PRINCIPLES OF SYSTEMS BIOLOGY

The Way Forward in Healthcare

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I. INTRODUCTION

I. 1. Aim

Our aim in this article is to follow up on a previous article in the RCHM Journal (Tasaki, Tasaki et al. 2012) to show how some of the ideas of the Ten Principles of Systems Biology are being developed and implemented in the multi-level Systems Biological research in our laboratory in the University of Oxford.

I. 2. What are the principles of Systems Biology?

In the previous article, we outlined the Ten Principles of Systems Biology (Figure 1), which are basic ideas derived from The Music of Life (Noble 2006) and related articles (Noble 2008, Kohl, Crampin et al. 2010). The central principle is the Principle of Biological relativity (principal 4) : no privileged level of causation (Noble 2012). The principle of Biological Relativity necessarily involves circular causality (Tasaki 2013) between the multiple levels of organisation.

The origins of the ideas leading to the Principle of Biological relativity and circular causality can be seen in some ancient Greek philosophical ideas, and in some 17th-century European medical ideas.

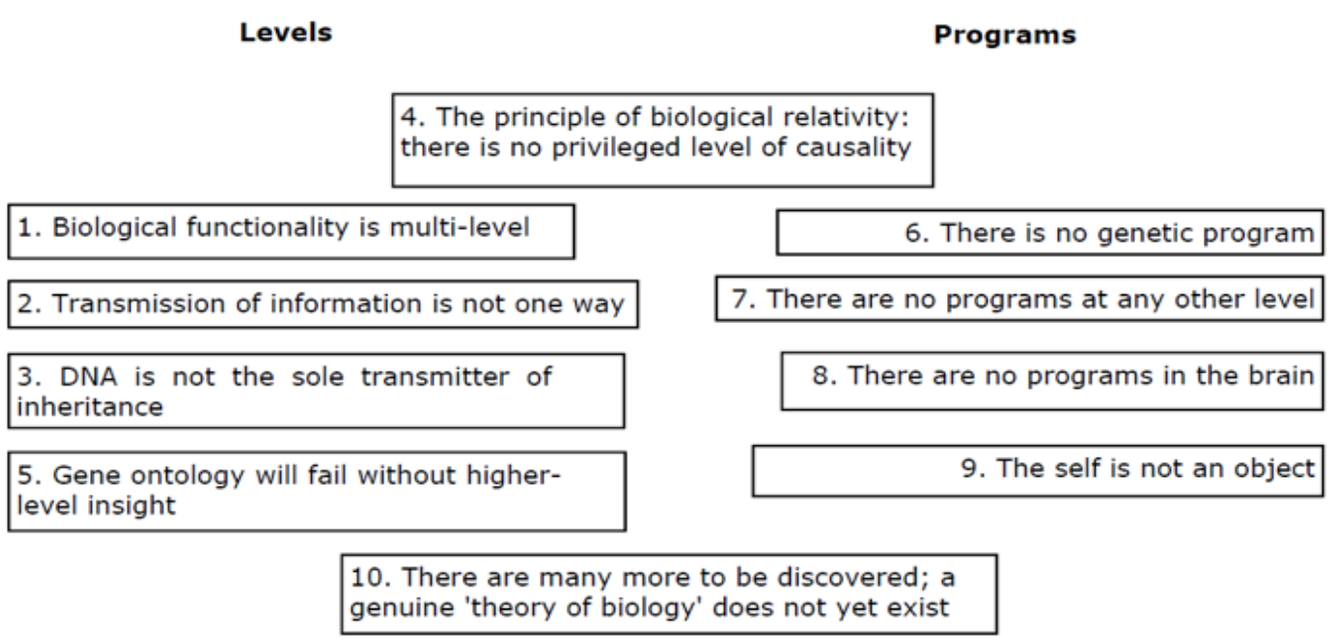


Figure 1: The Ten Principles of Multi-scale Systems Biology

I. 3. Aristotle's concept of Final Cause and Biological relativity: both are integrationist concepts.

The idea of Biological relativity is, for example, implicit in Aristotle's concept of Final Cause. Final Cause is what the action is used for in the sense of its function and its purpose.

