# Systems Biology and Traditional Chinese Medicine
# 系统生物学和传统中医药

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**ABSTRACT**
In this paper I outline some general principles that could form the basis of Systems Biology as a truly multi-level approach from a physiologist's standpoint. We need the insights obtained from higher-level analysis in order to succeed even at the lower levels. The reason is that higher levels in biological systems impose boundary conditions on the lower levels. Without understanding those conditions and their effects we will be seriously restricted in understanding the logic of living systems. The principles outlined are illustrated with examples from various aspects of physiology and biochemistry. Applying and developing these principles should form a major part of the future of physiology. The second part of the paper considers whether these principles could form the basis of bridge-building between the Western and Oriental medical traditions. In principle, that could be the case, but it will require much more work to be done in developing systems biology itself, in subjecting oriental medicine to rigorous research and evaluation, and in translating the terms used in the two traditions in ways that would enable such a bridge to be successful.
**Keywords** Systems Biology, Music of Life, Computational Physiology, Human Physiome Project, Oriental Medicine.

## INTRODUCTION: THE PRINCIPLES OF SYSTEMS BIOLOGY[1]

*The Music of Life* (Noble, 2006) is a radical revision of the central principles of biological science (see also Noble, 2008c; Kohl *et al.*, 2010; see also Noble, 2011b; Noble, 2011a). In order to explain why it can form a gateway between the Western and Eastern Medical traditions, I will explain what those revised principles are.

### FIRST PRINCIPLE: Biological functionality is multi-level

I start with this principle because it is obviously true, all the other principles can be shown to follow from it, and it is therefore the basis on which a modern physiological understanding of the phenomenon of life must be based. It is a more general statement of the insight originally contained in Claude Bernard's (Bernard, 1865, 1984) idea of the constancy of the internal environment. That functionality is attributable to the organism as a whole and it controls all the other levels.

Yet, the language of twentieth century reductionist biology often seemed to deny this obvious truth. The enticing metaphor of the 'book of life' made the genome into the modern equivalent of the 'embryo-homunculus', the old idea that each fertilised egg contains within it a complete organism in miniature (Mayr, 1982 page 106). That the miniature is conceived as a digital 'map' or 'genetic program' (Monod & Jacob, 1961; Jacob, 1970) does not avoid the error to which I am drawing attention, which is the idea that the living organism is simply the unfolding of an already-existing program, fine-tuned by its interaction with its environment, to be sure, but in all essentials, already there in principle as a kind of zipped-up organism. In fact, however, the stretches of DNA that we now call genes do nothing on their own. They are simply databases used by the organism as a whole (Atlan & Koppel, 1990). This is the reason for replacing the metaphor of the 'selfish' gene by genes as 'prisoners' (Noble, 2006, chapter 1). As Maynard Smith and Szathmáry (Maynard Smith & Szathmáry, 1999) express it, 'co-ordinated replication prevents competition between genes within a compartment, and forces co-operation on them. They are all in the same boat'. From the viewpoint of the organism, genes as DNA molecules are therefore captured entities, no longer having a life of their own independent of the organism.

[1] These principles are taken and revised from
Noble D (2008a). Claude Bernard, the first Systems Biologist, and the future of Physiology. *Experimental Physiology* **93,** 16-26.

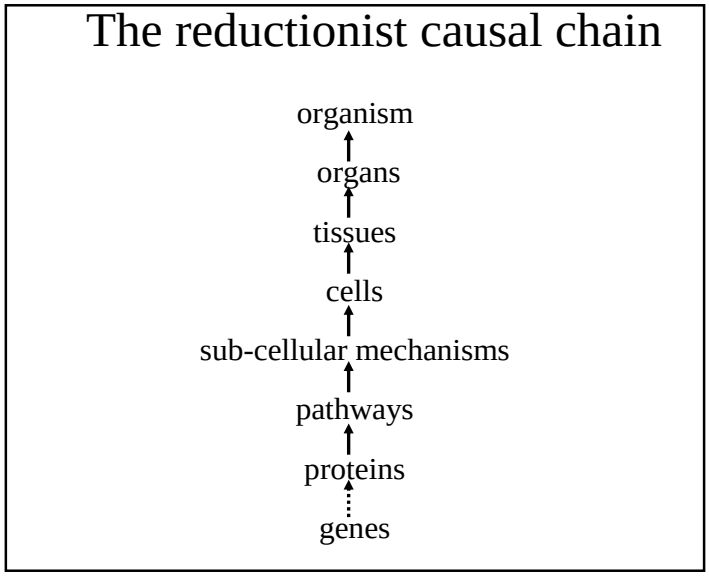



Figure 1 The reductionist 'bottom-up' causal chain (From Noble, 2006). This begins with the central dogma that information flows from DNA to proteins (bottom dotted arrow), never the other way, and extends the same concept through all the higher levels.

**SECOND PRINCIPLE: Transmission of information is not one way.**
The central dogma of molecular biology (Crick, 1970) is that information flows from DNA to RNA, from RNA to proteins, which can then form protein networks, and so on up through the biological levels to that of the whole organism. Information does not flow the other way. This is the dogma that is thought, incorrectly (Gissis & Jablonka, 2011; Shapiro, 2011), to safeguard modern neo-Darwinian theory from the spectre of 'Lamarckism', the inheritance of acquired characteristics. Applied to all the levels, this view is illustrated in Figure 1. It encourages the bottom-up view of systems biology, the idea that if we knew enough about genes and proteins we could reconstruct all the other levels.

