which allows it to change state at an instant in accord with the model's predictions pertaining to a later instant*" (Louie 2010).

As already noted, genes are like the merchants that provide the necessary materials to build a house: they are neither the architect, nor the builder but, without them, the house cannot be built. Put more formally, genes are neither the formal cause (the blueprint), nor the efficient cause (the builder) of the cell, nor of the organism: they provide the material cause, the gene products (Nijhout 1990). The formal cause is embedded in the RoE and the efficient cause in the phenotype.

The fundamental problem with the traditional 'gene-centred' view of biology that prevails today is that the information in the DNA sequence is taken to be both the formal and the efficient causes of the organism. In his modelling relationship, Robert Rosen emphasises the necessity of having both syntax and semantics (Rosen 1991). He asks if it is possible to define a language in terms of a formal syntax alone: it is not; a semantic component (vocabulary) is needed[68]. This is the issue that came to light with the problem of how the pluripotent zygote, stripped of its chromatin markings, could 'know' what it was from its DNA sequence alone. A second independent source of information was required and is assumed to be chromosome marking, but the origin of the information that places the marks is not known. This is the same problem as Gödel's incompleteness theorem and Turing's halting problem. The view of biology based on genetic regulatory networks alone is fundamentally flawed (Baverstock 2011).

Information is widely regarded as a key feature of biology. For example, Nurse, in a lecture[69] in Oxford in March 2020, refers to "life as information", linking it to "complex systems, their control and purpose." However, Nurse's idea of a complex system is very different from that being discussed here. Control, in the form of homeostasis, he proposes, is imposed through feedback mechanisms as originally proposed by Jacques Monod and François Jacob in connection with gene regulation in the lac operon[70] (Jacob and Monod 1961). Ludwig van Bertalanffy, in his "*General System Theory*", while acknowledging a role for feedback in biology, proposes that where biological organisation and homeostasis are concerned, his principle of equifinality applies (Bertalanffy 1969). This principle is precisely what we have discussed here in terms of attractor states and self-organisation. Feedback is primarily a feature of machine-based, or complicated, systems, whereas equifinality is a feature of complex[71] systems, although the former may be found embedded in the latter. In the IA model homeostasis is an emergent phenomenon arising in a complex system.

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[66] "*The general struggle for existence of animate beings is therefore not a struggle for raw materials—these, for organisms, are air, water, and soil, all abundantly available—nor for energy which exists in plenty in any body in the form of heat (albeit unfortunately not transformable), but a struggle for entropy, which becomes available through the transition of energy from the hot sun to the cold earth*"

[67] Richardson draws a parallel with how human speech is understood. Several features of speech sounds, including their timing, pitch, duration, etc., covary to define a word. The trained brain is adept at decoding these features simultaneously. Similarly, the organism is receiving information about its environment on several levels and using what Richardson calls biogrammars to ensure survival, to optimise available resources and to anticipate threats.

[68] See p 44 in: Rosen, R. (1991). Life Itself: a Comprehensive Inquiry into the Nature, Origin and Fabrication of Life. New York, Columbia University Press.

[69] https://www.oxfordmartin.ox.ac.uk/events/james-martin-memorial-2020/ (accessed 29.08.2021)

[70] https://en.wikipedia.org/wiki/Lac_operon (accessed on 10.04.2021)

[71] The distinction between the terms 'complex' and 'complicated' is important. It is often said that the mark of a complex system is that its output is 'more than the sum of its parts' and this results from the more than additive interaction between the components of the complex system. On the other hand the outut of a complicated system is simpy the sum of iits compoment parts. The concept of feedback, applicable in both, is prominent in cybernetics and, in the context of biology, can give rise to homeostasis, as, for example, in regulating body temperature. Bertalanffy's principle of equifinality refers to the concept of an attractor state where, if the initial state of a system lies within the boundary of attraction, it will reach a specific final state from wherever it starts. This applies only in thermodynamically open systems and yields homeostasis as an emergent property. This is the origin of the order that Stuart Kauffman discusses in his book: Kauffman, S. A. (1993). The Origins of Order: Self Organisation and Selection in Evolution. Oxford, Oxford University Press, and is at the root of the self-organisation proposed in the IA model, through the phenomenon of emergence.

