PRINCIPLES OF SYSTEMS BIOLOGY IN RELATION TO TRADITIONAL MEDICINE IN EAST ASIA

Kazuyo Maria Tasaki, Toshiaki William Tasaki and Denis Noble

I. Introduction

I.1. *Prescriptions from the Heart of Medicine, Ishinpo* (醫心方)

The stimulus that led to the writing of this article was a remarkable experience. In January 2012 the authors, as members of the University of Oxford Integrative Multi-Scale Systems Biology (IMSBiTM) project, were privileged to view some of the beautiful manuscripts of the *Ishinpo* (醫心方), *Prescriptions from the Heart of Medicine* [1], carefully preserved in the Imperial Palace Library in Tokyo. The thirty scrolls were originally compiled from around 200 sources from China, Korea and India by Tamba Yasuyori (丹波康頼), physician to the Emperor, and dedicated to the Emperor in 984.[2] One thousand years later, in 1984, the *Ishinpo* was designated as a National Treasure of Japan. We were accompanied by Ms. Sachiko Maki, who has worked for 40 years on the translation of the *Ishinpo* into modern Japanese, by Professor Paul Chen from Tokyo University, and by Professor Yoshihisa Kurachi from Osaka University, a leading systems biologist in Japan.

Our visit was a follow-up of a speech that one of us (Noble) made as President of the International Union of Physiological Sciences (IUPS) at its world congress in Kyoto in 2009, in the presence of HIH The Crown Prince of Japan. That speech highlighted the significance of the *Ishinpo*, and it led directly three years later to the visit to the Imperial Palace archives. We were allowed to view some of the 30 scrolls, and our choice was: 1, which is the introductory philosophy; 6, which concerns the organ systems of the body; 26, 27 & 28, which concern life style, prevention of disease and promotion of longevity.[4]

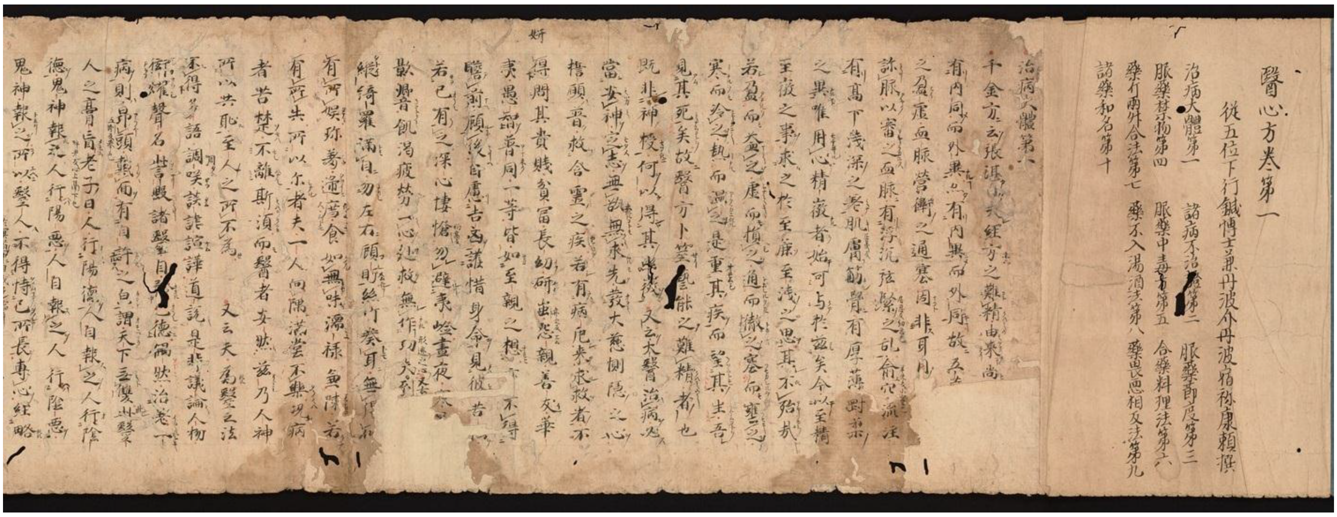

Figure 1: Part of volume 1 of the manuscript scrolls of the *Ishinpo* (*Nakarai-bon*). The *Ishinpo* was acquisitioned by the Japanese Government in 1982, and made into a National Treasure in 1984. [3]

Although there are printed versions of the *Ishinpo*, there are advantages in viewing a treasured handwritten scroll. For example, the scrolls have red marks (*wokoto ten*), and margin notes, in addition to the main text, which are not represented in the printed version. We also identified the formatting of a poem in scroll 1 quoted from Indian Buddhist poetry, which is also not indicated in the printed version.