There are two respects in which the dogma is at least incomplete. The first is that it defines the relevant information uniquely in terms of the DNA code, the sequence of C, G, A, T bases. But the most that this information can tell us is *which* protein will be made. It does not tell us *how much* of each protein will be made. Yet, this is one of the most important characteristics of any living cell. Consider the speed of conduction of a nerve or muscle impulse, which depends on the density of rapidly-activated sodium channels: the larger the density, the greater the ionic current, and the faster the conduction. But this relationship applies only up to a certain optimum density since the channel gating also contributes to the cell capacitance, which itself slows conduction, so there is a point beyond which adding more channel proteins is counter-productive (Hodgkin, 1975; Jack *et al.*, 1975: page 432). A feedback mechanism must therefore operate between the electrical properties of the nerve and the expression levels of the sodium channel protein. We now refer to such feedback mechanisms in the nervous system, which take many forms, as electro-transcription coupling (e.g. Deisseroth *et al.*, 2003).

Similar processes must occur in the heart (e.g. Bers & Guo, 2005) and all the other organs. One of the lessons I have learnt from many attempts to model cardiac electrophysiology (Noble, 2002) is that, during the slow phases of repolarization and pacemaker activity, the ionic currents are so finely balanced that it is inconceivable that nature arrives at the correct expression and activity levels without some kind of feedback control. We don't yet know what that control might be, but we can say that it must exist. Nature cannot be as fragile as our computer models are! Robustness is an essential feature of successful biological systems.

There is nothing new in the idea that such feedback control of gene expression must exist. It is, after all, the basis of cell differentiation. All nucleated cells in the body contain exactly the same genome (with the exception of course of the germ cells, with only half the DNA). Yet the expression pattern of a cardiac cell is completely different from, say, a hepatic or bone cell. Moreover, whatever is determining those expression levels is accurately inherited during cell division. This cellular inheritance process is robust; it depends on some form of gene marking. It is this information on relative gene expression levels that is critical in determining each cell type.

By what principle could we possibly say that this is not relevant information? In the processes of differentiation and growth it is just as relevant as the raw DNA sequences. Yet, it is clear that this information *does* travel 'the other way'. The genes are told by the cells and tissues what to do, how frequently they should be transcribed, and when to stop. There is 'downward causation' (Noble, 2006 chapter 4) from those higher levels that determines how the genome is 'played' in each cell. Moreover, the possible number of combinations that could arise from so many gene components is so large (Feytmans *et al.*, 2005) that there wouldn't be enough material in the whole universe for nature to have tried more than a small fraction of the possible combinations even over the billions of years of evolution (Noble, 2006 chapter 2).

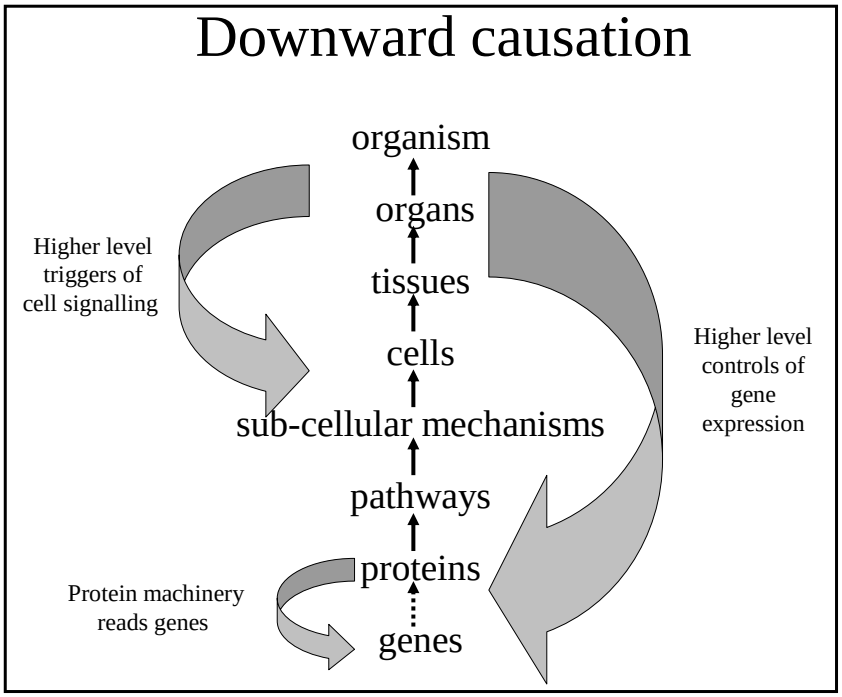



Figure 2. Figure 1 has been completed by adding the downward forms of causation, such as higher levels triggering cell signalling and gene expression. Note the downward-pointing arrow connecting from proteins to genes to indicate that it is protein machinery that reads and interprets gene coding. Loops of interacting downward and upward causation can be built between all levels of biological organisation; from (Noble, 2006).

So the dogma is at least incomplete. But I also think it is incorrect in several important ways. Sure, protein sequences are not back-translated to form DNA sequences. In this limited original form, as formulated by Crick (1970), the central dogma is correct. But there is growing evidence from work on all kinds of organisms that environmental factors *do* change the genome, particularly by gene transfer and genome reshuffling (Goldenfeld & Woese, 2007; Gissis & Jablonka, 2011; Shapiro, 2011). As Beurton, Falk and Rheinberger (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." We cannot therefore use the original central dogma to exclude information transfer *into* the genome, determined by the organism and its environment.