Since Boltzmann formulated his molecular theory of entropy in 1877 many physicists and biologists have assumed that increasing entropy inevitably means increasing disorder. This, however, only applies in closed systems: organisms are thermodynamically open and increasing entropy is fully compatible with increasing order and complexity (Annila and Baverstock 2016). There is a long history of physicists proposing complicated ruses to lower the internal entropy of an animate system to allow it to 'get around the 2nd law'[72]. Perhaps the best known is Schrödinger with his concept of negative entropy, or negentropy[73]. Many think that his book, "*What is Life?*" (Schrödinger 1944), has had a profound influence on biological thinking. He was, however, mistaken, not only in the context of the role of entropy but also in his metaphor for an organism as a 'clockwork'[74] or complicated system. As already noted, but worth repeating: given the right components, the appropriate environment, and an injection of free energy, self-organisation is a natural consequence, be it solitons, life, or consciousness (at the cellular level).

The preliminary announcement of the results of the HGP in 2001 decisively ended the 'one gene: one polypeptide' assumption. The result was unexpected by the genetics community[75]: it signalled that they had been working under a serious false assumption. In a Commentary in the journal Nature in February 2021 (Gates, Gysi et al. 2021), the authors list the benefits they see from the HGP. These include the catalogue of protein coding genes but, they point out, not a clearer definition of what constitutes a gene. This paper is a perspective of data scientists: it does not address what the HGP has taught us about the processes underlying biology, how it works, and how we can better understand common diseases. Particularly in advancing the understanding of common disease, I would argue that the HGP has not realised what was promised in the early 1990s.

Finally, the introduction of agency as a property of organisms is a challenge to how biological phenomena can be investigated. Biology is governed by physics and implemented by biochemistry. In his 1986 lecture, Popper (Niemann 2014) was challenged by Max Perutz on his assertion that biochemistry was not reducible to chemistry (Rose 1988)[76]. Rose was initially opposed to Popper's assertion but subsequently came to agree with it, noting that:
" *….while the problems of chemistry concern molecular structures in their own right, those of biochemistry concern the function of those molecules within a system and neither the system nor the function of the molecule within it can be explained merely from a study of the molecule itself*."
What Nurse (see above), from his reductionist standpoint, calls the "*component parts acting at lower levels of the system*", is the crowded milieu of "*intrinsically disordered proteins*" where chaos prevails (Fonin, Darling et al. 2018) but out of which, according to the framework described here, the phenotype emerges and the cell is regulated, i.e., Nurse's "*functions acting at higher levels*" emerge[77]. The gene products are not the tidily folded native protein structures that chemists and reductionists envisage, and Crick predicted in his sequence hypothesis (see above). Popper was correct in that such a 'biochemical' system cannot be reduced to conventional chemistry. Further, the intrinsically disordered proteins, and regions of proteins, are thought to play a key role in the process of learning (Csermely, Kunsic et al. 2020), which is essential to knowledge acquisition and, therefore, to agency. Furthermore, the knowledge upon which agency is based is internal to the system and cannot be inferred from external observations. The framework presented here requires that a very different approach be taken to gain an understanding of biology than has heretofore been applied.

In invoking agency as the biological component of evolution, the inheritance of acquired characteristics is invoked. Blyth speaks of an organism's "*agility, strength, or delicacy of sense,"* as being characteristics important in acquiring nutrient (see above). These are characteristics that can be acquired, and for evolution to advance, need to be inherited. Is this a fatal flaw in the IA model given the Weismann Barrier and Crick's Central Dogma? Johannsen was at pains to exclude the inheritance of acquired characteristics (see EN 25) and opted for the genotype/gene as the inherited component. In his book on biological relativism: "*Dance to the tune of life: biological relativity*" (Noble 2017), Denis Noble notes that Weismann's 'surgical' evidence for his barrier is weak[78]. Noble points out that Conrad Waddington's experiments on 'genetic assimilation' in response to environmental changes (Waddington 1942), although dismissed by Neo-Darwinists as phenotypic plasticity, is the inheritance of acquired characteristics under specific environmental conditions. Furthermore, he suggests that Crick's Central Dogma (Crick 1970) is "*better represented as an important chemical fact about coding …*" rather than a universal principle of biology. Therefore, agency in evolution, as invoked by the IA model is not precluded by evidence.

