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REVIEW

How the Central Dogma and the Theory of Selfish Genes Misled Evolutionary and Medical Sciences in Understanding Multi-factorial Diseases

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Abstract
This synthesis article deconstructs the incorrect interpretations of the Central Dogma of Molecular Biology in popular accounts of Selfish Gene Theory in evolutionary biology and in genomics. "Selfish" in the theory is invalid whether interpreted literally or metaphorically. This deep misinterpretation of twentieth century biology, emphasising the primacy of genes in functionality, has encouraged the search for the genetic origins of major multi-factorial diseases, even in the face of continuing failure of genomics to provide the route to prediction or cures for those common fatal diseases. Reliance on The Human Genome Project for such cures has led medical science into an expensive impasse. It is time to bury the scientific dogmas of the twentieth century. There is no place in science for dogmas of any kind. What we need are functional therapies through understanding the functional networks that control genes and their evolution. We present a new diagrammatic way of representing the causal interactions between functional physiological networks and the chemical processes represented by the Central Dogma. It then becomes evident that there are many ways in which the activity and nucleotide composition of DNA can be varied.

Keywords Central Dogma · Selfish Gene Theory · Gene association scores · Polygenic scores · Genome-wide association studies

Introduction

There is a growing realisation that, 25 years on from the first sequencing of the human genome, the early promises of many cures for all common diseases, including nervous diseases, cancers and cardiovascular diseases, emerging from genomics has not been fulfilled. Yet, when the Human Genome Project was launched during the 1990s, a nervous system disease, schizophrenia, was chosen as one of the major justifications for the project (Collins, 1999; Torrey, 2024). Cancers and cardiovascular disease were also expected to yield to genetic cures (Collins, 1999).

The reason was that some of these diseases have many of the usual signs of being an inherited disease since they can run strongly in families, and many genes have been identified as having association scores with them. We now know that the main reason for these associations is shared environmental conditions (Torrey, 2024), including epigenetic inheritance influencing reactions to trauma (Mulligan et al., 2025), rather than genetic inheritance. The physiological reasons why environmental conditions can be so influential are now also well documented as forms of epigenetic inheritance (Allis et al., 2015; Anastasiadi et al., 2021; Tollefsbol, 2014). The evolutionary importance of epigenetic inheritance is that Physiological Selection as an evolutionary process, using epigenetic inheritance, can provide a plausible and testable explanation in evolutionary biology for branching speciation (Noble & Phillips, 2024).

Quite simply, "Genes are not the Blueprint for Life" (Ball, 2024; Noble, 2024; Noble & Noble, 2023). It is therefore

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important to understand what genes, as DNA sequences, forming templates for proteins, can and cannot do in understanding nervous diseases. As Pascual and Noble (2025) recently concluded in relation to nervous diseases:

> "Gene-centrism has had influence way beyond biology or clinical medicine. The peak influence in the medical sciences was the representation of the genome as the "book of life"……..Instead through genome-wide sequencing we have encountered a failure of gene-centrism. Most association levels are small, so much so that we can be sure that such methods do not reveal causation. In reality, the regulatory networks simply buffer organisms from most genetic changes." (p. 72)

The detailed reasons why association scores cannot reveal causation were first outlined in Noble (2008, p. 3007), where the problem is referred to as the 'genetic differential effect problem'. The relevant quotation is.

> "….differences [i.e. association scores] cannot reveal the totality of functions that a gene may be involved in, since they cannot reveal all the effects that are common to the wild and mutated types. We may be looking at the tip of an iceberg. And we may be looking at the wrong tip since we may be identifying a gene through the pathological effects of just one of its mutations rather than by what it does for which it must have been selected. This must be true of so-called oncogenes, since causing cancer his unlikely to be function for which the genes were selected……Identifying genes by differences in phenotype correlated with those in genotype is therefore hazardous. Many, probably most, genetic modifications are buffered."

That article also outlined the 'problems with the central dogma' (p. 3008), which are further explained in Noble and Noble (2017, 2018).

Origins of the Problem

Our recent book, *Understanding Living Systems* (Noble & Noble, 2023), identifies the main sources of the problem as, first, the formulation of the Central Dogma of Molecular Biology (Crick, 1958, 1970) and second, the mistaken popularization of that dogma in the publication of *The Selfish Gene* (Dawkins, 1976, 2016) and its later editions. The Central Dogma then became widely interpreted to mean that, through enabling all proteins to be made, the development of an organism would be fully predictable from knowledge of the genome; it could even be used to recreate a clone of the same organism. As Dawkins proclaimed in a recent video discussion:

> "Suppose somebody put Denis's genome in a Petri Dish. And keep it going for 10,000 years. Well, it wouldn't keep going. It would decay, as you rightly say. However, the information, it could be preserved on paper. You could actually write it down in a book, you could carve the ATC and G codons in granite and keep it for 10,000 years. And then in 10,000 years, type it into a sequencing machine, which we already have, and it would recreate an identical twin of Denis Noble."[1]

The Selfish Gene also characterises the organism as a mere vehicle for its genes. In its more dogmatic form, the organism is represented as powerless to influence what is inherited from its life experiences by its progeny.