Aristotle's final cause could be seen as one of the origins of Biological Relativity, because it is a form of causation that interprets components and their behaviour in terms of the function of the whole. Thus, the heart is for the pumping of blood; the lungs are for the exchange of respiratory gases, oxygen and carbon dioxide; eggs and sperm are for the reproduction of the species, and so on. Functional significance, purpose, and therefore teleological causation, must arise from inter-level interactions in which the components at the lower level are constrained in a functional way by the properties at a higher scale.

I. 4. Spinoza's constraint of parts by the whole and Biological relativity: both are integrationist concepts.

This idea of constraint of the parts by the whole was first formulated specifically by the philosopher Spinoza in 1665:

"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" (Noble 2011).

This paragraph could stand even today as a succinct statement of one of the main ideas of Biological Relativity. Spinoza doesn't use a mathematical medium to express his idea, but this could be so expressed as the aim to understand how the initial and boundary conditions of a system constrain the parts to produce a particular solution to the differential equations describing their motions.

Spinoza's idea implies that if in scientific research we wish to understand how the components are constrained to behave as they do, we need to move to the complete system (with whatever boundary we choose to use to define that) in order to understand the parts.

I. 5. Claude Bernard's ideas and circular causality: both are integrationist concepts.

One of the ways in which the whole constrains the parts is circular causality involving feedback from one level to another. This idea was first recognised explicitly by Claude Bernard (Bernard 1865, 1984). His idea of the constancy of the internal environment necessarily requires circular causality (Noble 2008) to enable a high-level function to control lower-level processes, including molecular processes. Bernard's idea complements that of Spinoza since it provides an explanation for the restraint of lower level activity by higher level processes in terms of Aristotle's final cause. The function of the control determines the constraint that should be exerted on lower level events.

I. 6. Contrasting ideas: Descartes's view as reductionist

By contrast, Descartes's views, in his Treatise on the fetus (1664), were in direct contrast to Spinoza's ideas:

"If one had a proper knowledge of all the parts of the semen of some species of animal in particular, for example of man, one might be able to deduce the whole form and configuration of each of its members from this alone, by means of entirely mathematical and certain arguments, the complete figure and the conformation of its members." [1]

Descartes's view can be seen as the origin of the reductionist approach, because it is essentially the idea that there is a complete mathematical 'program' there in the semen, prefiguring Jacob and Monod's 'genetic program'. Complete because he writes "from this alone" (in the original French "de la seul").

I. 7. Scientific argument between reductionist and integrationist viewpoints

The argument in science between reductionists and integrationists therefore stretches back to Descartes's view, and to Aristotle's philosophy of causation, and to Spinoza's constraint of parts by the whole.

Aristotle's final cause is the form of causation that gives pure reductionists most concern and why they usually

wish to eliminate it from biological theory. They would argue that teleological cause can always be replaced by explanations in terms of efficient (mechanical) cause.

But that approach privileges the level at which causation is thought to occur, usually represented as molecular. There is no reason to make that assumption and in open systems it must be wrong to do so. That is why the Principle of Biological Relativity is needed.

I.8. Selected insights from Traditional Medicine

As discussed in our previous article, integrationist views can also be seen in selected insights from Traditional Medicine. In particular, circular causality could be used to analyse selected insights from Traditional Medicine, as seen in the Ishimpo (984).

II. How the Principles of Systems Biology are being developed?

In this section of the article we will illustrate how some of the ideas in the ten Principles of Systems Biology have been developed in a practical application in our laboratory in the University of Oxford.

II.1. Key Principles amongst the Ten Principles of Systems Biology

Principles 1 and 4 are the key ones in the practical application we will explain below.

Principle 1 (Biological functionality is multi-level) requires a careful analysis of the levels of biological organisation that are likely to be involved.

Principle 1 expresses the fact that function in a multi-level system must depend on processes at more than one level. This would be consistent with the possibility that causality is one way, from lower to higher levels. But the principle of Biological Relativity excludes this possibility since it states that any level can be causally efficient. This leads to the idea of circular causality, or feedback, and is what gives organisms the power of control.

