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TOPICAL REVIEW

Neo-Darwinism, the Modern Synthesis and selfish genes: are they of use in physiology?

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This article argues that the gene-centric interpretations of evolution, and more particularly the selfish gene expression of those interpretations, form barriers to the integration of physiological science with evolutionary theory. A gene-centred approach analyses the relationships between genotypes and phenotypes in terms of *differences* (change the genotype and observe changes in phenotype). We now know that, most frequently, this does not correctly reveal the relationships because of extensive buffering by robust networks of interactions. By contrast, understanding biological function through physiological analysis requires an *integrative* approach in which the activity of the proteins and RNAs formed from each DNA template is analysed in networks of interactions. These networks also include components that are not specified by nuclear DNA. Inheritance is not through DNA sequences alone. The selfish gene idea is not useful in the physiological sciences, since selfishness cannot be defined as an intrinsic property of nucleotide sequences independently of gene frequency, i.e. the 'success' in the gene pool that is supposed to be attributable to the 'selfish' property. It is not a physiologically testable hypothesis.

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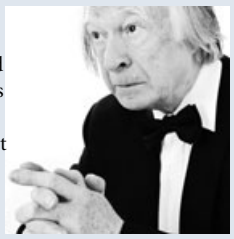
Introduction

Interpreting molecular genetic information in terms of higher level functions in the organism is a major current goal in the physiological sciences, as is the reverse strategy of bottom-up reconstruction: they complement each other. Computational systems biology is one of the tools being used (Kohl & Noble, 2009; Hunter *et al.* 2011). Achieving this goal could also be a route through which physiology can reconnect with developmental and evolutionary biology. I will explain why some central aspects of neo-Darwinism (or the Modern Synthesis – in this article I am not always distinguishing between them), and their most popular expression in *The Selfish Gene* (Dawkins, 1976, 2006), form a barrier to the new synthesis required between physiology and evolutionary theory. The barrier can be removed by taking an integrative, multilevel approach in which genes and many other components of organisms that are inherited are viewed as co-operating in networks to express what we call the phenotype (Kohl *et al.* 2010 Fig. 2, reproduced here as Fig. 1 below). In this paper, 'co-operative genes' carries this sense, which should be clearly distinguished from the idea of genes 'for' co-operative behaviour used widely in ecology, animal behaviour and economics. Attributes like 'selfish' and 'cooperative' have different meanings when applied to objects or ensembles at different levels. Cooperation at the level of protein networks, for example, may occur even if the organism in which they cooperate is 'selfish' at the level of the phenotype, and vice versa. The concept of level in evolutionary theory requires careful analysis



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(Gould, 2002; Okasha, 2006). Concepts and mechanisms do not necessarily carry through from one level to another – an important point to bear in mind also in multi-level physiology.

I start with a clarification of the relationship between neo-Darwinism, the Modern Synthesis and the selfish gene idea. Neo-Darwinism (a term introduced by the physiologist Georges Romanes (1883)) and its development (see Pigliucci & Muller, 2010*a* for the relevant history) into the Modern Synthesis (Huxley, 1942) as a gene-centred view of evolution can of course be stated without reference to the selfish gene idea. Neo-Darwinism is the term popularly used, even today, for the synthesis between Darwin's theory of evolution by natural selection and the assumption that the variations on which selection acts are produced solely or primarily by gene mutations, though the term Modern Synthesis is more correct since Romanes coined the term neo-Darwinism before Mendel's work on genetics was rediscovered. The Modern Synthesis adds discrete (Mendelian) inheritance to neo-Darwinism. Alternatives to the Modern Synthesis include: symbiogenesis, the idea that major steps in evolution, such as the formation of eukaryotes and multicellular organisms, resulted from cooperation and/or fusion between different organisms; horizontal gene transfer within and between organisms (Woese & Goldenfeld, 2009; Goldenfeld & Woese, 2011), a process now known to extend beyond prokaryotes (Keeling & Palmer, 2008); and the inheritance of acquired characteristics, commonly but mistakenly (Noble, 2010*b*) called 'Lamarckism'. For further examples see Pigliucci & Muller (2010*a*, particularly their Fig. 1.1; 2010*b*) and Jablonka & Lamb (2005).