But, instead of these misinterpretations of the Central Dogma, and the promises of leaders of the Human Genome Project, what we have found is that, with the exception of the rare monogenetic diseases such as cystic fibrosis, affecting around 5% of the population, such prediction is unreliable for cancers and cardiovascular diseases (Hingorani et al., 2023), as well as nervous diseases (Torrey, 2024). The predictions don't even satisfy the criteria for the statistical confidence levels for FDA approval of a new drug.

Moreover, for multifactorial common diseases, no cures have yet developed using gene therapy (Baverstock, 2024). Yet, the world has already spent billions on genomics research over the last 25 years. In the case of mental disorders, in the United States alone, the National Institute for Mental Health (NIMH) has spent $8billion. But, as Torrey (2024) says, "Not a single gene has been found that can be causally linked to schizophrenia and the research has produced no improvements in treatment."

As we show in *Understanding Living Systems* gene-centric biology depends on a deep misinterpretation of the Central Dogma of Molecular Biology, since the one-way chemical process of constructing proteins from knowledge of gene sequence data cannot prevent organisms controlling gene expressions. Nor can it prevent the immune system from responding to new viruses or bacteria, modifying the organism's genes by Natural Genetic Engineering of the genome as a read–write database for the organism (Shapiro, 2011, 2022). This mistake also led Julian Huxley in his second edition of The Modern Synthesis (Huxley 1963) to "dethrone proteins in favour of DNA" resulting in the hardening of the Modern Synthesis. These misunderstandings persist to the present day, as the summary of key assumptions in standard evolutionary biology show (Futuyma & Kirkpatrick, 2018, p 18).

[1] Transcript of discussion between Noble and Dawkins, 2022, https://www.denisnoble.com/wp-content/uploads/2023/02/TranscriptReferences.pdf at 13:01 min).

So, why have medical science and evolutionary biology been so seriously misled for so long by gene-centric biology? We identify that misleading with the publication of *The Selfish Gene* by Richard Dawkins in 1976 and its subsequent republished editions over nearly 50 years with no changes in the original text, despite the many changes that have occurred in genetics, as Dawkins admits (see Dawkins, 2016, p 145). That book was written as a superficially convincing and widely-popular argument for gene-centric interpretations of modern biology, based on Dawkins' misinterpretations of the Central Dogma of Molecular Biology (see chapters 1 and 2 of *Understanding Living Systems*). To unravel these misinterpretations, we begin by asking how Dawkins thinks that a gene should be defined.

The Problem: Varying Definitions of a Gene

The theory of *The Selfish Gene* is based on a one-way process of the development of an organism from its DNA. Evolution is represented as a single process of Natural Selection, targeted on genes as DNA sequences. Through this process genes are represented as ensuring their own 'selfish' reproduction, for which the organism is a mere vehicle to carry their 'selfish' genes to the next generation.

The problem begins when we ask the question: what, in Selfish Gene Theory, really is a gene? Richard Dawkins seeks to clarify that question in the Epilogue to the 40th anniversary edition of *The Selfish Gene:*

> "….. 'gene' in this book is used in a special sense, tailored to evolution rather than embryology. My definition is that of George C. Williams: ……..'A gene is defined as any portion of chromosomal material that potentially lasts for enough generations to serve as a unit of natural selection.'" (Dawkins, 2016, p. 345)

The first point to note about this definition is that such a gene is not the unit of inheritance discovered by Mendel in the nineteenth century, nor the definition of 'gene' (*gen* in German) first used by Johanssen (1909). 'Gene' in Mendel's and Johanssen's sense is an inherited trait. But a trait is the phenotype, not a 'portion of chromosomal material' supposed to be the *cause* of the phenotype.

Yet, when pressed, Dawkins reverts to something remarkably similar to the 1909 definition. In 2009, faced with a challenge in a debate with Lynn Margulis, who cited transgenerational membraneous inheritance in modified paramecium, he responded:

> "I would embrace that gladly as a new "honorary" gene. That's fine."

