



Discussion

Circular causality in integrative multi-scale systems biology and its interaction with traditional medicine

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ABSTRACT

This paper discusses the concept of circular causality in “biological relativity” (Noble, *Interface Focus* 2, 56–64, 2012) in the context of integrative and multi-scale systems approaches to biology. It also discusses the relationship between systems biology and traditional medicine (sometimes called scholarly medical traditions) mainly from East Asia and India. Systems biology helps illuminate circular processes identified in traditional medicine, while the systems concept of attractors in complex systems will also be important in analysing dynamic balance in the body processes that traditional medicine is concerned with. Ways of nudging disordered processes towards good attractors through the use of traditional medicines can lead to the development of new ways not only of curing disease but also of its prevention. Examples are given of cost-effective multi-component remedies that use integrative ideas derived from traditional medicine.

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1. Introduction

This article responds to the final discussion paper (Bard et al., 2013) in this focussed issue of the journal on *The Conceptual Foundations of Systems Biology*. It discusses circular causality, attractors and balance in systems biology, and the use of these concepts in multi-factorial diseases and multi-component remedies together with interactions between integrative multi-scale systems biology and traditional medicine (sometimes known as scholarly medical traditions).¹ The article is based on the ideas that systems biology is necessarily integrative and multi-scale, or multi-level² (Boyd and Noble, 1993); that “there is no privileged level or scale of causality” (the principle of biological relativity; Noble, 2012); and the idea that causality can be circular (Bernard, 1865; Bard et al., 2013). This paper shows how the interactions between these ideas and the concepts underlying traditional medicine help to explain why diseases with complex aetiology, which are more prevalent in aging populations, can be treated with multi-component remedies. It gives four examples of new forms of remedy that derive from such interactions. It also points a way towards new and broader approaches to health and longevity.

There are many sources for traditional medicine,³ and this paper refers mainly to the *Ishinpō* (医心方, *Prescriptions from the Heart of Medicine*)⁴ (Tamba, 984a,b,c). The *Ishinpō* was compiled from many important medieval medical sources from China, India and Korea by Tamba Yasuyori (丹波康頼), physician to the Imperial family, and was dedicated to the Japanese Emperor in 984. The underlying principles of the *Ishinpō* include the following: holistic conceptions of the body; ideas that are equivalent to downward causation from all levels, including the environment; circular processes within the body; and the idea of multi-component remedies for disorders and diseases. The *Ishinpō* 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.⁵

³ The main important sources include: *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; Mawang-dui (馬王堆) medical manuscripts (Harper, 1998); Dunhuang (敦煌) medical manuscripts (Lo and Cullen, 2005).

⁴ Online images of the Nakarai version of the manuscripts are available on the National Museum e-Museum website (Tamba, 984a).

⁵ Vol. 1 of the *Ishinpō* 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. They are relatively free from magical or superstitious aspects, and they do not include violent methods of therapy. (Sugitatsu, 1991; Maki, 2012).

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¹ This paper does not try to cover traditional medicine in general.

² It is important to distinguish between levels and scales, but downward causation and circular causality can be represented as occurring in both cases (Bard et al., 2013).

The ideas of systems biology and some insights of traditional medicine share much in common: systems biology involves the integration of parts into a whole, while holistic approaches consider the body as a whole. The multi-scale nature of systems biology, including downward causation and there being no privileged level of causality, map to some aspects of traditional medicine that identify causes of health and disease at all scales. Concepts of circular causality, open systems and balance in systems biology may correspond to circular processes of the body identified in traditional medicine. Those processes can be viewed as attractors in systems biology.

1.1. Integrative and multi-scale views of systems and processes

As Kitano (2007) and Noble (2009) point out, the development of integrative and multi-scale views of systems biology provide considerable insight into traditional medicine. This is because a systems biology perspective can identify integrative and multi-factorial views within traditional medicine. For example, when interpreting the Chinese characters for the organs of the body in texts for scholarly medical traditions, it is important to realise that the character for the word translated as heart (心, *shin/shin*)⁶ has several other meanings, such as the heart system, the chest, and the centre of the body. It is also clear that, in translating traditional medical texts, one should refer to the liver system, lung system, kidney system, and pancreatic system, rather than just the anatomically distinct organs (Hsu, 1999. Lu and Needham, 2002. Porkert, 1982).⁷

The concept of circular causality is one of the most important integrative and multi-scale views in systems biology and was first introduced into biology by Claude Bernard (Bernard, 1865, 1984. Noble, 2008) to help explain his concept of the constancy of the internal environment; this was later described as ‘feedback’ when the ideas of cybernetics were introduced (Wiener, 1948). In 1970, Humberto Maturana (quoted in Maturana and Varela, 1980) used the concept of circularity in the phenomenon of self-causation called *autopoiesis*. Circular causality also involves the concept of “downward causation” (Noble, 2006, 2012).

The idea of circular causality includes feedback both within the body and between the organism and its environment. Traditional medicine takes the view that all parts of the body interact with each other and the organism interacts with the environment so that the organism has to be viewed as an open system,⁸ for example in explaining ‘well-being’ (氣, *ki/qi*) (Noble, 2011–2012).⁹ The idea of an open system is of course important in modern physical and biological sciences, and is defined as a system that exchanges materials and energy across its boundaries with the environment.

The approaches of systems biology seem to map well to traditional views of health and disease¹⁰: health is regarded as a good balance of circularly-interacting processes, and disorder or disease result from lack of such balance. Since causes for diseases are multi-factorial, it is believed that the remedies should have multiple components to restore the balance.¹¹

⁶ (Modern Japanese pronunciation/modern Chinese pronunciation).