As an example in relation to life style and longevity, which will be explored more in the future in the context of the Ninth Principle of systems biology (II.9), scroll 28 refers to the three women Su nu (素女), Xuan nu (玄女) and Cai nu (采女), who are said to have taught the arts of the inner chamber as a prescription for longevity (Ye Te Hui 葉徳輝 1903; Needham 1954-; Wile 1992; Umekawa 2004; Umekawa 2008)

I.2. Integrative Multi-scale Systems Biology

The other meeting we were attending was an international symposium on computational systems biology at the University of Tokyo, organised by the High Definition Physiology Project, led by Professor Kurachi [8], where Noble gave a plenary lecture, in which he briefly mentioned the *Ishinpo* and suggested the future developments of systems biology. The link between this symposium and the visit to the Palace Library is the idea that systems biology can form a good basis for the development of the interaction between western and Asian forms of medicine.

Although this project began with its inspiration from the *Ishinpo*, it is important to emphasise that the project will be using other original sources of

Figure 2. Enlarged images of calligraphy in scroll 28 from the *Nakarai* version of *Ishinpo* showing the characters for the names of the three women, Su nu (素女), Xuan nu (玄女) and Cai nu (采女). [5]

The historical sequence of women being represented in this way may be seen as follows. The idea of instructresses dates back at least to the Mawangdui (馬王堆) tomb excavations in Changsha (長沙), circa 200 BCE (Li and McMahon 1992): three women are found briefly in MSIII: *Recipes for Nurturing Life*, with the names South Beauty, West Beauty and Young Beauty [6], and instructing the master on rejuvenation using the arts of the inner chamber (Harper 1998). The name of *Su nu* appears three centuries later in a poem, *Tong-sheng-ge* (同声歌), by Zhang Heng (張衡) (78-139 CE) [7] (Van Gulik 1974). One of the original texts of scroll 28 is The *Classic of Su Nu*, (素女経), listed by title in the history of the Sui dynasty (589-618) but lost as an original text, refers to the three women instructors *Su nu, Xuan nu* and *Cai nu* (Ye Te Tui 葉徳輝 1903)

Chinese medicine, including *Shang han za bing lun* (傷寒雜病論) in c. 150-219 by Zhang Ji (張機); *Shang han ming li lun* (傷寒明理論) in c. 1066-1156 by Cheng Wuji (成無己); *Bei ji qian jin yao fang* (備急千金要方) in c. 652 by Sun Simiao (孫思邈); anonymous *Wai tai mi yao fang* (外台秘要方) in c. 752. The project has been consulting collaborators, scholars and institutions of traditional medicine in the UK, China, Korea and Japan. The approaches will be to use the mathematical and computational methods provided by systems biology to analyse the examples that best enable the interaction between systems biology and traditional medicine to work effectively. Integrative Multi-scale Systems Biology is necessarily a holistic approach to processes of the body. Because of this feature it can naturally relate to the holistic aspects of traditional medicine.