Moreover, the DNA code itself is marked by the organism. This is the focus of the rapidly-growing field of epigenetics (Qiu, 2006). At least two such mechanisms are now known at the molecular level: methylation of cytosine bases and control by interaction with the tails of histones around which the DNA is wound. Both of these processes modulate gene expression. The terminological question then arises: do we regard this as a form of code-modification? Is a cytosine, the C of the code, a kind of C* when it is methylated? That is a matter of definition of code, and one which I will deal with in the next section, but what is certain is that it is relevant information determining levels of gene expression, and that this information does flow against the direction of the central dogma. In fact, a form of inheritance of acquired characteristics (those of specific cell types) is rampant within all multicellular organisms with very different specialised cell types (Noble, 2006: chapter 7). At the least we have to say that, during the lifetime of the individual organism, transmission of information is far from being one-way.

For a more systematic deconstruction of the Central Dogma see the article and book by Shapiro (2009; 2011)

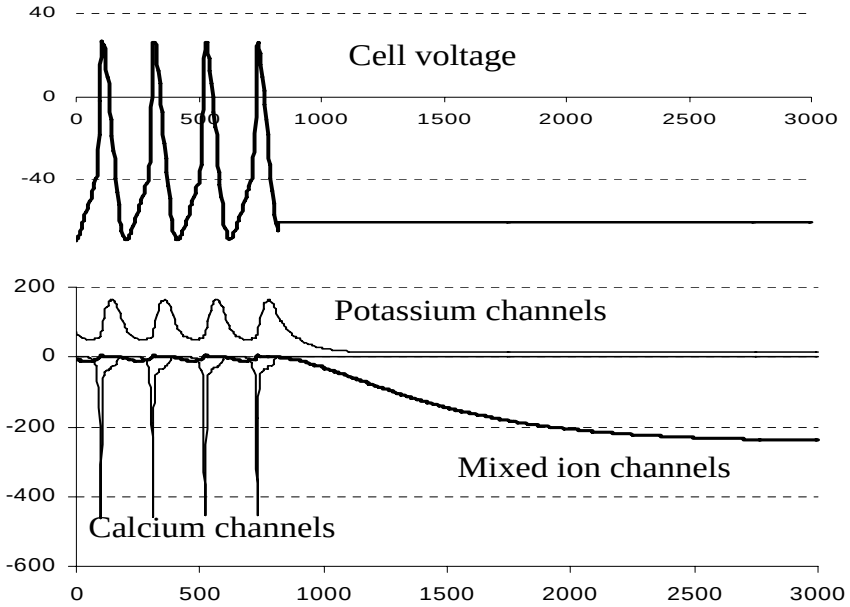
**THIRD PRINCIPLE: DNA is not the sole transmitter of inheritance**.
The defenders of the original version of the central dogma would argue that, while my conclusions regarding the second principle are correct, what happens when information is transmitted to the next generation through the germ-line nevertheless involves wiping the slate clean of epigenetic effects. Methylation of cytosine bases, and other forms of genome marking are removed. The genome is reset so that 'Lamarckism' is impossible.

But this is to put the matter the wrong way round. We need to explain *why* the genome (usually) reverts to an unmarked state. We don't explain that by appealing to the central dogma for that dogma is simply a restatement of the same idea. We are in danger of circular logic here. Later, I will suggest a plausible reason why, at least most of the time, the resetting is complete, or nearly so. In order to do that, we first need to analyse the idea that genetics, as originally understood, is just about DNA.

This is not the original biological meaning of 'gene'. The concept of a gene has changed (Kitcher, 1982; Mayr, 1982; Dupré, 1993; Pichot, 1999; Beurton *et al.*, 2008). Its original biological meaning was an inheritable phenotype characteristic, such as eye/hair/skin colour, body shape and weight, number of legs/arms – to which we could perhaps add more complex traits like intelligence, personality, sexuality etc. Genes, as originally conceived, are not just the same as stretches of DNA unless we subscribe to the view that the inheritance of all such characteristics is attributable entirely to DNA sequences. That is clearly false since the egg cell is also inherited, together with any epigenetic characteristics transmitted by sperm (Anway et al., 2005), perhaps via RNA in addition to its DNA, and all the epigenetic influences of the mother and environment. Of course, the latter begins to be about 'nurture' rather than 'nature', but one of my points is that this distinction is fuzzy. The proteins that initiate gene transcription in the egg cell and impose an expression pattern on the genome are initially from the mother, and other such influences continue throughout development in the womb. Where we draw the line between nature and nurture is not at all obvious. There is an almost seamless transition from one to the other. 'Lamarckism', the inheritance of acquired characteristics, lurks in this fuzzy crack (Jablonka & Lamb, 1995, 2005) to a remarkable degree that is beginning to be defined (Gissis & Jablonka, 2011). As the evolutionary geneticist Maynard Smith says, 'It [Lamarckism] is not so obviously false as is sometimes made out' (Maynard Smith, 1998).

