The Music of Life:
a systems biology view of Buddhist concepts of the self/no-self[1]

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Abstract

Systems Biology is the study of the interactions between the elements (genes, proteins and other molecules) of living systems. Genes do not act in isolation either from each other or from the environment, and so I replace the metaphor of the selfish gene with metaphors, many of them musical, that emphasise the *processes* involved rather than the molecular biological components. This may seem a simple shift of viewpoint. In fact it is revolutionary. Nothing remains the same. There is no ‘book of life’, nor are there ‘genetic programs’. The consequences for the study of the brain and the nature of the self are profound. They lead naturally to the concept

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of *anatman* (Pāli: anatta), no-self, and to a better understanding of the relation between the microscopic and macroscopic views of the world.

Introduction

Twentieth century biology was characterised by the identification and characterisation of the molecular components of living systems: their proteins, genes and other molecules, such as lipids and metabolites. Almost as an extension of this approach it was assumed by many that the higher functions, such as consciousness, the will, the self, would also eventually be identified as objects, in particular as parts of the brain. I believe that this was a profound mistake and that the biology of the 21st century, Systems Biology, is set to correct this mistake.

But, before tackling the question of the self we must clarify what systems biology is: is it just a 'next step' development of molecular biology, as many of my scientific colleagues think, or does it represent a revolution in biology? My reply is that it concerns a profound revolution. The philosophy of systems biology is completely different from that of molecular biology. To use a musical analogy, if molecular biology is the identification of the notes in a score, then systems biology is the music itself. If the molecular components are compared to the instruments of an orchestra, or the pipes of a pipe organ, then systems biology is the performance. Whichever musical metaphor one might prefer (and I use several in my book, *The Music of Life*, each highlighting a different aspect of the difference between molecular and systems biology) the microscopic alone, i.e. the identification of the smallest components, is not sufficient to characterise its function.

To use Buddhist terminology, if genes and proteins are the rūpa-kalāpas of biological systems, then we need a systems approach not only to understand the processes that characterise a living system, but also to understand those rūpa-kalāpas themselves. (I call them rūpa-kalāpas in this context because they are clearly not the ultimate 'particles' (kalāpas) of reality, but then nor are electrons and protons, nor, in all probability, the strings of string theory: the ultimate microscopic nature of reality is still, and perhaps always will be, a puzzle that physics struggles to unravel). Thus, the concept of a gene as a DNA sequence is in serious difficulty as a consequence of recent discoveries in the field of epigenetics. We need a systems approach even to assess what a gene is (Noble, 2008a).

Systems Biology is revolutionary

So, my first question is: why do we need a revolution in biology?

The turn of the century saw the ultimate achievement of the molecular biological revolution that can be dated as having its beginning in the discovery of the double helix by Watson and Crick in 1957. The announcement of the first drafts of the sequencing of the human genome was, appropriately, accompanied by governmental fanfares on both sides of the Atlantic Ocean. For it was a Herculean achievement. As DNA sequencing now becomes so common as to be used even in law courts, it will become progressively more difficult to remember how audacious and technically challenging the human genome project was when it was first proposed. Nevertheless, the acclaim was misplaced in a very important respect.

What was wrong with the acclaim was not any misjudgement of the scientific and technical achievement. It was rather the promises that were made as we were told that, at last, we could read the ‘book of life’. Cures for diseases would come tumbling out of the reading of that book. At last, molecular biology would deliver on its promise to reveal the secrets of life. Francis Crick was even bold enough to claim that it would solve the great riddles of consciousness and the nature of the self. “You, your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will, are in fact no more than the behaviour of a vast assembly of nerve cells and their associated molecules” (Crick, 1994). Two decades earlier, another prophet of the molecular genetic revolution, Richard Dawkins, had also claimed that “They [genes] created us body and mind” (Dawkins, 1976). All these claims are false.

First, the genome is not a book. It is not even a programme, despite the colourful metaphor of “le programme génétique” introduced by Jacob and Monod (1961). It is a quite simply a database, used by the organism as a whole. It needs the highly-complex eukaryotic egg cell to read it and to even begin to make sense of it. Focussing on it as containing the secret of life is almost as misguided as focussing on the bar code of a product in a supermarket. It is to mistake the, probably contingent, coding for the system itself.

