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Editorial

Why integration?

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ABSTRACT

The recent growth of the systems approach to biology provides a better conceptual framework within which to interpret holistic approaches to medicine. The reason is that systems biology respects the way in which the whole constrains the parts to behave in ways that are different from what they would do in isolation. Holistic treatments depend on the same insight and can therefore be successful in practice where reductionist approaches would fail.

The recent rise of Systems Biology has been one of the most significant developments in science since the turn of the century. It has brought together mathematicians, engineers, physicists, computer scientists and biologists in an interdisciplinary attempt to respond to a major problem that became fully evident following the success in sequencing whole genomes, including that of the human genome, announced in the year 2000. The problem is that, while those sequences form essential chemical templates for the formation of RNAs and proteins, they do not in themselves provide an answer to the question 'what is life?'

The genome is not the 'book of life', nor is it a 'genetic program'.[1] It is not a 'book' in the same sense in which the binary code that corresponds in my computer memory to the article I am currently writing is not the article itself. Without an interpretative program, such as Microsoft Word, the binary sequences would be incomprehensible gibberish. Similarly, without an organism, with its full complement of transcription factors, epigenetic markers, cell compartments and membranes, and many other inherited characteristics, there is no way in which the DNA sequences could be interpreted. If we could take the complete DNA of the genome out of a cell and put it in a petri dish with as many nutrients as one might wish, it would do absolutely nothing, even if we were to keep it for 10,000 years. The cell from which I had taken it would however continue to function until it needed to make more proteins and RNAs. Remember that red cells in our bodies function perfectly well for 100 days or so without a genome.

This need for interpretation by the organism as a whole is also evident in the observation that nearly all attempts at cross-species cloning fail. When the nucleus of one species is placed into the enucleated but fertilised egg cell of another species, the most common outcome is that the embryo does not develop beyond an early stage. There are very few cases in which cross-species cloning does produce an adult organism. Those cases show that the cytoplasmic influences change the way in which the genome is interpreted.[2] The resulting adult has some of the characteristics of the donor egg cell as well as of the species that provided the transferred nuclear genome. DNA sequences therefore have different outcomes depending on the context in which they are interpreted.

The genome is not a program either. To be a program it would require all the logic of a program. We don't find that logic in the DNA sequences. What we find is better characterised as a formatted database with switches. Through those switches and through epigenetic marking this database is used by the organism to maintain and reconstruct itself. Those switches are controlled by the networks of interactions (often miscalled 'genetic programs') through transcription factors and epigenetic mechanisms. As the Nobel-laureate, Barbara McClintock, said 'the genome is an organ of the cell'.[3] She received her Nobel Prize for the discovery of 'jumping genes' in plants. We now know that in animals also genomes contain long sections that originated as transposable elements and that this transposition of DNA domains has been an important process in evolution.[4]

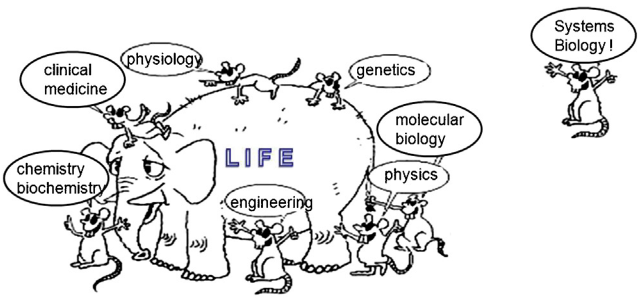

Fig. 1 – Cartoon produced by Professor Yung Earm to introduce a lecture by Denis Noble at the IUPS World Congress in Kyoto, Japan, in July 2009. The cartoon was inspired by the ideas of the Korean Buddhist monk, Won Hyo (617-86).

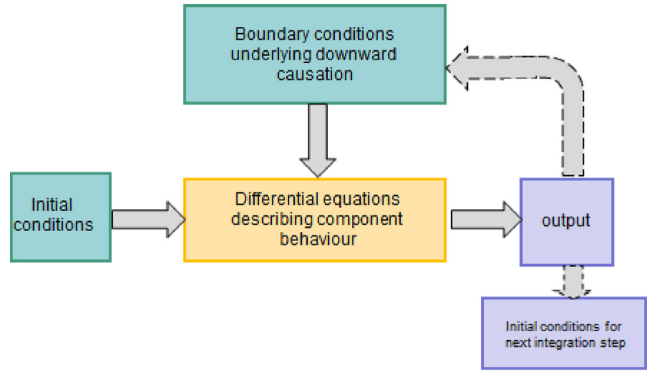

Fig. 2 – Many models of biological systems consist of differential equations for the kinetics of each component. These equations cannot give a solution (the output) without setting the initial conditions (the state of the components at the time at which the simulation begins) and the boundary conditions. The boundary conditions define what constraints are imposed on the system by its environment and can therefore be considered as a form of downward causation. This diagram is highly simplified to represent what we actually solve mathematically. In reality, boundary conditions are also involved in determining initial conditions and the output parameters can also influence the boundary conditions, while they in turn are also the initial conditions for a further period of integration of the equations. The arrows are not really unidirectional. The dotted arrows complete the diagram to show that the output contributes to the boundary conditions (although not uniquely), and determines the initial conditions for the next integration step.[7]