Principles 9 and 10 are very general philosophical principles that influence the overall strategy of theoretical Systems Biology. Principle 9 also has important implications for research on the brain (Noble, Noble et al. 2014). Principle 10 is an appeal for more development of theoretical Systems Biology, on which the reader is referred to a recent issue of Progress in Biophysics and Molecular Biology focussed on Integral Biomathics (Simeonov, Rosen et al. 2015).

On the other hand, Principles 5 and 6 (5: Gene ontology will fail without higher level insight, and 6: There is no genetic program) will not be used in a research project that does not seek to identify the genes involved in a function. Principle 8 only applies to the nervous system.

II. 2. Principle 1

In this section we will illustrate how the relevant principles are used in a specific project on a traditional medication.

Our research therefore is multi-level, including whole organ (whole muscle, whole heart), tissue (muscle strips from ileum and arteries), cells (isolated and cultured cells), molecules (molecular biological work on expressed ion channels) and pharmacological dissection to identify drug receptors involved.

II. 3. Principle 4
II. 3. 1. Causation occurring both ways
II. 3. 2. Health

In healthy states various parameters, such as Blood Pressure, temperature, pH, and concentrations of sugar and many metabolites are controlled to be kept within normal limits. This control of the internal environment was called homeostasis (a term introduced by Cannon in his 1932 book The Wisdom of the Body) to refer to Claude Bernard's idea.

II. 3. 3. Disease

In disease states parameters move towards values outside normal limits, any of which might interact with the action of the medication. A pathological state therefore, by contrast, is one in which that balance is disturbed.

II. 3. 4. Example from our laboratory research

The multi-scale Systems Biological viewpoint is implemented at all stages of our research from design of experiments to analysis of results.

For example, it is this way of thinking that led to one of our high-level hypotheses, which is the possibility that

the pathological state of muscle spasm or cramp might itself be facilitating the conditions in the system that allows a much lower dose of drugs (muscle relaxant) to have an effect.

This approach requires a high-level understanding of the interactions that could be occurring in strongly contracting muscles. There are many possibilities: metabolites, ions, circulation could all be contributing to the cramp or spasm state.

The reason for choosing potassium is that it is already known that interstitial potassium rises by at least 100% (from around 5 mM to around 10 M) in strongly contracting muscle (Green, Langberg et al. 2000). Potassium ions are also known to be a transmitter of relaxation effects from endothelial cells to smooth muscle cells in arteries (Edwards, Dora et al. 1998).

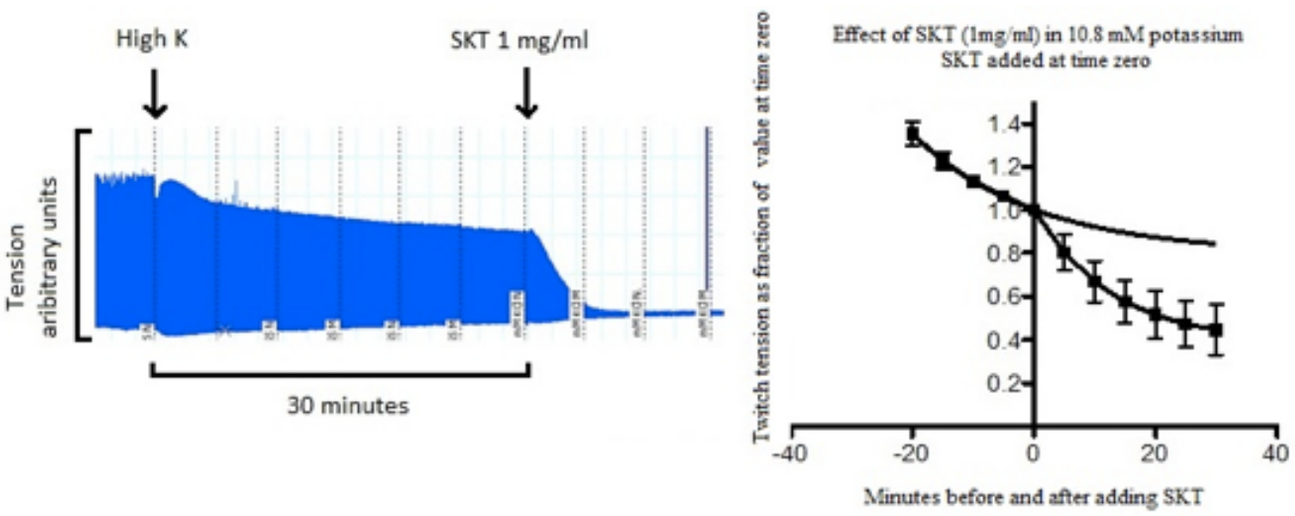
The following experimental results are described in two Abstracts presented at the Physiological Society Annual Meeting in 2015.