Second, the level of the "nerve cells and associated molecules" is simply too low for attributes like personal identity, intentions and similar attributes of a person even to be comprehensible. The astonishing thing about the title of Francis Crick's book, *The Astonishing Hypothesis*, is that it could ever have been seriously formulated by a highly intelligent scientist.

Third, as Dawkins himself acknowledges elsewhere in his later books "genes" simply "aren't us" (Dawkins, 2003).

It is therefore re-assuring to find that even the architects of the human genome sequencing are vastly more cautious. In his fascinating biography, Craig Venter writes "One of the most profound discoveries I have made in all my research is that you cannot define a human life or any life based on DNA alone…...". Why? Because "An organism's environment is ultimately as unique as its genetic code" (Venter, 2007). Precisely so and, one should add, the environment is an open system.

John Sulston is also cautious: "The complexity of control, overlaid by the unique experience of each individual, means that we must continue to treat every human as unique and special, and not imagine that we can predict the course of a human life other than in broad terms" (Sulston & Ferry, 2002). Sulston also understands the immensity of the combinatorial explosion that occurs when one considers the number of possible interactions between 25,000 genes. As he says, "just a few dozen genes …… can provide an immense amount of additional complexity". Even more mind-boggling, as I write in my little book *The Music of Life* (Noble, 2006), "there wouldn't be enough material in the whole universe for nature to have tried out all the possible interactions, even over the long period of billions of years of the evolutionary process." (see also a later part of this paper for the actual calculations)

Sequencing the human genome has therefore brought us right up against the problem of complexity in biological systems. This is the challenge that 21st century biology faces. Its foundations must therefore be built on how to integrate our knowledge, rather than simply follow a reductive mode. Having broken life down into its molecular components, the greater problem is going to be how to put those components back together again and to understand the logic of life at all the various biological levels. This raises difficult questions. Could there be a general theory of biology at a systems level? Or are living systems so 'history-dependent' as evolution has careered through its billions of years on earth that there will always be a contingent, unpredictable aspect to life? This is one of the reasons I referred earlier to DNA as a kind of 'bar code'. I admit though that we do not yet know how necessary or contingent the development of that code might have been.

To address these questions, we cannot rely on 'next step' science. We need some bold re-assessments of where we are going. I suggest that these re-assessments will be of at least two kinds. The first kind will be philosophical and linguistic. We need to identify and neutralise the misuse of metaphorical language that has for too long paraded as the truth in biological science. The second kind will be heuristic. Integrative approaches will be needed, and they must be at least as rigorous as the successful reductive approaches that characterised the second half of the 20th century. My belief is that this means that the integrative approaches must necessarily be mathematical.

'Selfish' and 'imprisoned' genes

I will take as an example of the problems created by metaphorical language the comparison between 'selfish genes' and 'prisoner genes'. The gene-centered view, the 'selfish gene' view, is a metaphorical polemic: the invention of a colourful metaphor to interpret scientific discovery in a particular way. It has provided valuable insights and these have been used to advance biological science in novel ways. But it is nevertheless a metaphor. It is not a straightforward empirical scientific hypothesis. To demonstrate this I want to challenge the reader to a thought experiment. I will first give you one of the central statements of the 'selfish gene' idea. I will then rewrite it so that each sub-phrase (except for one anodyne statement) is replaced by a possible alternative, based on an opposing metaphor: 'prisoner gene'. The challenge is to think of an empirical test that could possibly distinguish between these two diametrically opposed ways of seeing the relationship between genes and phenotypes.

> First, then, the original statement:
> **Now they** [genes] **swarm in huge colonies,**
> **safe inside gigantic lumbering robots** [that's you and me!],
> **sealed off from the outside world,** [an extension of the 'central dogma of biology']
> **communicating with it by tortuous indirect routes,**
> **manipulating it by remote control.** [a form of gene determinism]
> **They are in you and me;** [correct: this is the only empirical statement]
> **they created us, body and mind;** [more genetic determinism]
> **and their preservation is the ultimate rationale for our existence.**

And in case you didn't fully understand this statement, Dawkins added in a later book (Dawkins, 1982):

> "[readers] .. **Should imbibe the fundamental truth that an organism is a tool of DNA rather than the other way round"**

I would like the reader to think carefully about this statement to absorb its full import. Ask yourself whether you find the statement self-evident, shocking, implausible, likely, true, false, nonsense. Is it theory, fact, or neither? Form a view about it before you continue. Whichever of these views you hold (and all have been expressed by readers of *The Selfish Gene*) I believe you will find the test an interesting and even surprising challenge.