Inheritance of the egg cell is important for two reasons. First, it is the egg cell DNA reading machinery (a set of around 100 proteins and the associated cellular ribosome architecture) that enables the DNA to be used as a template to make more proteins. Second, the set of other cellular elements, mitochondria, endoplasmic reticulum, microtubules, nuclear and other membranes, and a host of chemicals arranged specifically in cellular compartments, is also inherited. Most of this is not coded for by DNA sequences. Lipids certainly are not so coded. But they are absolutely essential to all the cell architecture. There would be no cells, nuclei, mitochondria, endoplasmic reticulum, ribosomes, and all the other cellular machinery and compartments without the lipids. The specific details of all this cellular machinery matter. We can't make any old DNA do its thing in any old egg cell. Most attempts at inter-species cloning simply don't work. Invariably, a block occurs at an early stage in development. The only successful case so far in mammals is that of a wild ox (*bos javanicus*) cloned in a domestic cow egg. In fish, cross species cloming has succeeded between a carp and a goldfish (Sun *et al.*, 2005). The chances are that it will work only in very closely-related species, and the example in the work of Sun and his colleagues shows precisely the influences of cytoplasmic inheritance. The egg cell information is therefore also species-specific.

**FOURTH PRINCIPLE: The theory of biological relativity: there is no privileged level of causality.**
A fundamental property of systems involving multiple levels between which there are feedback control mechanisms is that there is no privileged level of causality. Consider, as an example, the cardiac pacemaker mechanism. This depends on ionic current generated by a number of protein channels carrying sodium, calcium, potassium and other ions. The activation, de-activation and inactivation of these channels proceed in a rhythmic fashion in synchrony with the pacemaker frequency. We might therefore be tempted to say that their oscillations generate that of the overall cell electrical potential, i.e. the higher level functionality. But this is not the case. The kinetics of these channels varies with the electrical potential. There is therefore feedback between the higher-level property, the cell potential, and the lower level property, the channel kinetics (Noble, 2006 chapter 5). This form of feedback was originally identified by Alan Hodgkin working on the nerve impulse, so it is sometimes called the Hodgkin cycle. If we remove the feedback, e.g. by holding the potential constant, as in a voltage clamp experiment, the channels no longer oscillate (Figure 3). The oscillation is therefore a property of the system as a whole, not of the individual channels or even of a set of channels unless they are arranged in a particular way in the right kind of cell.



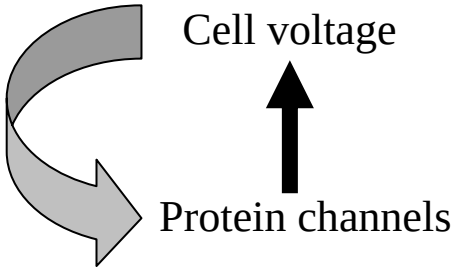



Figure 3. Computer model of pacemaker rhythm in the heart (Noble & Noble, 1984). For the first four beats the model is allowed to run normally and generates rhythm closely similar to a real heart. Then the feedback from cell voltage to protein channels is interrupted. All the protein channel oscillations then cease. They slowly change to steady constant values. The diagram shows the causal loop involved. Protein channels carry current that changes the cell voltage (upward arrow), while the cell voltage changes the protein channels (downward arrow). In the simulation, this downward arrow was broken at 800 ms.

Nor can we establish any priority in causality by asking which comes first, the channel kinetics or the cell potential. This fact is also evident in the differential equations we use to model such a process. The physical laws represented in the equations themselves, and the initial and boundary conditions, operate *at the same time* (i.e. during every integration step however infinitesimal), not sequentially.

It is simply a prejudice that inclines us to give some causal priority to lower-level, molecular events. The concept of level in biology is itself metaphorical. There is no literal sense in which genes and proteins lie *underneath* cells, tissue and organs. It is a convenient form of biological classification to refer to different levels, and we would find it very hard to do without the concept (figure 4). But we should not be fooled by the metaphor into thinking that 'high' and 'low' here have their normal meanings. From the metaphor itself, we can derive no justification for referring to one level of causality as privileged over others. That would be a misuse of the metaphor of level.