Significantly, the packed audience groaned.[2]
As we commented in *Understanding Living Systems*:

> "So, in that sense, Dawkins' trick is that a gene is anything and everything that is inherited. Yet, the thesis of *The Selfish Gene* requires genes to be discrete entities whose frequencies can be measured." (Noble & Noble, 2023, p.2)

Moreover, this definition would even allow any epigenetic marks on the chromosomal material, as found in the brains of schizophrenia patients (Wockner et al., 2014), to become 'honorary genes'. Those marks on both the DNA threads and on the chromatin proteins are just as much part of the "chromosome material". On the definition he adopts from Williams, this is necessarily true, so the great majority of epigenetic marks could then also count as 'honorary genes'. But epigenetic marks, like epigenetic processes in general, are sensitive to the environment inducing acquired characteristics. This must, surely, be excluded in Selfish Gene Theory since one of the primary aims of the theory, as an expression of neo-Darwinism, is precisely to exclude the inheritance of acquired characteristics. That was Weismann's deliberate intent in postulating the existence of his barrier sealing off the future eggs and sperm from any environmental or soma influences. At the least, on the Neo-Darwinist interpretation these influences should not be transmitted to the germline. Yet the overwhelming evidence is that they are (Phillips & Noble, 2023; Fitz-James & Cavalli, 2022). And we now know examples of the molecular biological processes by which such transmission is facilitated (Herridge et al., 2024). Boundaries are often *active* physiological processes (Noble et al., 2019).

We conclude that there is a deep confusion in the way Dawkins plays with the concept of a gene. As he writes:

> ''gene' in this book is used in a special sense, tailored to evolution rather than embryology'" (Dawkins, 2016, p 345)

If epigenetic effects can also be included, then 'gene' is indeed being used in a 'special sense'; so special that the theory becomes a tautology, no longer open to empirical investigation. That is why, as Dawkins confidently proclaims, the text of *The Selfish Gene* has remained unchanged for at least 40 years:

> "So many exciting things are fast happening in the world of genomics, it would seem almost inevitable—even tantalising—that a book with the word 'gene' in

[2] https://www.denisnoble.com/wp-content/uploads/2019/11/HOMAGE_COMMENTARY_Music-of-Life-1.pdf. page 24.

the title would, forty years on, need drastic revision if not outright discarding." (Dawkins, 2016, p. 345)

Indeed so. Anyone else might be suspicious that he must have hit on a tautological theory, since genetics and its molecular biological basis have transformed out of all recognition in those 40 years. So much so that much in molecular biology that seemed secure in the 1950s has been undermined as support for gene-centric biology (Noble, 2021; Noble & Noble, 2021). As we will see, the inability to be susceptible to experimental falsification is also evident from an analysis of the 'selfish' metaphor, as shown later in this article.

How do Epigenetic Effects Influence the Chromosomes and Inheritance?

To understand this question we need to complete the diagram on which Crick based his formulation of the Central Dogma. Figure 1 does this.

The original Crick diagram forms the bottom row, including his original 1958 formulation (DNA —> RNA —> Protein), and the 1970 additions (reverse transcription RNA —> DNA) and the self-replication of DNA and RNA.

Our diagram then includes five major additions:

1. Two downward dotted arrows from the functional networks to RNA and DNA. These are formed by the pathways via the tubulins and their molecular motors by which messages from surface cellular processes can be transmitted to targeted parts of the nucleus (Kar et al., 2016; Ma et al., 2014; Noble, 2023), and which are already identified as controlling gene expression. Interaction between transcription factors and the chromosomal material is not random (Suter, 2020). The nucleosome fibre topology guides transcription factor binding (O'Dwyer et al, 2024). The same targeted pathways can be speculated as functioning to enable targeted gene-editing (Noble, 2023). All of these interactions are both ways, up and down, as system properties. Causality cannot be attributed to just one level of organisation.
2. A downward (hatched) arrow from the functional networks to proteins. This represents the fact that the networks control the specific folding and function of proteins. Protein folding is not entirely specified by the