In the rest of this article reference to neo-Darwinism should be taken to include the Modern Synthesis. The selfish gene idea (Dawkins, 1976, 2006) is a popularization of neo-Darwinism which goes beyond it to characterise genes as elements in organisms with specific (selfish) behaviour. As we will see later, it was originally formulated as a literal scientific hypothesis. The question of its status is a major focus of this paper.

Another way of stating the claims of this article is that they are twofold: first, that neo-Darwinism is, at the least, incomplete as a theory of evolution. Second, that the selfish gene idea adds nothing since it is essentially empty. These are separate claims, even though in the minds of many biologists neo-Darwinism and the selfish gene idea are not always clearly distinguished. Neo-Darwinism is capable of falsification. Indeed, in its original form as a *complete* theory, it has already been falsified. We now need to admit processes outside its remit, so that it needs to be extended (Woese & Goldenfeld, 2009; Pigliucci & Muller, 2010*b*).

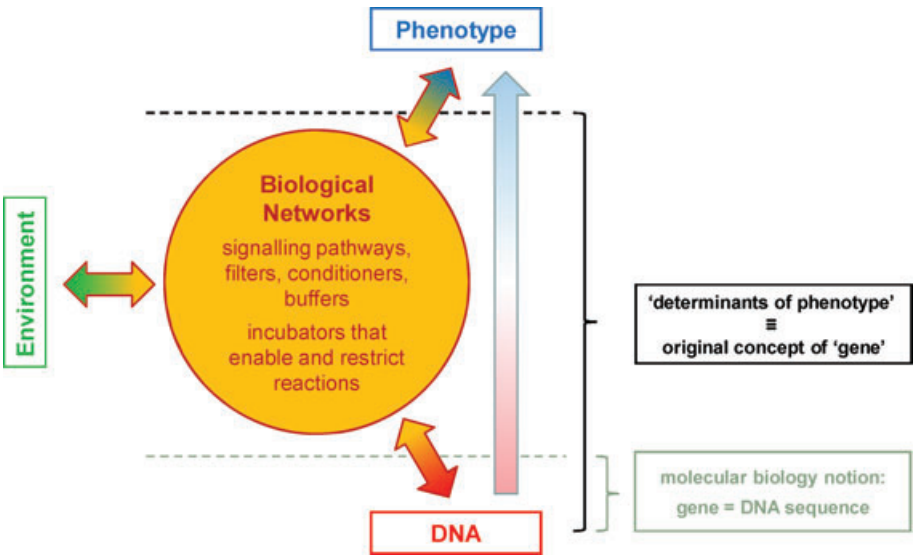

Figure 1. Relations between genes, environment and phenotype characters according to current physiological and biochemical understanding
This diagram represents the interaction between genes (DNA sequences), environment and phenotype as occurring through biological networks. The causation occurs in both directions between all three influences on the networks. This view is very different from the idea that genes 'cause' the phenotype (right hand arrow). This diagram also helps to explain the difference between the original concept of a gene as the cause of a particular phenotype and the modern definition as a DNA sequence. For further description and analysis of the ideas behind this diagram see Kohl *et al.* (2010) from which the diagram is reproduced. Reprinted by permission from Macmillan Publishers Ltd: *Clinical Pharmacology and Therapeutics* 88, 25–33; ©2010 .

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As I will show in this paper, the selfish gene idea is not even capable of direct empirical falsification; it has to be judged by different criteria.

The concept of a gene has changed, and is still changing, so what version do we use?

A serious problem in assessing the nature and utility of the selfish gene story in physiological research is that the concept of a gene has changed (see Fig. 1) in fundamental ways (Pichot, 1999; Keller, 2000; Beurton *et al.* 2008). We are dealing with a moving target. From being the (hypothetical allelic) cause of each phenotype character, such as eye colour or number of limbs, the developments in molecular biology have led to its being defined more narrowly and specifically as a DNA sequence that is used by the cell as a template for the synthesis of a protein or RNA. These are not at all the same thing when it comes to questions like 'what do genes do?' and 'what kind of causation is involved?' When Johannsen (1909) introduced the term 'gene' it was *defined* as the (necessary) cause of a phenotype, since it was defined as an inherited phenotype that could be attributed to an allele. But now it has to be *shown* to be a cause, and the nature of that causation needs clarification. The full implications of this difference are explained elsewhere (Noble, 2008). They are reinforced by the fact that most changes at the level of DNA do not have a measurable phenotypic effect under normal physiological conditions (see, for example, Hillenmeyer *et al.* 2008). By the original definition, these would not even have been identified as genes, since a gene was an entity that necessarily had a phenotypic manifestation.