So, now let's see what happens when we replace each phrase, except for the empirical phrase 'they are in you and me', by an alternative written from an opposing viewpoint:

Now they are trapped in huge colonies,
locked inside highly intelligent beings, [you and me!]
moulded by the outside world, [I have reversed the central dogma of biology]
communicating with it by complex processes,
through which, blindly, as if by magic, function emerges.

They are in you and me; [yes, correct]

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. [our joy not theirs!]
We are the ultimate rationale for their existence.

We can also reverse the explanatory text:

The fundamental truth is that an organism is the only tool by which DNA can express functionality, by which the "Book of Life" can be read. DNA alone is inert – dead

To many of my readers this test will appear strange and challenging. Such a different view of the same thing: surely scientists must already know which is correct? Yet, I have tried this test many times now, always with the same result, which is that no-one seems to be able to think of an experiment that would detect an empirical difference between the two statements. The statements cannot therefore be a matter of empirical science, except for the obviously correct statement 'they are in you and me', which is certainly empirical, but not a difference between the statements.

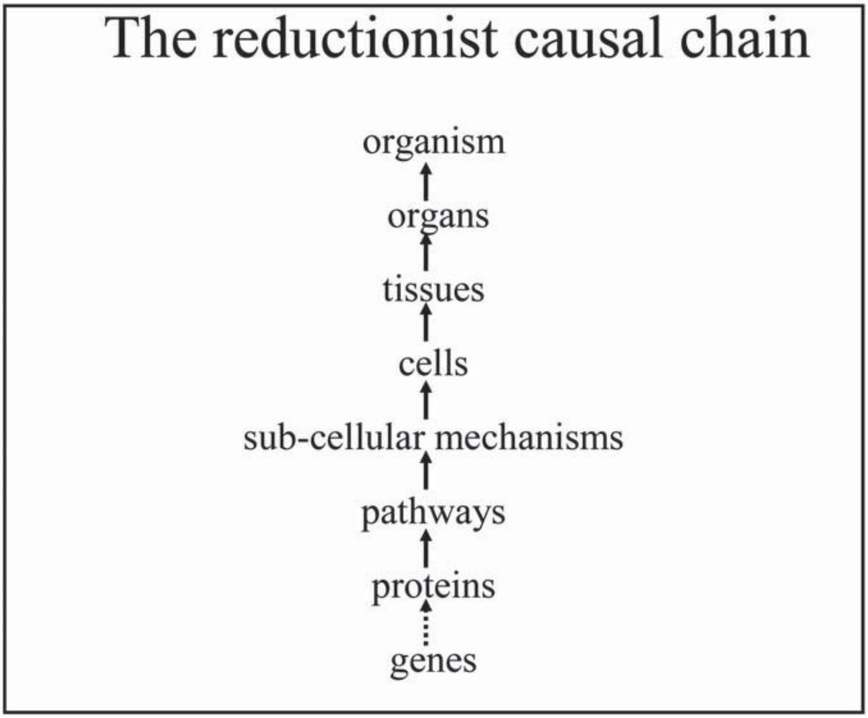
This reversal of perspective shows how easily one can take a completely different view. It is not for biological science to tell you which is correct. The social and ethical implications of your choice are, however, profound. Nature, of course, couldn't care less about such questions. They are rather like the old-fashioned version of this type of conundrum: 'which came first, the chicken or the egg?' Co-evolution is the obvious answer.

Nevertheless, it does seem to me more natural, and certainly more meaningful, to say that the rationale for existence lies at the level at which selection occurs. This is the level at which we can say why an organism survived or not. It is whole organisms that can live or die. So, it is at this level that we must search for the logic of life.

Biological functionality is multilevel

In order to characterise the philosophy necessary for such research we need to clarify the principles of systems biology. The first principle is that "Biological functionality is multi-level".