II. The Ten Principles of systems biology and traditional medicine

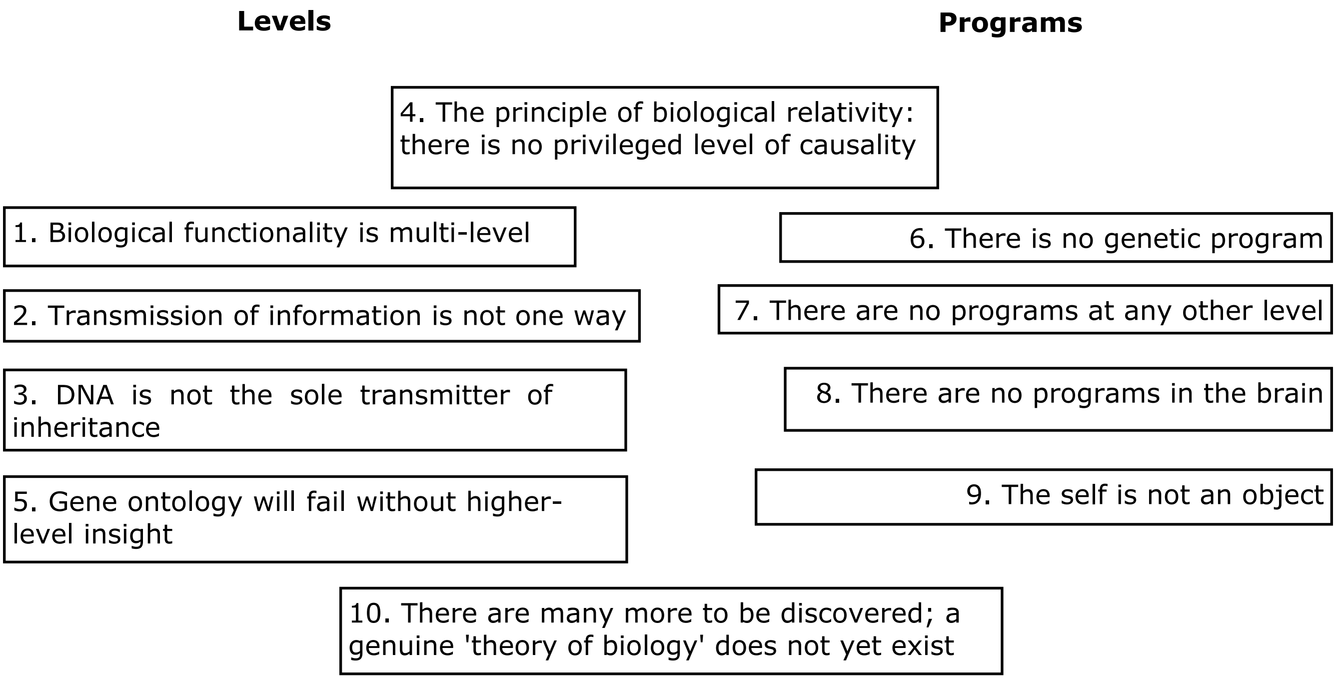

Figure 3. The ten principles can be divided into those primarily about levels (left) and those concerning the question of 'programs' (right). The theory of biological relativity is the central principle from which the others can be derived.

The concepts of systems biology have been summarized as a set of Ten Principles (Noble 2008). This section will extend those principles by asking in each case: what are the relationships with traditional medicine?

II.1. First Principle: Biological functionality is multi-level

The alternative to this principle is the idea that an organism is defined by its genome and that the genome is sufficient for the development of the organism. However, in fact, genes do nothing on their own. They consist in DNA sequences that are used by the organism as templates for the production of proteins and RNAs. They do not even initiate that production until activated by the organism through transcription factors and other forms of control of the genome. The genome is therefore better viewed as a formatted database. There is no 'genetic program'. The genome is not 'the book of life' (Noble 2006). The Nobel Prize winner Barbara McClintock described the genome in 1984 as 'an organ of the cell' (McClintock 1984). What she meant was that the cell uses the genome via various forms of downward causation to control when and to what extent transcription occurs, and so how it serves the cell's functions. Modern biology shows she was right (Shapiro 2011). The state of the cell as a whole, including the expression pattern of transcription factors and the epigenetic marking of the DNA control the genome. That is how it is possible for the same genome to be used to express many different cell types.

Traditional medicine of course does not refer to genes or to DNA. Those were not known at the time the texts were written. But it is possible to view traditional medicine also as a multi-scale approach, including the environment, the whole body, the organ systems, and the various channels through which feedback and circular causality could occur.

II.2. Second Principle: Transmission of information is not one-way

This principle refers to, and denies, the 'central dogma of molecular biology' (Crick 1970), which was an interpretation of the observation that DNA sequences form templates for amino acid sequences in proteins, but those protein sequences are not used to form templates for DNA sequences. Transmission of information was viewed as being one-way only. The genome was therefore thought to be 'sealed-off' from any influences running in the opposite direction. However, it is not true.

DNA sequences can be imported into the genome via reverse transcription of RNAs. In fact transposition of DNA sequences ('jumping genes') seems to have been common in evolution (Shapiro 2011). Moreover, information controlling the genome does pass from the organism to its DNA because, as emphasised in the first principle above, genes need to be informed to become active. There is 'downward causation' from all levels of the organism (Figure 4) to influence gene expression patterns and to mark the genome epigenetically.