In this article, I frequently refer to the selfish gene idea as a story since one of the questions I am addressing is whether it is more than a story or viewpoint. Colourful metaphorical stories can be highly influential: no-one can deny that the selfish gene idea has had a huge impact on the way in which both lay people and scientists view genetics, including the social implications (Midgley, 2010). Most of the time, people accept its implied scientific basis. It is important therefore to ask whether the idea could be interpreted as an empirical scientific hypothesis, particularly since Dawkins's own initial interpretation was that it was not metaphorical; in reply to Midgley (1979) he wrote: 'that was no metaphor. I believe it is the literal truth, provided certain key words are defined in the particular ways favoured by biologists' (Dawkins, 1981). 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. So, we must first clarify what the idea means.

Is the 'selfish gene' story metaphor or empirical science or both?

Genes, as DNA sequences, do not of course form selves in any ordinary sense. The DNA molecule on its own does absolutely nothing since it reacts biochemically only to triggering signals. It cannot even initiate its own transcription or replication. It cannot therefore be characterised as selfish in any plausible sense of the word. If we extract DNA and put it in a Petri dish with nutrients, it will do nothing. The cell from which we extracted it would, however, continue to function until it needs to make more proteins, just as red cells function for a hundred days or more without a nucleus. It would therefore be more correct to say that genes are not active causes; they are, rather, caused to give their information by and to the system that activates them. The only kind of causation that can be attributed to them is passive, much in the way a computer program reads and uses databases. The selfish gene idea therefore has to be interpreted not only as a metaphor, but as one that struggles to chime with modern biology. That is where the difficulties begin.

Ideas that incorporate or are based on metaphors have a very different relationship to empirical discovery than do standard scientific hypotheses with clear empirical consequences that ensure their falsifiability. There are several ways in which this is evident.

First, different or even opposing metaphors can both be 'true'. This is because metaphors highlight different aspects of the target to which they are applied, a fact that has long been familiar to metaphor theorists (Lakoff & Johnson, 1980; Kittay, 1987). Metaphors can correspond to different, even incompatible, aspects of reality. That is why, when comparing 'selfish' genes with 'prisoner' or 'cooperative' genes, as I do in chapter 1 of *The Music of Life* (Noble, 2006), there is no empirical test that will unequivocally show which is correct, a point which was conceded long ago by Richard Dawkins at the beginning of his book *The Extended Phenotype*: 'I doubt that there is any experiment that could prove my claim' (Dawkins, 1982, p. 1). This point is analogous to the sense in which no experiment could ever disprove a geometry, whether Euclidean or not (Poincaré, 1902, 1968). Significantly, Dawkins uses a geometric illusion (the Necker Cube) to illustrate his point.

(*The Extended Phenotype* was an even stronger statement of the selfish gene idea since it argued that "the phenotypic effects of a gene. . .may extend far outside the body in which the gene sits" (Dawkins, 1982, p. vi) Even effects "at a distance" are seen as being "for the benefit" of the selfish gene.)

Second, metaphors often appear circular if interpreted like a scientific theory. I will show that the selfish gene metaphor shows this circularity.

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Finally, even though there may be no single empirical fact that will distinguish between very different metaphors, this does not mean that empirical discovery has no impact on our choice of metaphor. The relationship is more nuanced than it may be for most scientific theories. It will usually require a judgment based on a large set of empirical facts to arrive at a conclusion. Much of the meaning associated with metaphorical statements is determined by viewpoints that are a matter of personal choice, even though influenced by empirical facts. I will illustrate this later in this paper.

What does 'selfish' mean in the selfish gene story?

First we must decide whether 'selfish' defines a property that is universal to all genes (or even all DNA sequences) or whether it is a characteristic that distinguishes some DNA sequences from others. This is not as easy as it may seem. I suspect that the original intention was that all genes could be represented as 'seeking' their own success in the gene pool, regardless of how effective they might be in achieving this. One reason for thinking this is that so-called junk DNA is represented in the selfish gene story as an arch-example of selfishness: hitching a ride even with no function.