The first experiments determined whether the cramped muscle relaxant SKT (1:1 combination of root extracts from paeony and licorice that was identified in the Shanghanlun as working to relieve muscle spasm) has action on muscles in a normal physiological state. The results of these experiments show that in isolated skeletal muscles, very high doses were required to obtain an effect, and which are high compared to likely therapeutic doses (Sam, Terrar et al. 2015).

The second series of experiments were designed to test a more critical hypothesis. Does one or other of the ionic or chemical changes that would occur in strongly contracted muscle facilitate the action of SKT? We chose to test the possibility that such an effect might be mediated by potassium ions as a marker of the strongly contracting state in muscle.

The experimental result shown in Figure 2 supports the hypothesis. A dose of SKT that is well below the threshold for an effect at normal potassium concentration produces a large reduction in contractile force.

Figure 2. Action of 1 mg/ml SKT on response of rat phrenic nerve-diaphragm showing reduction of twitch in response to both nerve stimulation and direct muscle stimulation remains in the presence of a 100% increase in potassium concentration from 5.4 to 10.8 mM. Vertical bars show standard error. N = 9 (Sam, Terrar et al. 2015)



Analysis

We therefore analysed the result to conclude that external potassium is a potent facilitator of the action of SKT.

It is important to note that a reductionist viewpoint would not naturally lead to that hypothesis, because the effect did not seem likely from a reductionist viewpoint.

There is no example so far where potassium can act as such a powerful facilitator through direct effects on a drug-receptor interaction. It is much more likely that the effect arises through a network (a system) of interactions. This example therefore vindicates the multi-level systems approach.

III. Discussion: a way forward for drug discovery and development in the future:

This article shows how two of the Ten Principles of

Systems Biology have been developed and actually implemented in our research by using one example. In this discussion section, we will suggest a general way forward for the future.

It is widely recognised that the search for new medication faces major challenges. Pharmaceutical companies worldwide have experienced a disappointing outcome during the last decade or two, with increased investment resulting in decreased output in terms of the drug pipeline.

We suggest that the Ten Principles of Systems Biology, in particular, Biological Relativity and circular causality could be useful in research in the context of health care.

For example, the Ten Principles of Systems Biology, in particular, Biological Relativity and circular causality, are ideal for investigating research in the combination of (a) and (b) (below).

There are three distinguishable strategies for new drug discovery:

(a) Isolation and synthesis of active compounds from natural products

Investigation of the physiological and pharmacological mechanisms of action of natural products is not new. In western pharmacological science the first example is that of William Withering's research over two centuries ago (Noble 1984). He was the first to standardize the dose level of digitalis (foxglove), which was a prelude to the isolation and, eventually, the synthesis of cardiac glycosides.

This is the approach that also gave the world the first antibiotic, penicillin [2], in the 1940s. More recently it is also the approach that has given the world a new anti-malarial drug, artemisinin (in Chinese qinghaosu), for which Youyou Tu (屠呦呦) has just been awarded the Nobel Prize in Physiology or Medicine.[3]

Youyou Tu's discovery follows the usual paradigm in this approach, which is to isolate the active principle in a plant and then synthesise it. As with antibiotics, the result is a pure chemical compound.

(b) Classical investigations of physiological and pharmacological mechanisms.