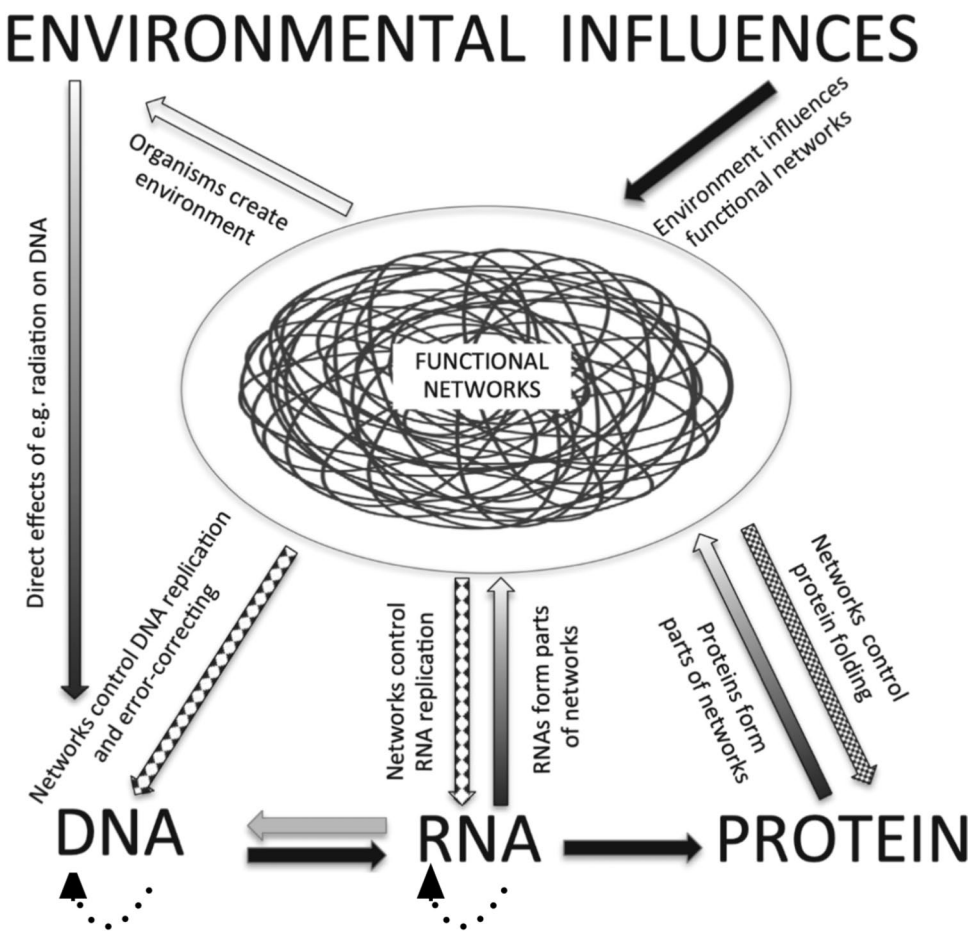

Fig. 1 Completion of the original 'Central Dogma' diagram by including the causal influences of the environment exerting effects through the functional physiological networks (From Figure 2.3 in (Noble & Noble, 2023, p. 26), as annotated in Noble (2023, Figure 3). Note also the replacement of solid arrows with dotted arrows for the *self*-replication of nucleotides. Self-replication outside a living cell achieves an error rate approaching 1 in around 4–10 K nucleotides. By contrast, the living cell orchestrates molecular proofreading processes that can achieve 1 in 10 billion

amino acid sequence. For example, the protein aconitase can switch from metabolising sugar to promoting iron intake into red blood cells (Frishman & Hentze, 1996). This lability depends on whether the protein sits in a lipid membrane to be constrained by its influence on its folding or function, or whether it sits as part of metabolic networks within the aqueous cell fluids. Around 70% of protein domains are disordered, and dependent in this way on cellular context for their functionality (Ball, 2024). Furthermore, comparison of genes for proteins from different species shows that some have evolved by accretion of existing functional domains (Noble, 2023, Fig. 2; Human Genome Sequencing Consortium, 2001, figure 42). Many proteins that have evolved in this way will have multiple functions, as also emphasised by Philip Ball (2024, chapter 4).

3. Two downward arrows from the environment, one representing direct radiation-induced changes in DNA, the other representing epigenetic changes via the functional networks.
4. Upward arrows representing the fact that RNAs and proteins form important elements in the functional networks, and that the activity of organisms contributes to changes in the environment (see Fig. 2 below).
5. We have represented the self-replication of DNA and RNA with dotted arrows to show that they are only very partial *self*-replicators. Strictly speaking, there should be further downward arrows from the functional networks to these arrows since the fidelity of replication is finally dependent on cut and paste enzymes controlled by those networks. They enable the living cell to orchestrate the faithful replication of DNA. DNA on its own cannot achieve that accuracy. It depends on the cell orchestrating the molecular proof-reading processes that can achieve and error rate of only 1 in 10 billion.

All these additional causal actions represented in this diagram are fully documented. It is no longer possible to consider Crick's original diagrams of the 'Central Dogma' in isolation from the living system itself. This is also obvious from the further fact that accurate replication of DNA is ensured by active processes in the living cell. Long sequences of DNA cannot be *self*-replicators. Therefore, the curved self-replication arrows for DNA and RNA are seriously inadequate for nucleotide sequences longer than a few tens of thousands of bases. Only small viral genomes can be expected to replicate "like a crystal" (Crick, 1970; Schrodinger, 1944). That is why we have replaced Crick's