But on that interpretation, the demonstration that the concept is of no utility in physiological science is trivially easy. Interpreted in this way, a gene cannot 'help' being selfish. That is simply the nature of any replicator. But since 'selfishness' would not itself be a difference between successful and unsuccessful genes (success being defined here as increasing frequency in the gene pool), nor between functional and non-functional genes, there would be no cashable value whatsoever for the idea in physiology. Physiologists study what makes systems work. It matters to us whether something is successful or not. Attributing selfishness to all genes therefore leaves us with nothing we could measure to determine whether 'selfishness' is a correct attribute. As metaphor, it may work. But as a scientific hypothesis it is empty.

Could we rescue the idea for physiological science? I doubt whether anyone would want to do that *ab initio*, but we live in a scientific culture that is now thoroughly permeated by the idea, and in a way that has strongly disfavoured physiology. The idea has either to be rejected or assimilated. One option would be to re-interpret selfishness to include reference to effectiveness. We could, for example, say that genes whose numbers of copies increase are selfish, or more selfish than their competitors. This move would give us an empirical handle on the idea.

It is a standard move in science to unpack a metaphor or simile in this way. Physicists make similar moves when they give empirical criteria for black holes, quarks, strings and many other strange new entities in their theories. Without an empirical handle they might as well not exist. Indeed, one of the arguments about string theory, for example, is precisely whether it has satisfied this fundamental criterion.

Moreover, including reference to effectiveness, which in evolutionary theory could be interpreted to be fitness, is surely the most relevant way to gain empirical leverage. We can measure changes in gene copies in a population. Now the question becomes whether we can develop the theory a bit further to become predictive. What, in a gene, could tell us whether or not it is selfish in this sense?

On the original definition of a gene as a hypothetical cause of a particular phenotype, this would have been fairly straightforward. We could look, at the functional level of the phenotype, for the reasons why a particular function would be adaptive. This is in practice what defenders of the selfish gene idea do. They refer to the gene (more strictly an allele) as 'the gene for' X or Y, where these are functional, phenotype characters. The phenotype view creeps back in through the terminology. Any 'selfishness' lies at least as much in the phenotype as in the genes.

But since we now define genes as particular DNA sequences, what in a DNA sequence could possibly tell us whether or not it is selfish? The answer is obvious: the sequences of Cs, Gs, As and Ts could never, by themselves, give us a criterion that would enable us to predict that the frequency of that sequence will increase in the gene pool. A DNA sequence only makes sense in the context of particular organisms in which it is involved in phenotypic characteristics which can be selected for. A sequence that may be very successful in one organism and/or environment, might be lethal in another. This is evident in the fact that almost all cross-species clones do not form an adult (see later for an important exception). The same, or similar, DNA sequence may contribute to different, even unrelated, functions in different species. The sequence, intrinsically, is neutral with regard to such functional questions.

The price therefore of giving the selfish gene idea some empirical leverage is to reveal yet again, though in a different way, that it is an empty hypothesis. There is no criterion independent of the only prediction that the hypothesis makes, i.e. that selfish genes increase their number. It is a strange hypothesis that uses its own definition of its postulated entity as its only prediction.

At this point, I suspect that a defender of the concept would shift back to referring to genes as hypothetical entities, defined as the cause(s) of particular phenotypes. Note, though, that this is to abandon the purely 'genes-eye' view since it shifts the focus back to the phenotype. As a physiologist, naturally I would say 'so it should'. I will discuss the consequences of that shift in a later section.

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How is the selfish gene story related to the central dogma?

In one of the central paragraphs of *The Selfish Gene* (page 21), Dawkins writes:

> 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.

The phrase 'sealed off from the outside world' is a colourful statement of the idea that genes are uninfluenced by their environment, a view that was strongly buttressed by the central dogma of molecular biology, originally formulated by Crick (1958, 1970) and taken to exclude information flow other than from genes to proteins. In fact, of course, what the molecular biology showed was simply that amino acid sequences are not used as templates for forming nucleic acid sequences. The unjustified extension was to think that *information* cannot pass from proteins to nucleic acids, whereas this is precisely what must happen for genes to be activated and for expression patterns to be formed. This extension (which can be seen in phrases like "the inheritance of instructively acquired adaptation would violate the 'central dogma' of embryology" (Dawkins, 1982, p. 173) was a godsend to the neo-Darwinists since it provided a basis, right down at the level of DNA itself, for regarding genes as 'sealed off' from the outside world. The original experimental basis for this idea was the Weismann (1893) barrier.