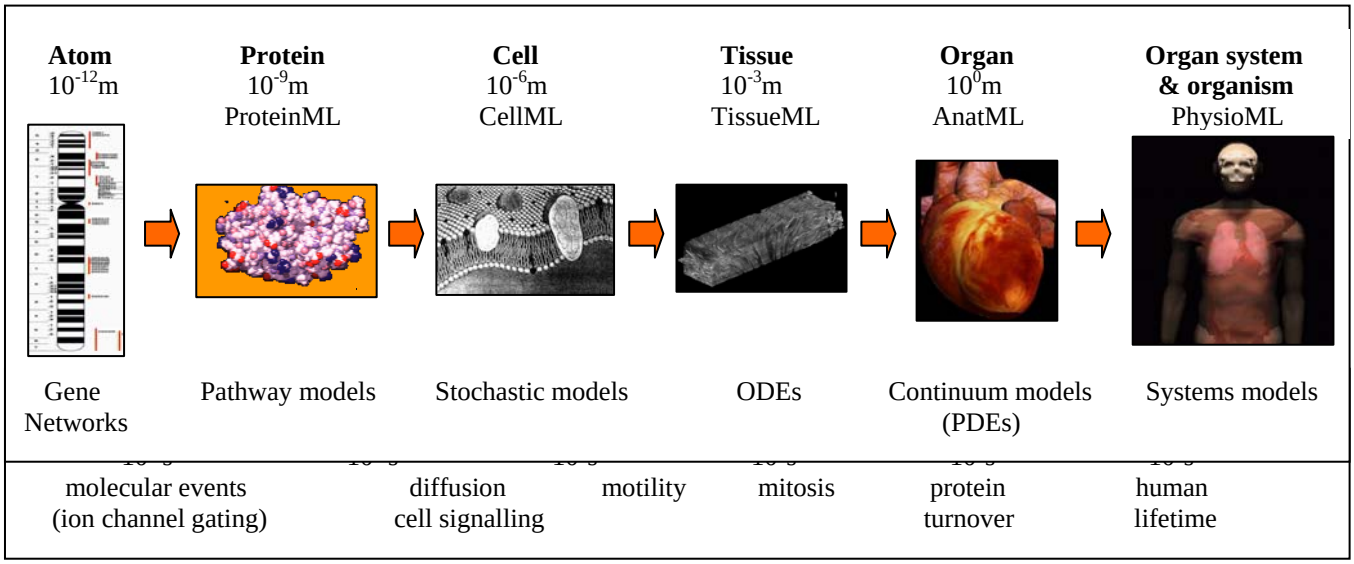



Figure 4. Spatial (top) and temporal (bottom) scales encompassed by the Human Physiome Project. The types of mathematical model appropriate to each spatial scale are also indicated. The last two images on the right in this figure, and all subsequent anatomical images, are from anatomically based models developed by the Auckland Bioengineering group. The tissue image is a 3D confocal microscopy reconstruction of a transmural segment of rat heart by the Auckland group led by Peter Hunter (Hunter *et al.*, 2002).

These points can be generalised to any biological function. The only sense in which a particular level might be said to be privileged is that, in the case of each function, there is a level at which the function is integrated, and it is one of our jobs as biological scientists to determine what that level may be.

**FIFTH PRINCIPLE: Gene ontology will fail without higher-level insight**

Genes, as defined by molecular genetics to be the coding regions of DNA, code for proteins. Biological function then arises as a consequence of multiple interactions between different proteins in the context of the rest of the cell machinery. Each function therefore depends on many genes, while many genes play roles in multiple functions. What then does it mean to give genes names in terms of functions? The only unambiguous labelling of genes is in

terms of the proteins they code for. Thus, the gene for the sodium-calcium exchange protein is usually referred to as *ncx*. Ion channel genes are also often labelled in this way, as in the case of sodium channel genes being labelled *scn*.

This approach, however, naturally appears unsatisfactory from the viewpoint of a geneticist, since the original question in genetics was not which proteins are coded for by which stretches of DNA (in fact, early ideas on where the genetic information might be found (Schrödinger, 1944) favoured the proteins), but rather what is responsible for higher level phenotype characteristics. There is no one-to-one correspondence between genes or proteins and higher level biological functions. Thus, there is no 'pacemaker' gene. Cardiac rhythm depends on many proteins interacting within the context of feedback from the cell electrical potential.

Let's do a thought experiment. Suppose we could knock out the gene responsible for L-type calcium channels and still have a living organism (perhaps because a secondary pacemaker takes over and keeps the organism viable – and something else would have to kick-in to enable EC coupling, and so on throughout the body because L-type calcium channels are ubiquitous!) Since L-type calcium current is necessary for the upstroke of the action potential in the SA node of most species we would find that we had abolished normal pacemaker rhythm. Do we then call the gene for L-type calcium channels the 'pacemaker' gene? The reason why this is unsatisfactory, even misleading, to a systems-level biologist is obvious. Yet it is the process by which we label many genes with high-level functions. The steadily-growing list of 'cancer genes' have been identified in this way, by determining which mutations (including deletions) change the probability of cancer occurring. We can be fairly sure though that this characteristic is not why they were selected during the evolutionary process. In this sense there are no 'cancer genes'. As the Gene Ontology (GO) consortium (http://geneontology.org/) puts it, "oncogenesis is not a valid GO term because causing cancer is not the normal function of any gene".

Another good example of this approach is the discovery of what are called clock genes, involved in circadian rhythm. Mutations in a single gene (now called the *period* gene) are sufficient to abolish the circadian period of fruit flies (Konopka & Benzer, 1971) This discovery of the first 'clock gene' was a landmark since it was the first time that a single gene had been identified as playing such a key role in a high-level biological rhythm. The expression levels of this gene are clearly part of the rhythm generator. They vary (in a daily cycle) in advance of the variations in the protein that they code for. The reason is that the protein is involved in a negative feedback loop with the gene that codes for it (Hardin et al., 1990). The idea is very simple. The protein levels build up in the cell as the *period* gene is read to produce more protein. The protein then diffuses into the nucleus where it inhibits further production of itself by binding to the promoter part of the gene sequence. With a time delay, the protein production falls off and the inhibition is removed so that the whole cycle can start again. So, we not only have a single gene capable of regulating the biological clockwork that generates circadian rhythm, it is itself a key component in the feedback loop that forms the rhythm generator.

However, such rhythmic mechanisms do not work in isolation. There has to be some connection with light-sensitive receptors (including the eyes). Only then will the mechanism lock on to a proper 24 hour cycle rather than free-running at say 23 or 25 hours. In the mouse, for example, many other factors play a role. Moreover, the clock gene itself is involved in other functions. That is why Foster and Kreitzman have written 'what we call a clock gene may have an important function within the system, but it could be involved in other systems as well. Without a complete picture of all the components and their interactions, it is impossible to tell what is part of an oscillator generating rhythmicity, what is part of an input, and what is part of an output. In a phrase, it ain't that simple!' (Foster & Kreitzman, 2004).

Indeed not. The *Period* gene has also been found to be implicated in embryonic development as the adult fly is formed over several days. And it is deeply involved in coding for the male love songs generated by wing-beat oscillations which are specific to each of around 5000 species of fruit fly and ensure that courtship is with the right species. Perhaps it should be renamed the 'fruit fly love gene'!