Using the concepts of downward causation and circular causality (Tasaki 2012), it is possible to analyze the relevant insights from traditional medicine. Downward causation is necessary to allow circular processes to occur. These ideas relate to the fourth principle below.

II.3. Third Principle: DNA is not the sole transmitter of inheritance

Evidence for non-DNA inheritance is now substantial, including a variety of alternative mechanisms (Jablonka and Lamb 2005), including transmission via RNAs (Rechavi, Minevish et al. 2011). Also, prediction of the diseases people may suffer from using knowledge their genomes is quite limited (Roberts, Vogelstein et al. 2012). One of the aims of genomics in medicine is to develop patient-specific therapy, but because genotyping has limited utility, combining genotype and phenotype information as predictors will be the way forward.

Although medieval people did not know about DNA and genetic mechanisms, they did treat patients individually. Some forms of traditional medicine are also patient-specific, and they see the body as a whole (phenotype characteristics).

II.4. Fourth Principle: Biological Relativity

The fourth principle is the central principle: Biological Relativity: there is no privileged level of causality in biological systems (Figure 3). Like theories of relativity in physics, it abandons privileged viewpoints for which there can be no *a priori* justification. Most importantly, it views processes, such as attractors, as causes as much as the components of a system. There are different forms of causation. Not all causes are best represented in lower-level mechanical terms. The full explanation of the Biological Relativity principle is in Noble (2012).

The relevance to traditional medicine is that a state of health should be viewed as a whole body. It is possible to analyze the state of health by using the concept of attractor. Good health is a whole-body attractor towards which the system gravitates. An attractor that has a large field of parameter space from which the system naturally gravitates can be seen as a form of robustness. This robustness depends on the various systems of the body being resilient in the face of pressures either from the environment or from changes in the genome. Systems biology is identifying this kind of robustness in both cases. This will be discussed more in the later section.

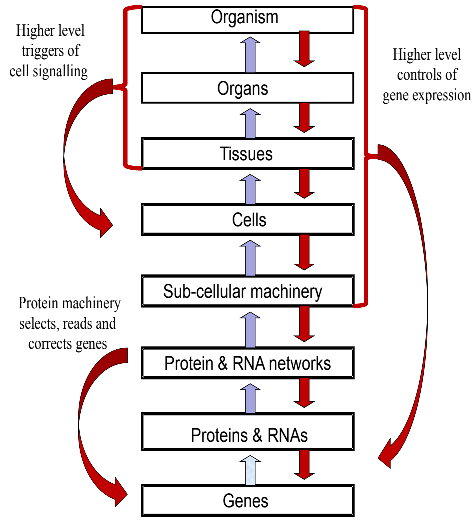

Figure 4. The levels of an organism and the forms of causal relations between them. The upward (blue) arrows show the causal relations assumed in a reductionist perspective in which genes determine the organism at all levels. There are two forms of downward causation: (a) between adjacent levels (e.g. protein machinery reads and corrects genes) and (b) across multiple levels (e.g. higher level controls of gene expression patterns).

Figure 4 illustrates the multi-level nature of the interactions involved in a systems biological approach to organisms and the various forms of causality between them. The multi-level nature of systems biology is one of the features that enable interaction with traditional medical ideas, although it is also important not to expect to map in a one-to-one or any other simple way to the equivalent representations of traditional medicine.

II.5. Fifth Principle: Gene ontology will fail without higher-level (functional) insight

It was originally thought that the connections between genes and functions might be simple. However, functions depend on the multiple interactions of many genes, and each gene is involved in many functions.

One of the problems with giving genes names based on the first observations of the effects of knockouts and mutations is that the nomenclature can give a limited view of the functions of a gene. For example, a 'cancer' gene is one which, when mutated or removed, predisposes the organism to develop cancer. However, that does not reveal the normal functions of that gene. Indeed the Gene

Ontology project [9] specifically excludes this kind of nomenclature for precisely that reason.

The problem goes even deeper. Most genes (and gene modules) are ancient on an evolutionary timescale. They functioned in forms of life (different species) without many forms of functionality. For example, many of the genes in a simple sea squirt are also found in humans, but they serve different functions: re-use and multiple use of genes are very common.