It is impossible to conceive biology without making reference to the concept of level. Between the molecular level of genes and proteins, and the level of the whole organism, we can distinguish between at least eight levels. From the reductionist viewpoint, the causal chain looks like this:



The chain runs upwards. It is a 'one-way' system, from the genes to the organism. The idea is that, if we knew all about the lowest level elements, genes and proteins, then everything about the organism would be clear to us. We could work out what happens at the higher levels, and explain it completely, in terms of our low-level knowledge. We could reconstruct the whole organism from the bottom up. The DNA sequences would be much more than bar codes. They would form a meaningful map of the entire organism – a 'book of life' indeed.

But this project is impossible. The molecular biologist and Nobel laureate, Sydney Brenner, has beautifully expressed this impossibility. "I know one approach that will fail, which is to start with genes, make proteins from them and to try to build things bottom-up" (in Novartis_Foundation, 2001 page 51).

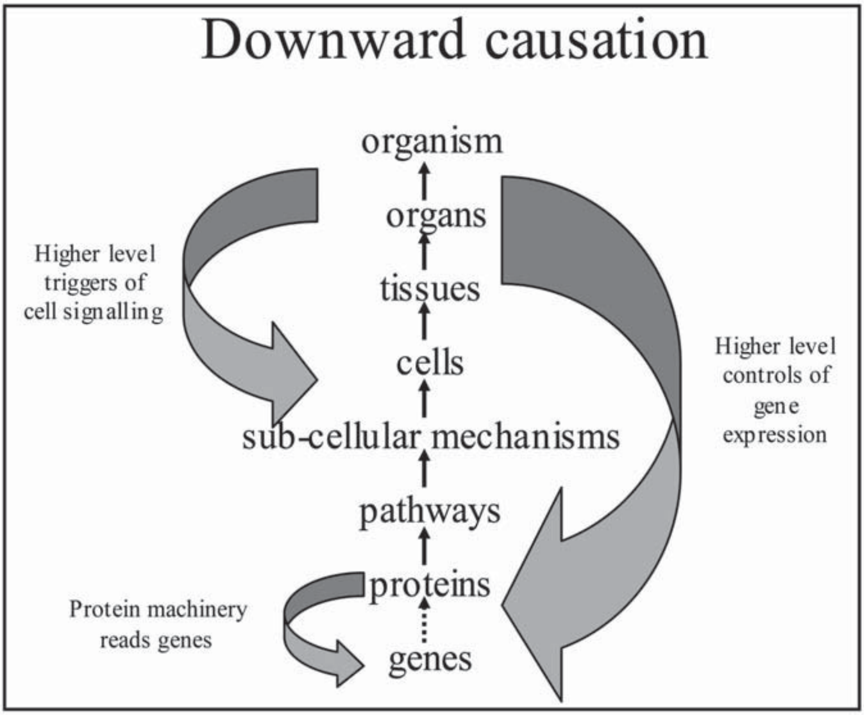
One of the reasons is that the number of possible interactions between 25,000 genes is enormous. Let's first ask a somewhat absurd question: if two genes are required to co-operate to generate a biological function, what would be the number of possible functions. The answer is (25 000 x 24 999)/2 which is about 300 million!

Now let's be a little more realistic: suppose that 100 genes are required for each function. What would be the possible number of functions that could be generated by a genome of 25,000 genes. The result is really gigantic: 10289! And what would happen if we removed the restriction of 100 genes and allowed any combination to generate a function? We would then have 2 x 1072403 possibilities (Feytmans et al., 2005).

These numbers are so large they are almost unimaginable, and certainly unattainable by evolution within the universe itself. There are thought to be 'only' 1080 atoms in the whole universe.

Downward causation

But combinatorial explosion (which is the technical term for this kind of problem) is not the only reason. My second principle is the existence of downward causation. Downward causation exists between all the levels between which there are feedbacks. Events at higher levels can trigger cell signalling, all the levels are involved in the control of gene expression, it is protein machinery that reads genes to ensure their expression, and all levels can determine epigenetic marking. This marking is very important. It consists of another level of information and control superimposed on the DNA: a kind of chemical pattern carried by the DNA and which differs according to the cell type. It is this marking that ensures the correct gene expression patterns are transmitted from generation to generation in the tissues of the body in multicellular organisms. There are many forms of downward causation. For example, triggering of cell signalling, the control of gene expression by higher levels, and epigenetic marking by all levels.