The point is obvious. We should not be misled by gene ontology. The first function a gene is found to be involved in is rarely if ever the only one and may not even be the most important one. Gene ontology will require higher-level insight to be successful in its mission. Moreover, current methods of relating genotype to phenotype suffer from a major methodological limitation: by determining the effects of *changes* (mutations) in the genome, we can say little a priori on the direct causal relations between wild type genes and the phenotype. They reveal simply the *differences* produced as a result of the *change* in genotype. All the causal effects *common* to both the wild type and the mutated gene are hidden. What is observed may be just the tip of the iceberg.

Gene ontology in its fullest sense, as originally conceived by geneticists to relate genes to high-level features, is therefore very difficult and subject to many traps for the unwary. This would explain why projects such as the Gene Ontology (GO) Consortium http://geneontology.org/) are more limited in their scope. Thus, GO assigns 3 categories to a gene – molecular function, biological process, and cellular component – which are not intended to deal with higher level function. It specifically excludes protein domains or structural features, protein-protein interactions, anatomical or histological features above the level of cellular components, including cell types, and it excludes the environment, evolution and expression. In other words, it excludes virtually all of what we classically understand by physiology, and most aspects of evolutionary biology.

**SIXTH PRINCIPLE: There is no genetic program**

No genetic programs? Surely, they are all over the place! They are the crown jewels of the molecular genetic revolution, invented by none other than the famous French Nobel Prize winners, Monod and Jacob (Monod & Jacob, 1961; Jacob, 1970). Their enticing idea was born during the early days of electronic computing, when computers were fed with paper tape or punched cards coded with sequences of instructions. Those instructions were clearly separate from the machine itself that performed the operations. They dictated those operations. Moreover, the coding is digital. The analogy with the digital code of DNA is obvious. So, are the DNA sequences comparable to the instructions of a computer program?

An important feature of such computer programs is that the program is separate from the activities of the machine that it controls. Originally, the separation was physically complete, with the program on the tape or cards only loaded temporarily into the machine. Nowadays, the programs are stored within the memory of the machine, and the strict distinction between the program, the data and the processes controlled may be breaking down. Perhaps computers are becoming more like living systems, but in any case the concept of a genetic program was born in the days when programs were separate identifiable sets of instructions.

So, what do we find when we look for genetic programs in an organism? We find no genetic programs! There are no sequences of instructions in the genome that could possibly play a role similar to that of a computer program. The reason is very simple. A database, used by the system as a whole, is not a program. To find anything comparable to a program we have to extend our search well beyond the genome itself. Thus, as we have seen above, the sequence of events that generates circadian rhythm includes the period gene, but it necessarily also includes the protein it codes for, the cell in which its concentration changes, the nuclear membrane across which it is transported with the correct speed to effect its inhibition of transcription. This is a gene-protein-lipid-cell network, not simply a gene network. The nomenclature matters. Calling it a gene network fuels the misconception of genetic determinism. In the generation of a 24 hour rhythm, none of these events in the feedback loop is privileged over any other. Remove any of them, not just the gene, and you no longer have circadian rhythm.

Moreover, it would be strange to call this network of interactions a program. The network of interactions *is itself the circadian rhythm process*. As Enrico Coen, the distinguished plant geneticist, put it "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). In short, the concept of a program here is completely redundant. It adds nothing to what a systems approach to such processes can reveal.

**SEVENTH PRINCIPLE: There are no programs at any other level**

I have introduced the analogy of the genome as a database, and the metaphor of 'genes as prisoners' in order to provoke the change in mindset that is necessary for a fully systems approach to biology to be appreciated. The higher levels of the organism 'use the database' and 'play the genome' to produce functionality. If the genome can be likened to a huge pipe organ (Noble, 2006 chapter 2), then it seems correct to ask who is the player, who was the composer? If we can't find the program of life at the level of the genome, at what level do we find it? The answer is 'nowhere'!

We should view all such metaphors simply as ladders of understanding. Once we have used them we can, as it were, throw them away. This way of thinking can seem strange to some scientists for whom there must be just one correct answer to any scientific question. I explore this important issue in The MUSIC of LIFE by analysing the 'selfish gene' and 'prisoner gene' metaphors linguistically to reveal that no conceivable experiment could decide which is correct (Noble, 2006 chapter 1). They highlight totally different aspects of the properties of genes. This philosophy is applied throughout the book as it answers questions like 'where is the program of life'? The conclusion is simply that there are no such programs at any level. At all levels the concept of a program is redundant since, as with the circadian rhythm network, the networks of events that might be interpreted as programs are themselves the functions we are seeking to understand. Thus, there is no program for the heart's pacemaker separate from the pacemaker network itself.

While causality operates within and between all levels of biological systems, there are certain levels at which so many functions are integrated that we can refer to them as important levels of abstraction. Sydney Brenner wrote "I believe very strongly that the fundamental unit, the correct level of abstraction, is the cell and not the genome" (Lecture, Columbia University, 2003). He is correct since the development of the eukaryotic cell was a fundamental stage in evolutionary development, doubtless requiring at least a billion years to be achieved. To systems physiologists though there are other important levels of abstraction, including whole organs and systems.