A godsend, except that it is not correct in the relevant sense, and never has been. Even at the time the dogma was formulated, it was sufficient to ask the question how do different cells in the body, with exactly the same genome, end up as different as bone cells and heart cells? The answer of course is that the way in which the genome is read leads to completely different patterns of gene expression. This requires flow of information onto the genome itself, which, as Barbara McClintock (1984) said, should be regarded as an 'organ of the cell', not its dictator. There are feedbacks and restraints, not only between the products of the genes (which might be consistent with a genes-eye view), but right down onto the genome itself, determining when, where and how much of each gene product is formed. As Beurton *et al.* (2008) comment 'it seems that a cell's enzymes are capable of actively manipulating DNA to do this or that. A genome consists largely of semistable genetic elements that may be rearranged or even moved around in the genome thus modifying the information content of DNA.'

The central dogma, as a general principle of biology, has therefore been progressively undermined. The only aspect of it still left intact is its original strictly chemical sense, i.e. that protein sequences are not used as templates for forming DNA or RNA sequences. All other aspects of the way in which the dogma has been extended to buttress neo-Darwinism have been deconstructed – by molecular biology itself. Shapiro's (2009) article is the best account of the demolition from a biochemical viewpoint, while Werner (2005) does so from an informatics perspective.

Are genes the only immortals?

A central distinction in the selfish gene story is that between replicators and vehicles. The distinction is based on considering inheritance only of *changes*. While the vehicle is also 'inherited' (genes on their own do nothing and certainly are not sufficient to 'make' an organism – since we *must* also inherit a complete fertilised egg cell), the story goes that *changes* in the vehicle are not inherited (so no inheritance of acquired characteristics) while *changes* in the replicator (e.g. mutations) are inherited. This approach is what enables the wholesale inheritance of the vehicle to be ignored.

Yet, the vehicle (the cell, or each cell in a multicellular organism) clearly does reproduce (indeed, it is only through this reproduction that DNA itself is transmitted), and in doing so it passes on all the phenotype characteristics for which there are no nuclear DNA templates and which are necessary to interpret the inherited DNA. An obvious example is the transmission of mitochondria, chloroplasts and other organelles, which almost certainly originated as symbionts ('invading' or 'engulfed' bacteria) at an early stage of evolution when eukaryotes were first formed. Many other transmitted cytoplasmic factors also exist (Sun *et al.* 2005; Maurel & Kanellopoulos-Langevin, 2008). All these replicate and, in the selfish gene story would have to be given the status of 'honorary genes'.

The existence of such cellular inheritance requires the selfish gene theory to distinguish between replication and reproduction. The next step in the story is to claim that replicators are potentially immortal, whereas reproducers are not.

Biologically speaking, this is evident nonsense. Through germline cells I am connected via many reproductions to the earliest cells, *even to those without genomes*. In some sense, the cell as a whole has achieved at least equivalent immortality to that of its DNA. Cells, even those without genomes in the postulated pre-DNA world of RNA enzymes (Maynard Smith & Szathmáry, 1999), clearly reproduce themselves, and in doing so they also pass on any differences among them (Sonneborn, 1970; Sun *et al.* 2005). Any difference between replication and reproduction (which, after all, are just synonyms; the distinction is a linguistic confusion) does not entitle one to say that one is immortal and the other is not. What were all those cells without genomes doing in early life on earth? We wouldn't be here to tell the story if they

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did not also form an 'immortal line'. As I have argued elsewhere (Noble, 2008) the main difference between DNA and non-DNA inheritance is simply that one is digital, the other analog. In developing the organism the 3D analog information is just as necessary as the 1D digital (DNA) information. Neither is sufficient by itself. They are mutually dependent. The amount of analog information can also be calculated to be comparable to that of the genome (Noble, 2011). Moreover, organisms are not in fact digital machines (Shapiro, 2005; Noble, 2010*a*).

The genetic differential effect problem

Clearly, many of the problems with the selfish gene story arise from unusual or imprecise use of the language of genetics, leading to untestable ideas. Another central muddle, both in neo-Darwinism and in the selfish gene story, is what I have called 'The genetic differential effect problem' (Noble, 2008, 2011), the idea that genetics is only about differences. This view is now unsustainable, since defining genes as DNA sequences clearly does identify a specific chemical entity whose effects are not merely attributable to differences in the sequence. We can say precisely for which proteins or RNAs the sequence acts as a template and analyse the physiological effects of those proteins or RNAs. The arguments for abandoning the difference perspective are overwhelming (see also Longo & Tendero, 2007).