Before the genomics era, the main approach was to investigate physiological mechanisms in order to identify possible targets, such as receptors, channels, enzymes etc. These were then used as screens to test many synthesised chemicals in order to discover chemicals that could interact with the target at low doses. One of the best examples of this approach was the discovery by Sir James Black of beta blockers such as propranolol and H2 receptor antagonists such as cimetidine, for which he won the Nobel Prize in 1988. [4] An example of successful use of this approach in our Oxford laboratory was the discovery of the i_f (funny) channel in 1979 (Brown, DiFrancesco et al. 1979), leading to the development of ivabradine by Servier. This work won the prestigious LeFoulon-Delalande Prize of the French Academie des Sciences for our co-worker, Dario DiFrancesco, in 2008.[5]

(c) Target new genes and related proteins discovered using genomics and proteomics.

The Human Genome Project, which succeeded spectacularly at the beginning of this century in sequencing the whole human genome (International Human Genome Mapping Consortium 2001), which also enabled comparisons with genomes of other species to be made, launched a new era in drug discovery. The expectation was that hundreds of new targets would be identified, and that this would result in many new cures for disease. Sadly, fifteen years on, this expectation has not been fulfilled. Even leaders of the Human Genome Project, such as Collins and Venter, admitted in articles in Nature (Editorial 2010) that the results have been "disappointing". This is not to say that sequencing whole genomes was not a worthwhile venture. But the outcome has been vastly more important for fundamental biological science in, for example, comparative genomics and evolutionary biology (Noble, Jablonka et al. 2014), than it has been for medical research (Joyner and Prendergast 2014).[6] Quite simply the level of the genome is too low. The relations between genes, defined as DNA sequences, and the phenotype are far too complex (Noble 2008, Kohl, Crampin et al. 2010) to enable this approach to work very often.

It is widely recognised that the search for new medication faces major challenges. Pharmaceutical companies worldwide have experienced a disappointing outcome during the last decade or two, with increased investment resulting in decreased output in terms of the drug pipeline. Could it be that we should return to the tried and tested strategies that worked in the past, before the genomics era?

We hope that, in future articles for this journal, we will be able to follow how Systems Biology will be further developed and contribute to health care.

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Notes

[1] http://gallica.bnf.fr/ark:/12148/bpt6k942459/f9.image
[2] See http://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html
[3] See http://www.nobelprize.org/nobel_prizes/medicine/laureates/2015/
[4] See http://www.nobelprize.org/nobel_prizes/medicine/laureates/1988/
[5] See http://www.beautiful-study.com/static/html/healthcare/ifcurrent.asp
[6] See also https://www.youtube.com/watch?v=A_q_bOWc8io

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The authors are members of Professor Denis Noble's laboratory at the Department of Physiology, Anatomy and Genetics, Medical Sciences Division, University of Oxford.

Professor Denis Noble CBE FRS FRCP developed the first mathematical model of cardiac cells in 1960 using his discovery, with his supervisor Otto Hutter, of two of the main cardiac potassium ion channels. These discoveries were published in Nature (1960) and The Journal of Physiology (1962). The work was later developed with Dick Tsien, Dario DiFrancesco, Don Hilgemann and others to become the canonical models on which more than 100 cardiac cell models are based today. All are available on the CellML website. The 1985 paper with DiFrancesco was selected recently to celebrate the 350 years of publication of Philosophical Transactions of the Royal Society.
He was elected President of the International Union of Physiological Sciences (IUPS) at its Congress in Kyoto in 2009. He was then elected for a second term at the 2013 Congress in Birmingham, UK.
He is the author of the first popular book on Systems Biology, The Music of Life, and his most recent lectures concern the implications for evolutionary biology. He has published more than 500 papers and 11 books. A new book is in preparation.

Kazuyo Maria Tasaki is Senior Researcher in Professor Noble's laboratory since 2011. She has been researching on the development of theoretical Systems Biology and investigations of experiments (in vitro) and mathematical modelling experiments (in silico). Under Professor Noble's supervision, she contributes to the development of a new approach to circular causality and she is the originator of the concept of "Innovative Systems Biology", bringing a novel approach to Systems Biology to multi-component medication. She received an "Award for Excellence" by the Department of Physiology, Anatomy and Genetics, Medical Sciences Division, University of Oxford, in April 2014. She was awarded her Masters degree by the University of Oxford in 2010, and her B.A. degree by Keio University, Japan.

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