What then is a gene? Is it a stretch of DNA? A protein code? Or a function? The metaphorical analogies for genes are discussed in Noble (2006). Some biologists have proposed that we should change or not use the concept of a gene (Beurton, Falk et al. 2008; Shapiro 2011).

The relevance of this point to traditional medicine is that biological science needs to revert to characterising an organism in terms of its function (phenotype), for which interaction with insights from traditional medicine could help.

II.6. Sixth Principle: There is no 'genetic program'

The French Nobel Prize winners, Jacob and Monod, introduced the idea of the genome as the 'program of life' in the 1960s (Jacob and Monod 1961; Jacob 1970). It was based on the fact that, in those days, computer programs were written on paper or magnetic tapes to be fed into computers to instruct them on what calculations to perform. It was an attractive, but incorrect, idea. As emphasised earlier in this article, the causality runs both ways. The organism also instructs the genome what to do.

The plant geneticist, Enrico Coen, also made a very similar point when he stated in *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)

Figure 5. Images from the debate with Sydney Brenner at the conference of the virtual liver network in Leipzig in May 2012. There was agreement on the central question of genetic programs. Both participants agreed that the concept was of no value in modern biology.

This was brought out very clearly in a recent debate in May 2012 in Leipzig. between Noble and the Nobel Prize winner, Sydney Brenner. [10] This was the first time that some of the central ideas of the integrative view of systems biology were debated with a leading molecular biologist. Very significantly, Noble and Brenner agreed that "there is no such thing as a genetic program".

The relevance of this principle to traditional medicine is that, by including both directions of causality between organisms and their genomes, it leads to a more balanced way of viewing the body, and therefore corresponds well to the concept of balance in circular processes. Human beings are not programmed to do what they do. They are open systems, including interaction with the environment, which are also identified in traditional medical ideas.

II.7. Seventh Principle: There are no programs at any other level

If the genome is not a program, are there programs anywhere? The computer analogy has become so pervasive in modern biological science that it may seem obvious that, for any given function of an organism, there should be a program that runs that function. For example, if the heart beats regularly, must there be a program for regular heartbeat? The mechanism of heart rhythm is now well understood, and computer programs have been written that simulate it (Noble and Noble 2011). These are based on developing differential equations for the various protein components that are involved in the pacemaker cells of the heart. When these equations are solved, the electrical changes that generate heart rhythm can be accurately reproduced. However, the interactions between the protein components are not driven by a separate program. Their interactions *form* what we call heart rhythm. They are themselves the function. There is no need for the concept of a separate program in the body.

The relevance of this principle to traditional medicine is that it is more consistent with holistic views of the body.

II.8. Eighth Principle: There are no programs in the brain

A function involving the brain is also not a program for the same kind of reason. It *is* the function itself, not a separate program for the function. Yet, there is a tendency in neuroscience to compare the brain to a computer. The analogy can be helpful, up to a point. The nervous system can be seen as a set of 'wires', the nerve axons and dendrites, which connect together in the way that the components of a computer are connected together. However, other aspects of the computer analogy are clearly incorrect (Noble 2010). For example, the brain does not work on digital information, and it is not a serial computer. The better analogy would be a parallel computer, although that analogy should not be taken to mean that programs will be found in the brain.

The implications of this point for understanding traditional medical views are not clear since the idea of a program in the brain is a modern concept which has no strict analogy in traditional medicine.

II.9. Ninth Principle: The self is not an object

In recent centuries, at least since Descartes, western ideas have tended to reify the self, mind and consciousness (Hacker 2012). This principle proposes that the self is better viewed as a process. An attractor constrains the system components to behave in ways that maintain the process. This is a form of causation.

This view fits well with Taoist and Buddhist (no-self, *anatman*) ideas, including Zen meditation. Harmonising the processes of body and mind is important for broader approaches to well-being and longevity.

II.10. Tenth Principle: There are many more to be discovered

The work of systems biology in medical science is only just beginning. The formulation of the Ten Principles is intended as a guide to the systems approach. As the systems approach develops, many more insights can be expected to emerge.

III. Discussion: The way forward: nudging body systems back to health

III.1. Examples of levels of integration of function

As discussed, the central principle is that of biological relativity, i.e. that *a priori* there is no privileged level of causation. Any level might be the one at which integration of function occurs.