Differences in DNA do not necessarily, or even usually, result in differences in phenotype. The great majority, 80%, of knockouts in yeast, for example, are normally 'silent' (Hillenmeyer *et al.* 2008). While there must be underlying effects in the protein networks, these are clearly buffered at the higher levels. The phenotypic effects therefore appear only when the organism is metabolically stressed, and even then they do not reveal the precise quantitative contributions for reasons I have explained elsewhere (Noble, 2011). The failure of knockouts to systematically and reliably reveal gene functions is one of the great (and expensive) disappointments of recent biology. Note, however, that the disappointment exists only in the gene-centred view. By contrast it is an exciting challenge from the systems perspective. This very effective 'buffering' of genetic change is itself an important systems property of cells and organisms.

Moreover, even when a difference in the phenotype does become manifest, it may not reveal the function(s) of the gene. In fact, it cannot do so, since *all* the functions shared between the original and the mutated gene are necessarily hidden from view. This is clearly evident when we talk of oncogenes. What we mean is that a particular change in DNA sequence predisposes to cancer. But this does not tell us the function(s) of the un-mutated gene, which would be better characterised in terms of its physiological function in, e.g., the cell cycle. Only a full physiological analysis of the roles of the protein it codes for in higher-level functions can reveal that. That will include identifying the real biological regulators as systems properties. Knockout experiments by themselves do not identify regulators (Davies, 2009).

So, the view that we can only observe *differences* in phenotype correlated with *differences* in genotype both leads to incorrect labelling of gene functions and falls into the fallacy of confusing the tip with the whole iceberg. We want to know what the relevant gene products do in the organism as a physiological whole, not simply by observing differences. Remember that most genes and their products, RNA and proteins, have multiple functions.

To see the poverty of the view that we can only observe differences, just ask the question what engineer would be satisfied simply to know the *difference* between the cement he used this time to construct his building compared to what he used previously, or to know just the differences between two electronic components in an aircraft? Of course, he might use the difference approach as one of his experimental tools (as genetics has in the past, to good effect), but the equations and models of an engineer represent the relevant totality of the function of each component of a system. So does physiological analysis of function, which is why physiology cannot be restricted to the limitations of the 'difference' approach.

Second, accurate replication of DNA is itself a system property of the cell as a whole, not just of DNA. DNA on its own is an extremely poor replicator. It requires a dedicated set of proteins to ensure correction of transcription errors and eventual faithful transmission. Both in ensuring faithfulness of DNA replication and in creating robustness against genetic defects, systems properties are the important ones. The cell as a whole 'canalises' the way in which DNA is interpreted, making it robust and reproducible. The famed 'immortality' of DNA is actually a property of the complete cell.

The distinction between replicator and vehicle is therefore out of date from a physiologist's viewpoint. It stems from the original 'genetic program' idea, in which organisms are viewed as Turing machines with the DNA being the digital tape of the computer (tape–computer is much the same distinction as replicator–vehicle – this was the basis of Jacob and Monod's concept of the 'genetic program'; Jacob, 1970). Organisms are interaction systems, not Turing machines (Shapiro, 2005; Noble, 2008). There is no clear distinction between replicator and vehicle (Coen, 1999).

Finally, the story implies that the 'vehicles' do not themselves evolve independently of their DNA. There is no reason why this should be true. In fact it is certainly false. Egg cells from different species are different. So much so that cross-species hybrids using nuclear transfer usually do not survive, and those that do, as in the elegant experiments of Sun *et al.* (2005) – see Fig. 2 –

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transferring nuclei between different fish species, reveal precisely the influence of the species-specific cytoplasmic factors on development (see also Jaenisch, 2004; Yang *et al.* 2007). Crossing a common carp nucleus with a goldfish enucleated egg cell produces an adult fish that has an intermediate shape and a number of vertebrae closer to that of the goldfish. These factors can therefore determine a phenotype characteristic as fundamental as skeletal formations. Over 50 years ago, McLaren & Michie (1958) showed a similar phenomenon as a maternal effect in mice. The number of tail vertebrae (4 or 6 in the different strains) was determined by the surrogate mother, not the embryo. Of course, such cytoplasmic influences are dependent on the DNA of the mother, but these influences will necessarily include *patterns* of gene expression that are also dependent on other influences. There is interplay here between DNA and non-DNA inheritance, as there must always be. Moreover, maternal and paternal effects in response to the environment have been shown to be transmitted down two generations (grandparents to grandchildren) in humans (Pembrey *et al.* 2006) and could therefore be a target for natural selection.