The systems approach in biology recognises these points. Breaking the organism up into all its molecular components was a dominant paradigm of the twentieth century. But like a child that has pulled a complex toy apart, we need to know how to put it all back together again. To use another analogy, without integration we are rather like the blind people in the famous Buddhist parable of the elephant (Fig. 1). Each discipline can identify the parts that it is good at finding and characterising, but to understand the elephant itself we require a more global view. That is why the systems approach is necessarily interdisciplinary. I would argue that systems biology is not itself a discipline. It is an approach that combines disciplines.[5]

A central discipline in this approach is mathematics. The great nineteenth century French physiologist, Claude Bernard, foresaw this when he wrote in his classic book, *Introduction à l'étude de la Médecine Expérimentale*:[6] "this application of mathematics to natural phenomena is the aim of all science, because the expression of the laws of phenomena should always be mathematical." But with a few exceptions, biological science did not incorporate mathematics at its core in the way in which physics and engineering did so. In part, that was because, as Bernard himself realised long ago, there wasn't enough hard data in his time. But that has changed. We are now awash with genomic, proteomic and metabolomics data. The problem is to understand it. Simply accumulating yet more data will not solve that problem (Fig. 2).

Mathematics can also provide another way of expressing the need for integration. The word 'integration' has a very specific meaning in mathematics. It is the opposite of differentiation. There is an analogy here. Differential equations are the means by which mathematical modelling is often achieved in biology. We measure the properties of each component in a system and then characterise those properties in a dynamic way by using differential equations for the way in which each component changes with time or space or both. This approach was used in the ground-breaking work of Hodgkin and Huxley in 1952 to analyse the function of a nerve axon,[8] and the same approach has been used to understand the heart, the pancreas, the liver, and many other types of cell in the body. In the case of the heart, there are now more than 100 such models corresponding to different parts of the heart and to different species.[9]

However accurate our differential equations may be, however, they will not help us understand how the system works until we integrate the equations. And to do that, we need to incorporate initial and boundary conditions. It is through those conditions that the functioning of the parts is influenced by the rest of the system, i.e. the context in which the parts function as part of the whole.

The analogy with integration in biology is quite close. Whether we use mathematics or not, we need to understand the ways in which the whole constrains the parts. This is an essential aspect of the systems approach.

Recently, I was looking for ways in which this insight has been expressed in the past. I have already indicated with the Elephant parable the way in which it was understood in the East Asian Buddhist tradition. A very good example in the western philosophical tradition comes from the work of Benedict de Spinoza in 1663. He was in correspondence with the first secretary, Henry Oldenberg, of the then young Royal Society, which was founded in 1660. In letter XV he writes (English translation from Spinoza's Latin):

> "Let us imagine, with your permission, a little worm, living in the blood, able to distinguish by sight the particles of blood, lymph etc, and to reflect on the manner in which

each particle, on meeting with another particle, either is repulsed, or communicates a portion of its own motion. This little worm would live in the blood, in the same way as we live in a part of the universe, and would consider each particle of blood, not as a part, but as a whole. He would be unable to determine, how all the parts are modified by the general nature of blood, and are compelled by it to adapt themselves, so as to stand in a fixed relation to one another" (Elwes 1951 letter XV to Henry Oldenburg)[10]

It is hard to improve on this statement. To understand how all the parts are modified by the whole and are compelled by it to adapt themselves to the functioning of the whole *is* the aim of the systems approach in biology.

The rise of systems biology is therefore important for biological science in general. But it is also important for another reason. Twentieth century reductionist science was not at all sympathetic to the various forms of Asian traditional medicine, including Korean Sa-sang Constitutional Medicine, traditional Chinese medicine and Japanese kampo. In any case, those traditions make no reference to molecular biology. Nor did molecular biology refer to holistic concepts. It was therefore antipathetic to many aspects of higher-level biology, including whole organism physiology. The systems approach, ideally, does reach out towards holistic interpretations. The concept of a system is itself holistic since the fundamental nature of a system is that it is not entirely defined by its parts. It is therefore possible to envisage ways in which systems biology could be used to map modern biological science to traditional forms of medicine.[11] It is important to do this because the medical challenges of the twenty first century are not ones that are easy to solve with the reductionist approach.

Twentieth century medicine succeeded very well indeed in protecting people from the diseases that caused people to die young. Antibiotics and other 'reductive' approaches (such as western-style targeted drugs) have eliminated or controlled those diseases so well that we now have aging populations with greatly increased longevity. Some medical scientists think that the natural human life span could eventually exceed 100 years, perhaps rising to 120.

But aging populations suffer more from multi-factorial diseases, and from conditions that might better be described as 'not-healthy'. When there are multiple factors involved in producing such conditions, a single intervention may not work. Multiple interventions require multi-component remedies. The various remedies of traditional medicine have used this approach for thousands of years. Typically, herbal remedies are multi-component. Treatment of the person as a whole often includes physical interventions like acupuncture and massage. Importantly also it includes the mind, with various forms of meditation.

Sa-sang is particularly important in this context since it is based on a classification of patients according to defined types. Treatment is determined in part by those types (constitutions). It is possible to envisage how the systems approach to biology could be used to extend constitutional medicine to become a fully-fledged patient-specific form of treatment using the best of traditional and modern medicine.

Conflict of interest

None.

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