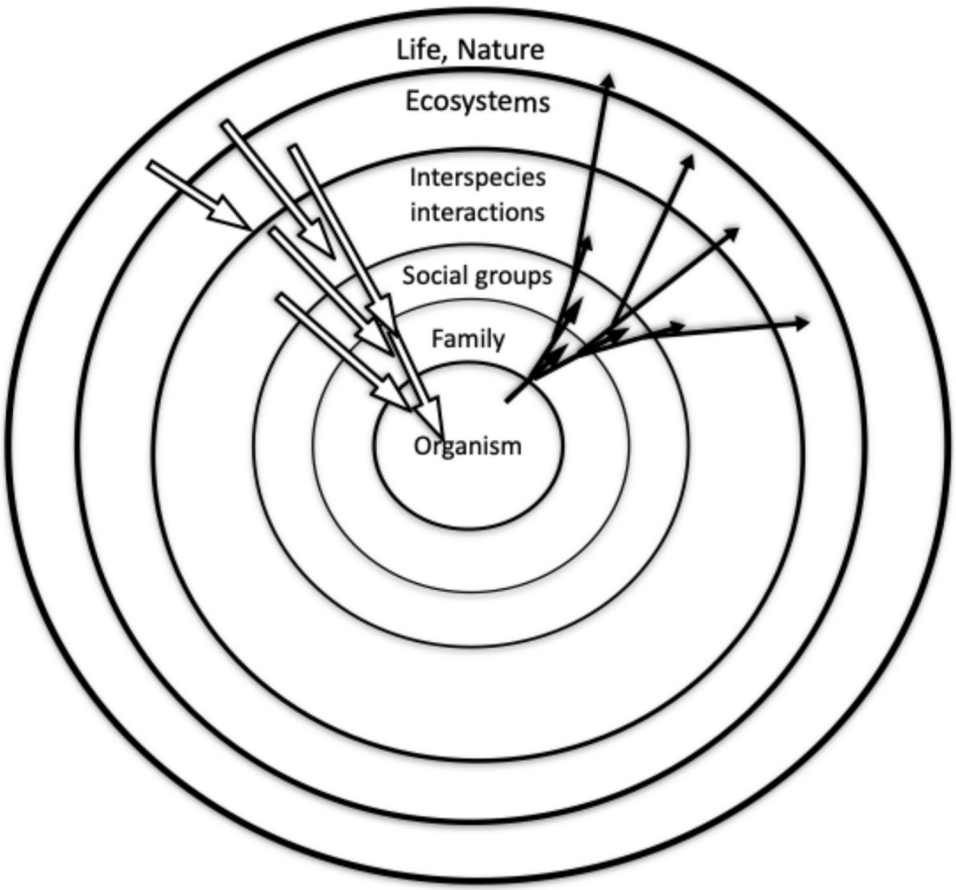

Fig. 2 represents the interactions between organisms and their environment, with particular emphasis on the environmental impact of the social interactions (From Figure 4-3 in *Understanding Living Systems*)

solid arrows with dotted arrows to represent the fact that self-replication of nucleotides is only partial, and is far from accurate enough for cell division to pass on a faithful copies of the genome.

Crick's important chemical fact (DNA —> RNA —> proteins) is therefore no longer a 'central dogma' since it cannot exclude the processes of gene regulation and gene editing by the organism in response to environmental conditions. So the so-called 'dogma' then becomes simply the lowest molecular part of the functional openness of living organisms (see also Fig. 3 below). This is the very opposite of Crick's intentions when he first formulated the 'dogma' in 1958, and its revision in 1970. Anyway, there should be no dogmas in science. They are the very antithesis of what science is about, and what it can do. Science progresses by being open to new interpretations in the light of new evidence. Dogma restricts science in the search for new ideas.

How the Environment, Including Social Environment, Influences Organisms, and Vice-Versa

A major feature of our recent book, *Understanding Living Systems*, is that it derives much of its philosophical outlook from regarding organisms as definitively purposive. The fact that the tendency for schizophrenia to run in families derives from environmental factors rather than simple genetic causation is highly relevant to that outlook. So also is search for ways to alleviate or remove the problem, since it is then clearly important for therapy to consider purposive social interactions between people. What Charles Darwin called Sexual Selection, and which we include in what we call Social Selection, is a major part of what forms the environment of social beings like humans, and many other organisms. We, like other organisms, are niche creators and a fundamental part of our niche is our interaction with others and is psychosocial. This psychical space is full of uncertainty. It cannot therefore be genetically determined.

How, though, to represent this form of causation? Social interactions are not just another level of organisation since social causation inevitably introduces the criterion of meaning. An immaterial cause of this kind cannot be represented as just another level of physical causation. Instead, we represent it as a series of concentric circles: family, social groups, interspecies interactions, ecosystems and nature as a whole. Looked at from this perspective, surprisingly little of the environment is physical. Much is attributable to the purposive actions of other organisms as agents. Such forms of causation, where organisms conform to the social values of their group, have a form of priority within the principle of Biological Relativity (Noble & Ellis, 2022; Noble & Noble, 2020).