Inheritance is not determined by DNA alone

The third principle is that DNA is not the sole transmitter of inheritance.

DNA does not come to us in a 'pure', unalloyed form. It must necessarily be inherited together with a complete egg cell. From the viewpoint of systems biology, the genome is incomprehensible as a 'book of life' unless it is read and translated into physiological functions by cellular mechanisms, beginning with the egg cell. I maintain that this functionality is not to be found at the level of genes. It is impossible because genes are blind to what they do, just as are the proteins and higher-level structures such as cells, tissues and organs.

To these I want now to add two more important points. Proteins are not the only molecules in biological systems that determine function. Function is also dependent on the properties of water, lipids and many other molecules that are not coded for by genes. The lipids are essential for the construction of membranes and intracellular structures like mitochondria, ribosomes, the nucleus, the reticulum.

Moreover, a lot of what their products, the proteins, do is not dependent on instructions from the genes. It is dependent on the poorly understood chemistry of self-assembling complex systems. It is as though the genes specify the components of a computer, but not how they should be put together. They just do this by doing what is chemically natural to them.

The effects of this cellular environment on the genome are enormous. As we have seen, DNA carries a kind of chemical epigenetic marking that is different for each type of cell: heart, liver, pancreas etc.

No privileged level of causality

The fourth principle is that there is no privileged level of causality. This is necessarily true in systems with multiple levels and feedbacks downward and upward between the levels.

The fundamental point is that, to the extent that all the levels can be the point of departure for a causal chain, any level can be used as the starting point for a simulation. In biological systems there is no privileged level that dictates the behaviour of the rest of the system. Moreover, the levels are not equivalent. The relations between them are non-linear. For this reason we need to model at all levels and we need to analyse the interactions between the levels. I sometimes call this principle a theory of biological relativity: a relativity of causation (Noble, 2008b). I find that there are interesting parallels of this idea in some Buddhist commentaries (e.g. Sahn_Master_Seung_Sahn, 1997 page 91). Some relativity theorists have also pointed this out (Nottale, 2000 page 111). In this context, it is worth acknowledging the ideas developed by Auffray and Nottale (Nottale & Auffray, 2008) on the relation between a particular form of relativity theory (scale relativity) and a possible theoretical basis for systems biology.

Gene ontology requires higher-level insight

The fifth principle is that gene ontology will fail without higher-level insight.

The majority of genes (and the modules of DNA that form them) are very ancient. Genes are a little like linguistic metaphors. Evolution repeatedly re-uses them for new functions. The genetic codes also share another aspect in common with languages. Even if, originally, the modules had simple functions (what we call meaning in languages), the system as a whole is far from simple. In fact, when one tries to unravel it, the first impression is that of a form of chaos. Evolution: that is the problem. As the genomes (or languages) have evolved, the functions (meanings) have changed. And they have often changed along routes that have little connection with their original functions (meanings). Half the genes found in a simple sea squirt correspond to ones that we humans have. But we have functions served by those genes that the sea squirt does not know about. 500 million years of evolution are responsible for these differences.

The genome is not a program of life

The sixth principle is that the genome is not a program that determines life.

It must be admitted that the idea of a genetic program, introduced by Monod and Jacob in the 1960s, has been very powerful.

At that time computers were machines that could not keep all the programs in their memory. One had to write the programs on paper tape, or later on punched cards, that were inserted into the reader of the machine each time one wished to do a calculation. So, the programs were a series of instructions completely separate from the machine itself.

But there is no reason at all why nature should have developed separate programs if this wasn't necessary. As Enrico Coen, the distinguished plant geneticist, put it in his lovely book, *The Art of Genes*, "Organisms are not simply manufactured according to a set of instructions. There is no easy way to separate instructions from the process of carrying them out, to distinguish plan from execution" (Coen, 1999).

There are no programs of life

The seventh principle is that there are no programs at any other level. Living systems are not Turing machines, they are interaction machines (Neuman, 2008).