**EIGHTH PRINCIPLE: There are no programs in the brain**

In his book *The Astonishing Hypothesis* Francis Crick proclaimed "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). This is a variation of the idea that in some sense or other, the mind is just a function of the brain. The pancreas secretes insulin, endocrine glands secrete hormones ……. and the brain 'secretes' consciousness! All that's left is to find out how and where in the brain that happens. In one of his last statements, Crick has even hinted at where that may be: "I think the secret of consciousness lies in the claustrum" (Francis Crick, 2004, quoted by V.S. Ramachanran, in *The Astonishing Francis Crick* Edge 147— October 18, 2004, www.edge.org ). This structure is a thin layer of nerve cells in the brain. It is very small and it has many connections to other parts of the brain, but the details are of no importance

to the argument. The choice of brain location for the 'secret of consciousness' varies greatly according to the author. Descartes even thought that it was in the pineal gland. The mistake is always the same, which is to think that in some way or other the brain is a kind of performance space in which the world of perceptions is reconstructed inside our heads and presented to us as a kind of Cartesian theatre. But that way of looking at the brain leaves open the question: where is the 'I', the conscious self that sees these reconstructions? Must that be another part of the brain that views these representations of the outside world?

We are faced here with a mistake similar to that of imagining that there must be programs in the genomes, cells, tissues and organs of the body. There are no such programs, even in the brain. The activity of the brain and of the rest of the body simply *is* the activity of the person, the self. Once again the concept of a program is superfluous. When a guitarist plays the strings of his guitar at an automatic speed that comes from frequent practice, there is no separate program that is making him carry out this activity. The patterns and processes in his nervous system and the associated activities of the rest of his body simply *are* him playing the guitar. Similarly, when we deliberate intentionally there is no nervous network 'forcing' us to a particular deliberation. The nervous networks, the chemistry of our bodies, together with all their interactions within the social context in which any intentional deliberation makes sense, *are* us acting intentionally. Looking for something in addition to those processes is a mistake.

**NINTH PRINCIPLE: The self is not an object**

In brief, the mind is not a separate object competing for activity and influence with the molecules of the body. Thinking in that way was originally the mistake of the dualists, like Sherrington and Eccles, led by the philosophy of Descartes. Modern biologists have abandoned the separate substance idea, but many still cling to a materialist version of the same mistake (Bennett & Hacker, 2003), based on the idea that somewhere in the brain the self is to be found as some neuronal process. The reason why that level of integration is too low is that the brain, and the rest of our bodies which are essential for attributes like consciousness to make sense (Noble, 2006 chapter 9), are tools (back to the database idea again) in an integrative process that occurs at a higher level involving social interactions. We cannot attribute the concept of self-ness to ourselves without also doing so to others (Strawson, 1959). Contrary to Crick's view, therefore, our selves are indeed much "more than the behaviour of a vast assembly of nerve cells and their associated molecules" precisely because the social interactions are essential even to understanding what something like an intention might be. I analyse an example of this point in much more detail in chapter 9 of *The* MUSIC *of* LIFE. This philosophical point is easier to understand when we take a systems view of biology since it is in many ways an extension of that view to the highest level of integration in the organism.

**TENTH PRINCIPLE: There are many more to be discovered; a genuine 'theory of biology' does not yet exist.**

Well, of course, choosing just ten principles was too limiting. This last one points the way to many others of whose existence we have only vague ideas. We do not yet have a genuine theory of biology. The Theory of Evolution is not a theory in the sense in which I am using the term. It is more a historical account, itself standing in need of explanation. We don't even know yet whether it consists of events that are difficult, if not impossible, to analyse fully from a scientific perspective, or whether it was a process that would have homed-in to the organisms we have regardless of the conditions. My own suspicion is that it is most unlikely that, if we could turn the clock right back and let the process run again, we would end up with anything like the range of species we have today on earth (Gould, 2002).

But, whichever side of this particular debate you may prefer, the search for general principles that could form the basis of a genuine theory of biology is an important aim of Systems Biology. Can we identify the logic by which the organisms we find today have succeeded in the competition for survival? In searching for that logic, we should not restrict ourselves to the lower levels. Much of the logic of living systems is to be found at the higher levels since these are often the levels at which selection has operated (Keller, 1999; Gould, 2002) and determined whether organisms live or die. This is the level at which physiology works. Physiology therefore has a major contribution to make to Systems Biology.

A BRIDGE?[2]

Could Systems Biology and the principles I have outlined here form the basis for some kind of dialogue at least, and perhaps even a synthesis, between the western and oriental traditions, as suggested for example by Jane Qiu (2007)? This was the subject of a meeting held in Oxford in 2008 at which scientists from both traditions were present. There was general agreement that System Biology, and particularly the existence of 'downward causation' (i.e. higher level constraint of lower level processes), does open up the possibility of constructive dialogue between the western and oriental medical traditions in a way that was not possible within the dominant reductive mode of biology.

The reasons for this agreement were:

The characterisation of forms of 'downward causation', including both feedback and constraint, could be a way of linking the two traditions.

[2] This part of the paper is based on parts of
Noble D (2009). Could there be a synthesis between western and oriental medicine? *Evidence-based Complementary and Alternative Medicine* **6,** 5-10.

Systems Biology can identify multiple actions as being more beneficial than single site actions (e.g. multiple action drugs within the western medical tradition, most recently ranolazine – see e.g. (Noble, 2008b)). This could open the way to a better understanding of, and development of, herbal medicine, since this also depends on synergistic actions of multiple components.