The Neo-darwinist Modern Synthesis view of evolution simply ignores these forms of causation. As Futuyma and Kirkpatrick say in their book, *Evolution* (Futuyma & Kirkpatrick, 2018, p. 20), "The concept of purpose plays no part in scientific explanation." This is unfortunate because, although it is uncertain, it is a major ingredient of life and a primary determinant of our behaviour. By contrast, Charles

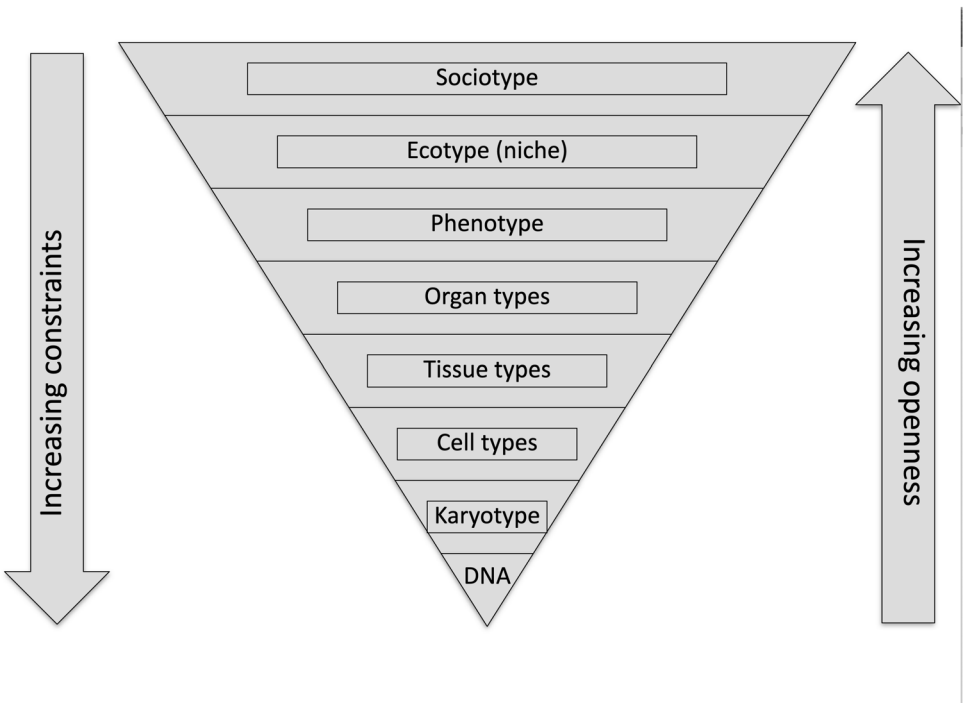

Fig. 3 The multiple levels of organisation in organisms (From Figure 8-2 of *Understanding Living Systems*). Note that the top levels would be better represented as in Fig. 2, but it is difficult to see how to represent such features in a 2 dimensional diagram

Darwin in 1871 (Darwin, 1871, p. 245) introduced the concept of Sexual Selection as *intentional* conscious choice in organisms. We completely agree. From a medical science perspective, as the Schizophrenia story tells us, it is impossible for a complete approach to nervous diseases to ignore purpose and agency. How else could therapists manage their treatments? Those therapies are not called *psycho*therapy for no reason!

The Openness of Organisms

Figures 1 and 2 clearly demonstrate that organisms, including their genes, are open systems, interacting with and on their environment. Intentionality *requires* an organism to be an open system. It is incorrect to isolate genes as "sealed off from the outside world" (Dawkins, 1976, p. 21), since the 'Central Dogma' should not be interpreted to mean that organisms cannot edit their genomes. They clearly do so, as the immune system demonstrates every time it makes new immunoglobulins (Odegard & Schatz, 2006), and as must be the case generally since mutation rates have long been known to be sensitive to stress conditions (McClintock, 1984; Shapiro, 2011, 2022).

Figure 3 expresses this openness in terms of a triangular arrangement of the levels of organisation in living systems. This diagram reverses the normal way in which twentieth century biology interpreted the levels. DNA, at the bottom of the triangle is the most constrained and least 'free' level. That must be so since it is just a chemical, and must do what the chemical energy levels of interactions dictate. To serve the functional purposes of the organism itself they must be constrained by organisation at the higher levels. At the top, we represent the sociotype as the most open and 'free' level. That must be true. It is the level least constrained by the laws of chemistry. Going down the triangle we encounter increasing constraint since each level of organisation constrains the level below it. Going up the triangle represents increasing openness, as more and more conditional processes are represented in the patterns of organisation progressively superimposed during evolution of, and at, all levels (see Fig. 4).

What Does 'Selfish' Mean Metaphorically?