Heart rhythm, for example, is integrated at the level of the cell. The proteins and other components interact with the cell as a whole to generate rhythmic activity (Noble and Noble 2011). Many functions in organisms are integrated at the level of cells. But there are also many functions that require other levels to be taken into account, including that of the organism as a whole and its environment. By contrast, genes are too low in the hierarchy of levels for function to be ascribed to their interactions alone.

For example 80% of gene knockouts in yeast show no phenotypic effect under normal physiological conditions (Hillenmeyer, Fung et al. 2008). The networks of interactions effectively buffer the genome changes such that if the organism cannot achieve a particular function by mechanism X it does so via alternative mechanism Y. Further examples of this kind of genetic robustness can be found in (Noble 2011).

How did the idea of privileging genes – the genes-eye view – become so dominant? The second half of twentieth century biology was the period of the molecular biology revolution. To be able to discover and determine the structure and chemical reactions of the smallest components of organisms was the culmination of the microscopic approach. It was natural to ask what would happen if individual genes were removed or modified. Sometimes this approach is very revealing. Knockouts and mutations of genes have been the way in which many aspects of molecular genetics were developed. But, as we noted earlier in this article, this approach works in only a minority of cases. In most cases the organism is sufficiently robust that it can manage to function even when some of its molecular mechanisms no longer function.

There are also many examples of robustness in physiological control mechanisms. Here we will consider one case that illustrates the basic principles. It is well-known that high salt intake is a disease factor, and that one of the resulting disease states is hypertension. What is not so well-known is that for people in good health the body has mechanisms, involving the kidney and the renin-angiotensin system, that can almost completely buffer the rise in blood pressure. This was demonstrated experimentally by Guyton and his colleagues many years ago, and the effect was explained using a computational model (Guyton 1990) that can, today, be regarded as an excellent example of systems biology in practice. The feedback loops involved form part of an attractor that draws the system towards a particular 'safe' level of blood pressure.

III. 2. General properties of attractors

These examples lead to an important clinical application of the attractor idea. It is possible to think of the state space within which the system tends towards the attractor as a multi-dimensional volume, represented in Figure 6 as a shaded circle. Within that volume, the system is extremely resistant to disease; the healthy state is robust. But there are limits to that robustness. If any of the parameters is already in a state towards the edge of the state space that defines the range of the attractor, then the robustness will be small. Even a relatively small perturbation can take the system outside the 'safe' area. By one criterion, the body is still healthy. By another criterion, which is the amount by which a parameter like salt intake could be changed, the body is in a 'sub-healthy' state. The clinical application of this way of thinking is to design combined interventions that can nudge the system back towards a safer area of the state

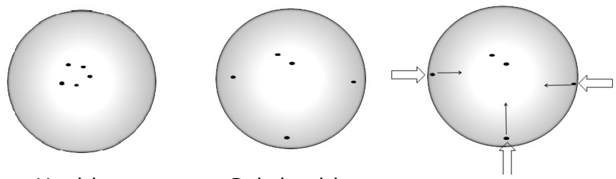

Figure 6. Interpretation of sub-healthy states in terms of an attractor state space diagram. The circles represent the state space within which parameters may occur in order for the system to move towards the healthy attractor. The state spaces will in fact be multi-dimensional, so this diagram is simply a two-dimensional representation. In the left diagram, all the parameters (black dots) are well within the boundaries of the state space and the system will be very robust. In the middle diagram, three of the parameters are represented as being in the shaded border areas. Since they are still within the attractor state space, the system will still show an apparently healthy attractor. But relatively small parameter changes could shift parameters outside the state space so that the system would move to a different (diseased) attractor. This represents the 'sub-healthy state'. The best remedy is to nudge the parameters back towards the central area to restore robustness (right). In this case, three interventions (arrows) would be required, i.e. a multi-component remedy.

Figure 6 is a simplified representation of this idea. State spaces for an attractor are multidimensional and cannot be properly represented by a two-dimensional diagram. There will also be different state spaces for each parameter. Lumping them all together in one 'space' is also a simplification. Moreover, the values of each parameter may affect the state spaces of other parameters.
In conclusion, the development of Integrative multi-scale Systems Biology has recognised the inter-relatedness of processes. In this sense, modern biology is using some of the concepts of physics which has recognised inter-relatedness for around 100 years in its theories of relativity and quantum mechanics. It is time for biological and medical science also to adopt the relativistic approach, and mutual interaction with relevant insights from traditional medicine could help such development.