Conclusions

As physiological and systems biological scientists, we need to reconnect to evolutionary theory. It was difficult to do this during most of the 20th century because the neo-Darwinist synthesis more or less excluded us, by relegating the organism to the role of a disposable vehicle. It also, unjustifiably, excluded Lamarck (Noble, 2010*b*). Darwin himself was not so sure; in the first edition of *The Origin of Species* (Darwin, 1859) he wrote 'I am convinced that natural selection has been the main, but not the exclusive means of modification', a statement he reiterated with increased force in the 1872, 6th edition. As many evolutionary biologists now acknowledge, the Modern Synthesis (neo-Darwinism) requires extending (Jablonka & Lamb, 2005; Pigliucci & Muller, 2010*b*).

If physiology is to make the contribution it should to the fields of evolution and development, we need to move on from the restrictions of the differential approach. The integrative approach can achieve this by reverse engineering using computational modelling, as I have shown elsewhere (Noble, 2011). The genes-eye view is only one way of seeing biology and it doesn't accurately reflect much of what modern biology has revealed. In fact, its central entity, the gene, 'begins to look like hardly definable temporary products of a cell's physiology' (Beurton *et al.* 2008).

Finally, I want to return to the role of metaphor and the selfish gene idea.

When I first read Richard Dawkins's acknowledgement in *The Extended Phenotype* ('I doubt that there is any experiment that could be done to prove my claim') I was strongly inclined to agree with it (both in relation to the original selfish gene idea and its development in *The Extended Phenotype*) since, if you compare the selfish gene metaphor with very different metaphors, such as genes as prisoners, it is impossible to think of an experiment that would distinguish between the two views, as I argued earlier in this paper. For any given case, I still think that must be true. But I have slowly changed my view on whether this must be true if we consider *many* cases, looking at the functioning of the organism as a whole. There are different ways in which empirical discovery can impact on our theoretical understanding. Not all of these are in the form of the straight falsification of a hypothesis, a point that has been well-understood in theoretical physics for many years (Poincaré, 1902, 1968). Sometimes it is the slow accumulation of the weight of evidence that eventually triggers a change of viewpoint. This is the case with insights that are expressed in metaphorical form (like 'selfish' and 'prisoners'), and that should not be intended to be taken literally. The first mistake of the differential approach was to interpret the selfish gene idea as literal truth. It is clearly metaphorical metaphysics, and rather poor metaphysics at that since, as we have seen, it is essentially empty as a scientific hypothesis, at least in physiological science. But in social evolution also, the idea is simply one of several viewpoints that can account for the same data (Okasha, 2010).

Figure 2. Cross-species clone
The nucleus of a common carp, *Cyprinus carpio* (middle), was transferred into the enucleated egg cell of a goldfish, *Carassius auratus* (left). The result is a cross-species clone (right) with a vertebral number closer to that of a goldfish (26–28) than of a carp (33–36) and with a more rounded body than a carp. The bottom illustrations are X-ray images of the animals in the top illustration. Figure kindly provided by Professor Yonghua Sun from the work of Sun *et al.* (2005).

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The weight of evidence in the physiological sciences is now much more favourable to the metaphor of 'co-operation' than of 'selfishness'. Gene products all co-operate in robust networks one of whose functions is precisely to insulate the organism from many of the vagaries of gene mutation, and stochasticity at lower levels. Investigating these networks and their mechanisms is the way forward.

It is therefore time to move on and remove the conceptual barriers to integrating modern physiological science with evolutionary and developmental theory. The integrative approach can achieve this since it avoids the simplistic fallacies of the gene-centred differential approach and it is essentially what successful systems physiology has employed for many years.

Further reading

This article has been written for a physiological readership that may not be very familiar with the current debates in evolutionary and genetic theory. If you learnt evolutionary biology and genetics a decade or more ago you need to be aware that those debates have moved on very considerably, as has the experimental and field work on which they are based. Amongst the references cited, the following may help the reader to catch up: Margulis (1998); Jablonka & Lamb (2005); Noble (2006); Okasha (2006); Beurton *et al.* (2008); Shapiro (2009); Pigliucci & Müller (2010*b*). For those interested in the philosophical and social impacts of the metaphors used, Midgley (2010) gives a very readable account.

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