⁷ Examples are found in volume 6 of the *Ishinpō*, which concerns organs and related systems.

⁸ Examples are found in volume 27 of the *Ishinpō*, which concerns health and wellbeing.

⁹ ‘Well-being’ is one possible representation of the concept of *qi*. There are many others (Hsu, 1999).

¹⁰ Examples are also found in volume 27 of the *Ishinpō*.

¹¹ For example, chapter 1, volume 12 of the *Ishinpō* concerns diagnosis of a condition 消渴 (*shōkatsu*, *shōkachi/xiao ke*) that could be described as a form of diabetes in a general sense (Slak Rupnik, 2012), and there is no 1:1 mapping of the traditional and modern concepts of diabetes. The formulae for remedies proposed have multiple combinations of herbs and/or minerals.

One important systems concept is that of attractors: these are self-perpetuating processes (self-generating systems) towards which the system naturally moves from many possible initial starting points (Gleick, 1987). Their existence depends on circular causality or feedback. The dynamic balance of traditional medicine is a state of health towards which the body naturally gravitates and so can also be seen as an attractor. A healthy state can be represented as a robust global attractor, with many parameters, and other attractors which underpin its existence and maintenance. The treatment of multi-factorial disorders and diseases and the promotion of good health can be seen as nudging the disordered body processes towards good attractors and, in principle at least, techniques from computational biology might be used to determine which multi-component interventions might be useful. Such analyses could assess the relative importance of various feedback loops within the attractors (Boyd, 2012), and so identify better strategies for prevention.

Methods of prevention can be seen as important aspects in particular traditional medicines. For example, the *Ishinpō* refers to lifestyle as a whole, including the effects of interactions with the environment, the selection of foods and exercise as significant in maintaining a state of health and in preventing disease.¹² A healthy body can be interpreted as one that displays the processes of a good attractor that can be maintained indefinitely. The processes of a good attractor could be a way of interpreting or crystallizing the traditional concept of ‘wellbeing’ (氣, *ki/qi*) from a modern scientific perspective (Noble, 2011–2012). These ideas would lead to the development not only of more cost-effective remedies (since prevention is the best remedy) but also towards a more integrative approach to health.

1.2. Examples of multi-component therapies that combine traditional and modern components

Multi-component remedies for complex multi-factorial diseases that derive from the treatments and ideas of traditional medicine are now being developed, as these four examples show.

First, arsenic was a traditional treatment for diseases that we now call cancers and has recently been revived as a part of multi-component remedies. Combined with retinoic acid and chemotherapy, it has been possible to produce complete remission in some leukemias with a 5-year survival rate of 90% (Chen et al., 2011). The precise molecular mechanisms by which this impressive result has been obtained have also been determined. They include interactions between arsenic and a number of proteins, and the results suggest that this multi-component approach may also form the basis of remedies for other forms of cancer (Liu et al., 2012).

Second, an important notion in traditional medicine is that one component in a multi-component therapy may enhance the action of another. Some of the enhancers being used in modern therapy come from herbal remedies. A good example is piperine derived from black pepper. In combination with an anti-TB drug, rifampicin, it reduces the amount of rifampicin required by 60%, thus minimising unwanted side-effects (Randhawa et al., 2012).

Third, curcumin is a component of turmeric, a herbal root widely used in curries. It has been shown to be an effective enhancer of chemotherapy in a variety of cancers, including colon cancer. In that particular case, there have been several clinical trials showing that it is safe and trials testing efficacy in treatment are now under way (Johnson and Mukhtar, 2007). A key factor in this case is that curcumin enhances the efficacy of the chemotherapy.

Finally, a component of herbal medicines called dihydromyricetin has been shown to have a potential in the treatment of alcohol

¹² For example, volumes 26–30 of the *Ishinpō* concern various methods of prevention of disease. 1.

intoxication and the mechanisms of its action have been elucidated in experiments on the nervous system (Shen et al., 2012).

These examples offer cost-effective remedies since the traditional herbs and minerals used are widely available and relatively inexpensive compared to manufactured drugs; and because, in the second and third examples, use of traditional enhancers reduce the quantities of expensive drugs required.

How could systems biology in general help to explain the way in which multi-component remedies of traditional medicine work? Systems biology provides mathematical tools for calculating multiple actions, while traditional medicine allows multiple components to be varied independently. The ideal methodology investigates parameter space for good attractors using sensitivity analysis to identify concentrations that nudge the diseased system back to the attractor state. Mathematical modeling of the type discussed above should demonstrate why certain combinations will work and others fail. This approach should also apply to prevention as well as to cure.

2. Discussion

This paper discusses a number of suggestive and important ways in which systems biology can be of use in understanding and developing the insights of traditional medicine. Moreover, some of these insights may well aid the development of the principles of systems biology, particularly in the concepts of circular causality, attractors and balance in biological relativity.

At the larger scales of the body as a whole, much work needs to be done using the methodologies of systems biology to understand the insights of traditional medicine. One significant development is the way in which the Physiome Project is now reaching up towards whole-body systems analysis (De Bono and Hunter, 2012). De Bono and Hunter outline a vision for the application of community-based modeling standards in support of an automated integration of models across physiological systems and scales. Computational physiology produces many such models and standards at multiple levels from organism down to organ, cell and subcellular process (Hunter, 2012). This will be an important source of ideas for the further development of integrative multi-scale systems biology, and its interaction with traditional medicine.

In conclusion, the interaction between systems biology and traditional medicine may achieve: further development of integrative multi-scale systems biology; new approaches to mathematical modeling suitable for applications in traditional medicine; new methods for the prevention of disorders and diseases, including cost-effective remedies; and may point the way towards novel approaches to health and longevity.

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