Acknowledgements

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Notes

[1] The *Ishinpo* may be susceptible to scientific analysis by the methodologies of systems biology since it covers theory and practice, including pragmatic diagnosis and multi-component remedies which are based on many sources which were selected from the original compiler's perspective, a perspective which is consistent with the integrative ideas of systems biology (Tasaki, 2012).

[2] The texts are written in classical Chinese and they have recently been completely translated into modern Japanese (Maki, 1993-2012). Only a few volumes of the texts have been translated into English (Wile, D. 1992).

[3] E-museum *Prescriptions from the Heart of Medicine* (*Ishinpo*) website, 2012: http://www.emuseum.jp/detail/100173?x=&y=&s=&d_lang=en&s_lang=ja&word=&class=&title=&c_e=&region=&era=&cptype=&owner=&pos=41&num=8&mode=detail&century=

[4] Vol. 1 of the *Ishinpo* includes theory and philosophy for medicine, and vols. 2-30 include descriptions of diagnosis, causes of health and disease, remedies, formulae of herbal/ mineral medications, methods (including nutrition and lifestyle) for good health and longevity (Tasaki, 2012).

[5] E-museum *Prescriptions from the Heart of Medicine* (*Ishinpo*) website, 2012.

[6] It is not known whether these three women can be identified specifically with the later names. Reference to them in the Mawangdui texts is very brief. (Harper, 1998)

[7] He was a famous mathematician and astronomer as well as poet. Very few of his poems survive (Van Gulik, 1974)

[8] http://hd-physiology.jp/sympo2012/program/

[9] http://www.geneontology.org/

[10] http://www.virtual-liver.de/wordpress/en/2012/07/16/the-virtual-liver-network-keynote-debate/

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About the Authors

The authors are participants in the University of Oxford Integrative Multi-Scale Systems Biology in Interaction with Traditional Medicine (IMSBiTM) Project, Department of Physiology, Anatomy and Genetics, University of Oxford

Professor Denis Noble CBE FRS FRCP held the Burdon Sanderson Chair of Cardiovascular Physiology at Oxford University from 1984 to 2004 and was appointed Professor Emeritus and co-Director of Computational Physiology. He is one of the pioneers of systems biology and developed the first viable mathematical model of the working heart in 1960. His research focuses on using computer models of biological organs and organ systems to interpret function from the molecular level to the whole organism. Together with international collaborators, his team has used supercomputers to create the first virtual organ, the virtual heart.

As Secretary-General of the International Union of Physiological Sciences 1993-2001, he played a major role in launching the Physiome Project, an international project to use computer simulations to create the quantitative physiological models necessary to interpret the genome, and he was elected President of the IUPS at its world congress in Kyoto in 2009.

He is also a philosopher of biology, and his book *The Music of Life* challenges the foundations of current biological sciences, questioning the central dogma, a unidirectional view of information flow, and its imposition of a bottom-up methodology for research in the life sciences.

Kazuyo Maria Tasaki read literature at Keio University, and was awarded the degree of Master of Studies by the University of Oxford Faculty of Oriental Studies in October 2010, for a comparative study of virtues of human beings in medieval Europe (mainly England and France) and Heian Japan. Maria has been working for this project as a researcher since its launch in October 2011, as well as continuing her studies as a student. Maria has been contributing to identification of the relationships between the concept of Integrative Multi-scale Systems Biology and insights from traditional medicine, to writing of material for publication, and to building of relationships for collaboration.

Toshiaki William Tasaki read politics, and has currently been studying philosophy and literature at Keio University, Tokyo. William has been working for this interdisciplinary project since its launch in October 2011, as the Japan Representative. He contributed to the arrangement of our visit to Tokyo in January 2012, including negotiations with the Imperial Palace Library and publishers, as well as the formation of relationships for collaboration. William has started working on the translation of Prof. Noble's *A journey in Physiology towards Enlightenment* (2012) into Japanese. William has been also contributing to charity activities and international exchanges as a former executive of an industrial company, and as a member of cross-cultural organizations, including the Rotary Club of Osaka-North, and the Japan British Society of the Kansai.

Address: University of Oxford Integrative Multi-Scale Systems Biology in Interaction with Traditional Medicine (IMSBiTM) Project, Department of Physiology, Anatomy and Genetics, University of Oxford, Parks Road, Oxford, OX1 3PT, UK