My book, *The Music of Life*, was written a little like a detective novel. If the genome itself is not a program, where then is the program of life? Is there really a program, or are there programs, located somewhere in organisms? I lead the reader through all the levels. I hesitate a little at the level of the cell. Sydney Brenner said at a Conference in Columbia University in 2003, "I believe very strongly that the fundamental unit, the correct level of abstraction, is the cell and not the genome." But even at this level, so important, particularly in evolution, the reason for its importance is that many functions are integrated at the cellular level, and this is the level at which transmission occurs between the generations. But, the concept of a programme is superfluous. The cellular networks of interactions are themselves the biological functions necessary for life. Effectively, the 'music of life' functions without a conductor. Everything emerges by itself. The grand composer, evolution, was even blinder than Beethoven was deaf!

No programs in the brain

The eighth principle is that there are no programs, even in the brain, and with this principle I begin, at last, to approach the central question of this paper: how does Systems Biology help us with questions of the self?

I hesitated a little at the level of the cell. But some of my readers will already have concluded that there is an obvious answer to the question 'what controls the processes of the body?' Yes, the nervous system is certainly a central integrator and controller of some kind. The question is what kind. Must we go along with Crick, and many other biologists, in looking for a place in the brain where it all, as it were, comes together in a central consciousness? Could a bit of the brain, or any other part, do this?

For example, the claustrum, as Francis Crick proposed (see later).

And, if so, how does this conscious centre see what it sees, hear what it hears, feel what it feels? Does the nervous system serve up our sensations to it in a special form, converting the light, sound and pressure waves into special qualitative phenomena (some philosophers and scientists call them sense data or qualia) that exist inside our heads? This is an area where biology and philosophy strongly interact and, some would say, overlap. So how do biologists and philosophers think that we perceive the world?

My arguments against these ideas are difficult to explain briefly in an article like this. They depend on philosophical ideas developed during the 20th century, particularly by philosophers like Wittgenstein. In chapter 9 of my book I try to explain these ideas in relatively simple language by using dialogues and little stories. The essence of the argument is that biological interpretations that suppose the existence of a part of the brain responsible for central control resemble the mistake to which I have already referred, i.e. of imagining that there must be programs that determine functions in the body. There are no such programs, because the only networks that could correspond to such programs *are themselves the biological function*. If I play a piece of guitar, for example, neural networks are activated, of course, but these are not programs that *determine* how I play the music. These networks, and the movements of my fingers, *are* me playing the guitar.

The self is not a neural object

The ninth principle therefore is that the self if not a neural object. It is an integrative process. It is the highest *process* of the body. The all-singing, all-dancing, ninth symphony of systems biology!

The mind is not a separate object. It seems to me that the idea that it is was based on an error that greatly resembles Descartes' error. Bennett and Hacker, in their masterly book *The Philosophical Foundations of Neuroscience* (Bennett & Hacker, 2003), use the term "mereological fallacy" to describe this kind of problem, which consists in attributing to a part of an object a property which cannot be ascribed other than to the whole of the object. At the level of the brain, the self is more a process than an object. And the brain contains only part of the processes involved.

Despite these philosophical problems, many biologists look in the brain to find the self, or consciousness. Thus, Ramachanran refers to a conversation with Francis Crick: "I think the secret of consciousness lies in the claustrum—don't you? Why else would this one tiny structure be connected to so many areas in the brain?" And as I have already referred in my introduction, Crick himself wrote "You, your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will, are in fact no more than the behaviour of a vast assembly of nerve cells and their associated molecules" (Crick, 1994).

The activities of the self, such as intentional actions, cannot be understood on the basis of neural activity alone without taking into account the social context in which intentionality can have any meaning. I tell a story to illustrate this problem in chapter 9 of *The Music of Life*.

It is interesting to note that western philosophy has taken a long time to reach these conclusions. But they strongly resemble the ideas of oriental philosophers, such as the Taoists and Buddhists, on non-dualism. Their ideas were formulated more than 2000 years ago.