Interpreting the word 'selfish' in Selfish Gene Theory literally is therefore clearly a mistake. Chemicals are not free to choose what they do. Furthermore, such freedom is a necessary capacity for choosing to be selfish as opposed to being cooperative. Chemicals can be neither. Yet, in 1982, reacting to criticism from a philosopher (Midgley, 1979) writing in passing "this metaphor, the selfish gene…", Dawkins replied:

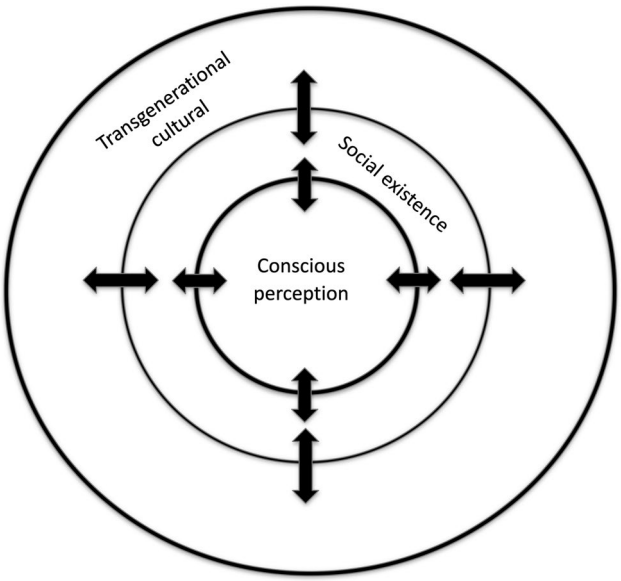

Fig. 4 Functional interactions between social existence and conscious organisms with agency. Agents with conscious perception interaction across functional boundaries with their social existence, which in turn facilitates interaction through trans-generational cultural inheritance, allowing the creation of cultural ideas, viewpoints, opinions, attitudes and actions. The double-headed arrows indicate that there is no privileged circle of interaction (From Figure 6-2 in *Understanding Living Systems*)

> "That was no metaphor. I believe it is the literal truth, provided certain key words are defined in the particular way favoured by biologists." (Dawkins, 1981)

This is strange for two reasons. Surely no scientist familiar with the rules of chemistry can be serious about saying that a chemical is *literally* selfish. But, look carefully at Dawkins' qualification "provided certain key words are defined in the particular way favoured by biologists". A metaphor is precisely using one word, defined in a particular new way, to redefine the meaning. What Dawkins may not have realised is that his qualification is precisely the *definition* of what the word metaphor *means*: changing the use of a word from its common meaning. But:

> "A metaphor does not cease to be a metaphor simply because one defines a word to mean something other than its normal meaning. Indeed, it is the function of metaphor to do *precisely* this" (Noble, 2011, p. 1009).

We conclude that there is no way in which 'selfish' can be literal in Selfish Gene Theory.

How then does it fare as a metaphor? One of the most colourful metaphorical passages in *The Selfish Gene* is this paragraph:

> "Now they swarm in huge colonies, safe inside gigantic lumbering robots, sealed off from the outside world,

> communicating with it by tortuous indirect routes, manipulating it by remote control. **They are in you and me**; they created us body and mind; and their preservation is the ultimate rationale for our existence." (Dawkins, 1976, p. 21)

This paragraph contains almost the entirety of the Selfish Gene thesis and is a tribute to the brilliance of Dawkins' writing. Every phrase is metaphorical, except for the boldface sentence "**They are in you and me**" which is clearly literal. The metaphors correspond to 1. The organism is a mechanical robot, 2. genes are isolated from the environment and the organism, 3. they manipulate that organism, 4. creating us 'body and mind'; 5. they, not we, are why we exist.

Since all these key phrases are metaphorical *The Music of Life* (Noble, 2006, chap 1) proposed a metaphorical experiment to test whether the ideas are susceptible to any empirical verification: change each metaphorical phrase to mean its opposite. We then have:

> "Now they are trapped in huge colonies, locked inside highly intelligent beings, moulded by the outside world, communicating with it by complex processes, through which, blindly, as if by magic, function emerges. **They are in you and me**; we are the system that allows their code to be read; and their preservation is totally dependent on the joy we experience in reproducing ourselves. We are the ultimate rationale for their existence." (Noble, 2006, p. 12).

Once again, the only literal phrase is the same sentence in **bold face**. All the rest are metaphorical opposites of the phrases in the original text. The challenge is to think of any biological experiment that could distinguish between the two metaphorical paragraphs. After nearly 2 decades from publication of *The Music of Life* in 2006 no-one has proposed such an experiment. There isn't one because there is no *empirical* difference between the two opposing metaphorical statements. Dawkins implicitly admits this fact when he writes that he could have chosen "The Cooperative Gene" as his title for *The Selfish Gene* and that this title would also have been "true to its content". (Dawkins, 2016, p. 195) Selfish Gene Theory, whether interpreted literally or metaphorically is not a scientific theory (Noble, 2011). It is not testable. It is a deep philosophical muddle, presenting itself in the clothes of a valid scientific theory.