Further, the framework based on self-organisation has a plausible explanation for abiogenesis (Annila and Baverstock 2014) in terms of Alexander Oparin's theory of the origin of life (Oparin 1953), as modified by Freeman Dyson (Dyson 1999). The kind of complex self-organised system proposed, with its emergent properties, is one that Murray Gell-Mann would expect to exhibit consciousness (Gell-Mann 2001) and, therefore, agency. When did consciousness arise? In the context of the two-stage Oparin/Dyson model (protein-only proto-life, followed by the acquisition of RNA/DNA to code for peptide sequences), it must have been present at the proto-life stage, since the second stage requires agency and, therefore, must be the product purely of protein chemistry (Baluska, Yokawa et al. 2016)

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[72] Other examples: Nicolis, G. and I. Prigogine (1989). Exploring complexity : an introduction. New York, W.H. Freeman; Penrose, R. (2011). Cycles of time : an extraordinary new view of the universe. New York, Alfred A. Knopf.
[73] Which he regrets at some length in a note at the end of Chapter 6 in: Schrödinger, E. (1944). What is life? Cambridge, Cambridge University Press.
[74] Ibid. See p 89.
[75] In a sweepstake organised in 2000 and drawn in 2003, the winning prediction, the lowest prediction out of 460 bets, was 25,947. The current estimate is between 22,000 and25,000.
[76] After the lecture, Perutz questioned Popper, who did not hear the question clearly and the Chairman repeated it for him: "*'Dr Perutz wants to know why you think biochemistry cannot be reduced to chemistry'. 'Ah, yes', Popper finally replied benignly, 'that surprised me too, but I suggest you go away and think about it for an evening, and you will see that I am right*.'" This encounter led to a long-running dispute between Popper and Perutz, Perutz remaining unconvinced at the time of Popper's death in 1994.
[77] By any standard of comparison with what can be simulated in a laboratory test tube, the cellular cytoplasm is extraordinary. As well as housing organelles, such as the mitochondria and the nucleus, up to 40% of the 'aqueous volume' is comprised of dissolved macromolecules, the gene products. Yet despite this high concentration, the cytosol is translucent with a viscosity roughly equivalent to a 10% solution of glycerine. This can be determined by centrifuging a suitable injected pellet, which moves freely through the cytosol: Hillman, H. and P. Sartory (1980). The Living Cell: a reexamination of its fine structure. Chichester, Packard Publishing Ltd. In the test tube, the folding of peptides to proteins can only be achieved in very dilute solution otherwise the peptides form aggregates. Partially denatured proteins are also stably present in the cytoplasm and may play an important role in that state, as already noted. One solution being suggested to better understand how chemistry can be so specific in the cytoplasm is liquid-liquid phase separation Li, X. H., P. L. Chavali, R. Pancsa, S. Chavali and M. M. Babu (2018). "Function and Regulation of Phase-Separated Biological Condensates." Biochemistry **57**(17): 2452-2461. Here, membrane-less condensates ordering gene products are posited to play a role in regulation of the cell. What is clear is that the chemistry taking place in the cytoplasm will not be able to be replicated in the test tube. This, however, does not really matter because that chemistry is causing an emergent property, the cellular phenotype, and, as such, its causes cannot be deduced
[78] See pp 126-127.

8. Conclusions

Crick chose the word 'dogma' to name what is, in fact, a hypothesis: the true 'dogma' in biology is the concept of the gene. The gene does have the role that, according to Roll-Hansen, Johannsen proposed in 1910, namely, to represent "*an experimentally identifiable difference between genotypes*" but it has, over more than a century, acquired a much greater prominence than its true role deserves. Arguably, defending it as that central functional feature of biology has distorted the scientific method and rejected important empirical evidence.

At the outset, I said I would follow the example of Annila in his book "*Back to Reality*" (Annila 2020) and look for simple and intuitive explanations for how the complex system that is the cell, works. I would argue that the dogma of the gene and the dominance of a complicated, or machine-oriented, rather than a complex, model for biological systems, are among the impediments to appreciating the simplicity of self-organisation. In his book "*The Nonlinear Universe: Chaos, Emergence and Life*" (Scott 2007), Alwyn Scott reminds us that the natural world is replete with nonlinear phenomena, including self-organisation. I believe the explanations I have proposed for inheritance, evolution, development, and morphogenesis should be more intuitive than molecular genetics based on Johannsen's genotype-conception, and are, if the focus on the gene does not obscure the vision of the real world.

And finally, for what reason did life originate some 3.5 billion years ago? To help to equilibrate the free energy disequilibria, according to Maupertuis' principle of least action, caused on planet Earth, by its sun shining in the cold of the universe?

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10. Conflicts of Interest

I have no conflicts of interest

11. References

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