While it is important to recognise and acknowledge these resemblances between my conclusions as a systems biologist and the conclusions of the Buddhist tradition, from its very beginning, it is important to note a very important difference in the way in which the conclusions have been derived. My route to these insights has come from long reflection on the nature of biological science. I started my biological research as a rather naïve reductionist as I analysed some of the lowest-level components of biological systems, the proteins that form ion channels in the heart (Noble, 2004). I developed my view of a systems approach through many years of interactions with philosophers and other scientists. I have been constrained in my thinking to abandon the reductionist approach as the only means by which we can analyse living systems by the very nature of biological science as I think it is developing.

The Buddhist tradition has used a completely different route: that of direct personal experience through meditation. As I understand it, *anatman* (Pāli: antta), the idea of no-self, is an *experiential* fact. Ultimately, however, our understanding of science and our direct experiences of ourselves must coincide. Whether we have reached that point of coincidence with the development of systems biology is a fascinating question.

Conclusions

In conclusion, systems biology is very different, both from a philosophical and from a heuristic point of view, from molecular biology, even though it greatly profits from the results of molecular biology. Reduction and integration are both necessary as tools to develop a good reply to the question "what is life?" Systems Biology requires a revolution in the way in which we study life. One of the important results of this revolution is that we cannot understand living beings on the basis of DNA alone, or the proteins. It is necessary to understand more than the molecular components. We must understand also how these components act in processes at the higher levels. The highest such process is the self, which should be analysed as a process that depends, like all other functions in living beings, on the environment, including the social environment.

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[Postscrip]

The Music of Life – Late Discovery and Revisions to Speech

I wish therefore to [present] a remarkable discovery that I made, while researching [material for the Keynote Speech], in the above work of the Korean monk, Won Hyo元曉（원효） (617-686).

The text below comes from the Kŭmgang sammaegyŏng ron 金剛三昧經論 (quoted in Kim, 2004: 119) where he uses a seed and the fruit to illustrate the application of four-cornered logic (derived I believe from Nagarjuna) to illuminate the concept of being/ non-being.

"The fruit and the seed are not the same, for they have different shape.
However, they are not different.
Besides the seed and the fruit are not annihilable,
for the fruit is produced from the seed.

However, they are not eternal,
for there is no seed when it is in the state of the fruit.
The seed did not enter into the fruit,
for the seed does not exist when it is in the state of the fruit.
The fruit does not extinguish the seed,
for the fruit does not exist when it is in the state of the seed.
Since it neither enters nor is extinguished, there is no arising.
Since it is neither eternal nor annihilable, there is no ceasing.
Since there is no ceasing, non-being cannot be proclaimed.
Since there is no arising, being cannot be proclaimed.
Since it is free from the two extremes [being and non-being],
it cannot be stated as both being and non-being.
Since it does not correspond to the middle,
it cannot be stated as neither being nor non-being.
Therefore it is stated that it is free from the four perspectives
and cut off from verbal expression.
As such the amala fruit transcends language."

This is a version of the main point in my comparison earlier in this paper of the two metaphors for genes (selfish genes and prisoner genes). To illustrate this, in the second version below I have replaced 'seed' with 'genotype' and 'fruit' with 'phenotype':

"The phenotype and the genotype are not the same, for they have different shape.
However, they are not different.
Besides the genotype and the phenotype are not annihilable,
for the phenotype is produced from the genotype.
However, they are not eternal,
for there is no genotype when it is in the state of the phenotype.
The genotype did not enter into the phenotype,
for the genotype does not exist when it is in the state of the phenotype.
The phenotype does not extinguish the genotype,
for the phenotype does not exist when it is in the state of the genotype.
Since it neither enters nor is extinguished, there is no arising.
Since it is neither eternal nor annihilable, there is no ceasing.
Since there is no ceasing, non-being cannot be proclaimed.
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Since it is free from the two extremes [being and non-being],
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Since it does not correspond to the middle,
it cannot be stated as neither being nor non-being.
Therefore it is stated that it is free from the four perspectives
and cut off from verbal expression.
As such the amala fruit transcends language."

In this form, his text could then appear almost as a modern text of systems biology! Anyone who understands this text will see that a strict distinction between the replicator (the genome) and the vehicle (the phenotype), which is the fundamental basis of the Selfish Gene theory, can illuminate only a part of the relation between the two. They are also totally interdependent.