Systems Biology recognises the importance of control of the genome by higher levels (via epigenetic marking and control) including even the role of behavioural and social factors. This can be seen, for example, in the work of Weaver et al (Weaver *et al.*, 2004; Weaver *et al*., 2007; Weaver, 2009) on epigenetic inheritance of stroking behaviour in rats. This form of downward causation spans all the levels of biological organisation and could open the way to dialogue on the central role of the mind in Oriental Medicine.

Some versions of Oriental Medicine, Korean Sasang in particular, can be viewed as a patient specific form of treatment. Genomics and Systems Biology are also looking towards the development of patient specific medication and treatment. However, Systems Biology is not looking towards ancient Galenic or other interpretations of constitution. The question therefore arises whether Oriental Medicine could be open to investigation on this question. I think it can. Kim et al (Kim *et al.*, 2009) chart the way forward in applying genomics to Sasang.
Could Oriental Medicine become consistent with the need for regulation and clinical trial evidence? There are already examples of successful clinical trials of acupuncture for pain relief and of meditation therapy for depression. Oriental Medicine should not be fearful of clinical trials, though it has to be admitted that there are special difficulties in establishing effective controls in such trials. The correct placebo for a treatment like acupuncture is much more difficult to arrange than is a sugary pill!

But perhaps the biggest problem is not scientific at all. It is rather historical and cultural. In the West, Oriental Medicine is thought by many people to include many kinds of 'magic', mysterious effects that are perceived as anti-scientific. This raises the question whether Oriental Medicine could be de-mythologised?

What do I mean by demythologising? I mean whether it would be possible to map concepts like 気 (*ki, qi*), that at first sight closely resemble that of 'vital energy', to systems-level concepts that are empirically testable and do not simply resurrect the old concept of vital energy, a concept that was specifically rejected by scientists like Claude Bernard. There are similar questions with concepts such as 精 (*jing* essence*?*), 神 (*shen* spirit*?*), 陰 (*yin*), 陽 (*yang*), 脉 (*mai* vessel), and as Kim & Pham show (2009), for the various Chinese characters for organ systems. My proposal is that we might more profitably identify these with systems *processes* not as separate *substances.* In this context, it is interesting that in a recent study of the practice of Traditional Chinese Medicine in modern China, Hsu (1999) ends with the conclusion:

"It was the *process* which brought about disharmony, not the material aspects….this conception of the body in its disordered state was common to *qigong* and Chinese medicine"

**CONCLUSIONS**

I suggest that dialogue and synthesis will need to take place in several stages:

Translation and interpretation. The outlines for some of this work are already clear (Porkert, 1974, 1982; Hsu, 1999, 2001; Kim & Pham, 2009; Lu & Needham, (1966) 1970). A good example of the approach required is to be found in Lu and Needham's study of acupuncture and moxibustion, relating the historical oriental texts to interpretations using modern biology (Lu & Needham, 2002). There is a solid base, therefore, on which to build. But much more work will be required. It is not as simple as producing a better dictionary of oriental medical terms. Those terms acquire their meanings within a complete semantic frame, in turn determined by historical and sociological backgrounds that need to be understood. Moreover, translation and interpretation depends not only on understanding the source language, but also on the target language into which the interpretation is done. An important conclusion of this paper is that the language of Systems Biology is still developing. Since we do not yet know the higher-level concepts that will form its foundations in the future, we cannot yet know what would be the best way to map oriental medical concepts onto those of Systems Biology. The processes of translation and interpretation are therefore on-going tasks, working within the frameworks of the two cultures involved, each of which is developing.
An essential component of future work will therefore be the development of Systems Biology in a direction that enables understanding of physiological and pathological processes at the higher levels of organisation. We are a long way from achieving this at the current time. The greater effort and funding in systems biology is at the lower levels of gene-protein networks. The Physiome Project attempts to redress the balance here, but it also is a long way from integrating together organ systems that could correspond, for example, to those postulated by traditional Oriental Medicne.
The application of Systems Biology to oriental medicine. Systems Biology is a highly quantitative discipline. Some even define it in terms of the ways in which mathematics is applied to biology. In addition to molecular biology, genomics, proteomics and bioinformatics, it also has roots in biological engineering and in mathematical biology. It is nothing less than a revolution in biology, bringing to it the same rigour as mathematics has brought to physics, engineering and chemistry. Oriental medicine, by contrast, is not mathematical, though concepts of balance of the kind discussed in some of the articles in this volume could obviously be expressed mathematically.

I suspect therefore that, in addition to changing the nature of modern biological science, Systems Biology may eventually also change the nature, or at least the characterisation of traditional oriental medicine.

This conclusion is particularly relevant to the tradition of Sasang constitutional medicine, and other forms of oriental medicine that emphasise patient-specific treatment. It could examine its fundamental basis in two ways.

The first, as outlined by Kim et al (35), is that the concept of constitutional types could be re-examined via genomic studies. The main challenge here will be that the concepts of constitutional type at the phenotype level (as in Sasang) and at the genomic level are different since there is no simple relation between genotype and phenotype. The causal links are complex (15). But Sasang and other oriental medical scientists are in a good position to do this work since they have access to patients who are naturally classified according to phenotype constitutional group. Relating these classifications to genotypes would be a very important first step.

The second is that the concept of balance between systems could be treated mathematically, just as Claude Bernard (18, 19) envisioned the mathematical analysis of his concept of homeostasis, the processes that maintain the constancy (via various forms of balance) of the internal environment. As the Physiome Project advances, such an application to the balance concept in some forms of oriental medicine could become possible.

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