Selfishness can only be understood at the level of reason and situational logic, and its literal meaning involves the freedom to choose, As we have shown, reason and situational logic, including emotional intelligence, influence material functionality. By ignoring purpose, it removes such reasoning as causal. In *Understanding Living Systems* we use the example of 'Jack and Jill going up the hill to fetch a pail of water'. We can only understand their behaviour from their purpose, yet we cannot always, if ever, be certain of it. This openness and uncertainty can itself be causal in creating emotions, anxieties. It also carries an ethical burden; the responsibility for the consequences of our decisions and actions. These are only understood at the level of reason. Pejorative judgements, such as selfishness, assumes the ability to choose, but also the understanding that we are free to choose. Being selfish is often used pejoratively. We worry about what others think of us; Our psychosocial being is a powerful causal constraint on our physical wellbeing. Mental illness can then be a consequence.

Analysis of the Literal and Metaphorical Uses of "Selfish Genes"

Table 1 summarises the status of literal and metaphorical uses of the phrase "selfish genes". For all molecules and molecular systems that do not have agency, the literal use is clearly meaningless. Literal selfishness or its opposite, altruism, can only be meaningfully and literally attributed to systems capable of choice. In practice that means whole organisms, or perhaps AI systems that might be developed to have agency.

Table 1 Analysis of Literal and Metaphorical Uses of "Selfish Genes"

What is a gene?	Literally selfish?	Metaphorically selfish?	Metaphor empirically verifiable?
DNA	No—attribution to chemicals meaningless	Yes	No—no difference between opposing metaphors
Chromosomal material	No—attribution to chemicals meaningless	Yes	No—no difference between opposing metaphors
Any 'honorary gene'	No—attribution to chemicals meaningless	Yes	No—no difference between opposing metaphors
All epigenetic inheritance	No—attribution to chemicals meaningless	Yes	No—no difference between opposing metaphors
All traits	Yes—if this amounts to the whole organism	Yes—but not useful	No—since cause and effect are the same thing, the whole organism

For each possible definition of "gene" we have asked whether an empirical test could distinguish between opposing metaphorical statements, as in the example above from *The Music of Life*. Very similar opposing metaphors could be developed for all definitions of "gene" so those tests would also fail.

The only way for a literal interpretation of "selfish" to work would be to define "gene" to be the whole organism. That, of course, would necessarily be self-defeating for a gene-centric theory of living organisms.

Conclusions

This article has already summarised the philosophical difficulties with Selfish Gene Theory. It is not an empirically testable scientific theory. Its metaphorical components amount to tautologies, while its reliance on accurate *self*-replication of DNA is simply incorrect.

Ultimately, though, theories are also judged by the practical outcome of following and using them. By that criterion also, gene-centric biology has been a failure. We conclude with quotations from the four of the most important assessments using that criterion.

> "Polygenic risk scores performed poorly in population screening, individual risk prediction, and population risk stratification. Strong claims about the effect of polygenic risk scores on healthcare seem to be disproportionate to their performance." (Hingorani et al., 2023, p. 1)

The conclusion of this important study is compatible with the fact that most association scores between genes and common diseases are very small.

> "the Human Genome Project may ultimately justify its $2.7 billion cost outside the realm of medicine. It has already contributed significantly to our understanding of human evolution." (Torrey, 2024)

As this article implies, genomics is best viewed as contributing to fundamental science, rather than as a quick way to solve clinical problems.

> "Most association levels are small, so much so that we can be sure that such methods do not reveal causation. In reality, the regulatory networks simply buffer organisms from most genetic changes." (Pascual & Noble, 2025).

Philip Ball (2024) refers to what is needed as the 'New Biology' and concludes:

> "…we may start to see the benefits of new ways of thinking that acknowledge the autonomies of life's hierarchical organisation, the absence of any privileged level of significance, and the organic uniqueness of its modes of operation—in what we can cure, what we can make, and what we can understand. (p 451)

These conclusions are clear. Gene-centric biology may still contribute to treatments of the 5% of the population suffering from mono-genetic disorders, and the contribution of genomics to fundamental biology is important, particularly for reconstructing the evolutionary trees of life, but the promises of cures for common diseases affecting the great majority of people have simply not materialised. Popular gene-centric interpretations of evolution have encouraged this misunderstanding, which is why less dogmatic interpretations of evolutionary biology are now necessary. Therapeutic approaches need now to be focussed on functional understanding of physiological networks that control the ways in which organisms use their DNA templates. Without understanding that control, genomics alone cannot deliver its promises.

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Declarations

Conflict of interest The authors declare no competing interests.

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