



# A dynamic network model of the similia principle



Paolo Bellavite<sup>a,\*</sup>, Debora Oliosio<sup>a</sup>, Marta Marzotto<sup>a</sup>,  
Elisabetta Moratti<sup>a</sup>, Anita Conforti<sup>b</sup>

<sup>a</sup> Department of Pathology and Diagnostics, University of Verona, 37134 Verona, Italy

<sup>b</sup> Department of Public Health and Community Medicine, University of Verona, 37134 Verona, Italy

Available online 8 September 2013

## KEYWORDS

Homeopathic theory;  
Similia principle;  
Network model;  
Complexity science;  
Homeopathic  
methodology;  
Symptoms analysis

**Summary** The use of drugs in high dilutions and the principle of similarity (or ‘similia’) are two basic tenets of homeopathy. However, the plausibility of both is a subject of debate. Although several models have been proposed to explain the similia principle, it can be best understood and appreciated in the framework of complexity science and dynamic systems theory. This work applies a five-node Boolean network to show how self-organization and adaptation are relevant to rationalizing this traditional medical principle. Simulating the trajectories and attractors of the network system in the energy state-space provides a rudimentary and qualitative illustration of how targeted external perturbations can have pathological effects, leading to permanent, self-sustaining alterations. Similarly, changes that conversely enable the system to find its way back to the original state can induce therapeutic effects, by causing specific shifts in attractors when suitable conditions are satisfied. Extrapolating these mechanisms to homeopathy, we can envisage how major changes in the evolution of homeodynamic systems (and, eventually, healing of the entire body) can be achieved through carefully selected remedies that reproduce the whole symptom pattern of the ill state.

© 2013 Elsevier Ltd. All rights reserved.

## Contents

Introduction.....	751
A Boolean five-element model .....	751
The state-space of energy.....	754
A dynamic vision of pathology.....	754
Stress and acute disease .....	756
Chronicization.....	756
Blocking of communication.....	756
Healing dynamics and “the similia” .....	757
The logic of symptoms .....	758

\* Corresponding author. Tel.: +39 458202978.

E-mail address: [paolo.bellavite@univr.it](mailto:paolo.bellavite@univr.it) (P. Bellavite).

Conclusions and perspectives .....	759
Conflict of interest statement.....	760
Acknowledgements.....	760
References.....	760

## Introduction

The plausibility and clinical evidence in favour of homeopathic principles is a matter of current scientific debate.<sup>1</sup> The principle of similarity or “similia” (“let like be cured by like”), which is the central pillar of homeopathy, states that patients who exhibit particular signs and symptoms can be cured by giving them a drug that produces similar symptoms in healthy individuals. This ancient therapeutic approach can be summed up by the “action-reaction” principle that governs homeodynamics, and we have previously presented a model based on feed-back regulation.<sup>2,3</sup> However, simple feed-back is unable to accommodate the full complexity of physiological regulations and pathological changes, so that more elaborate models may be needed to understand the general rules that underlie the homeopathic principle. Other authors have suggested, starting from different perspectives, that homeopathy should be interpreted as a network-regulatory medical approach.<sup>4–7</sup> In particular, a growing body of findings illustrates the importance of state-dependency in learning, physiological experiences, and pharmacological interventions. The effects of any external stimulus are not only determined by the properties or quantity of that stimulus, but also by the activation state of the target system.<sup>8–11</sup> This may provide a basic explanation for the similia principle: the “same” homeopathic medicine may provoke symptoms in an initially healthy person, and yet reverse them in a person who is in a disease state to which the remedy is relevant.

Medical traditions such as those of oriental origin and homeopathy are inherently based upon holistic and vitalistic paradigms, which can at least in part be interpreted according to the conceptual framework of dynamic systems and complexity theory. The ancient Chinese cycle of “five elements” envisages life energy as being rhythmically channelled through a network of reciprocal influences between the different organs and the different elements that make up the body. These elements are interconnected in a circular cycle of influences whereby each element exerts activation (also called “generation”) on the element immediately after it in the cycle, and inhibition (also called “submission”) on the element immediately following the one which it activates. Drawing from this scheme, we have in a previous work described the properties of a typical Boolean network system, made up of five nodes.<sup>12</sup> Our aim here is not to formulate some explanation of the Chinese medical system (which is far more sophisticated and refined), but to update this scheme and show how it may be applied to the homeopathic similia principle.

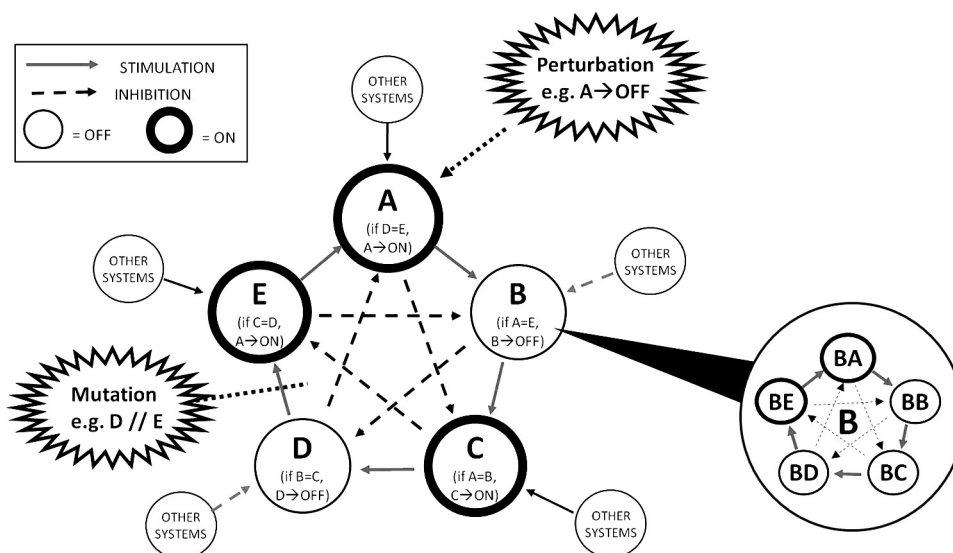
The network which we present (Fig. 1) is not technically speaking a mathematical model, but is rather intended as a conceptual model that qualitatively illustrates how a process may work. Here, we use a five-node model system in a ideal “energy space” to simulate the systemic and dynamic

changes that occur during disease and healing processes. In particular, we shall describe the changes in attractors induced by a pathological perturbation, and observe how the reversal of those changes (healing) can be induced by a “similar” perturbation. The specialist terminology used and the basic definitions from complex systems and network theory are given in Table 1.

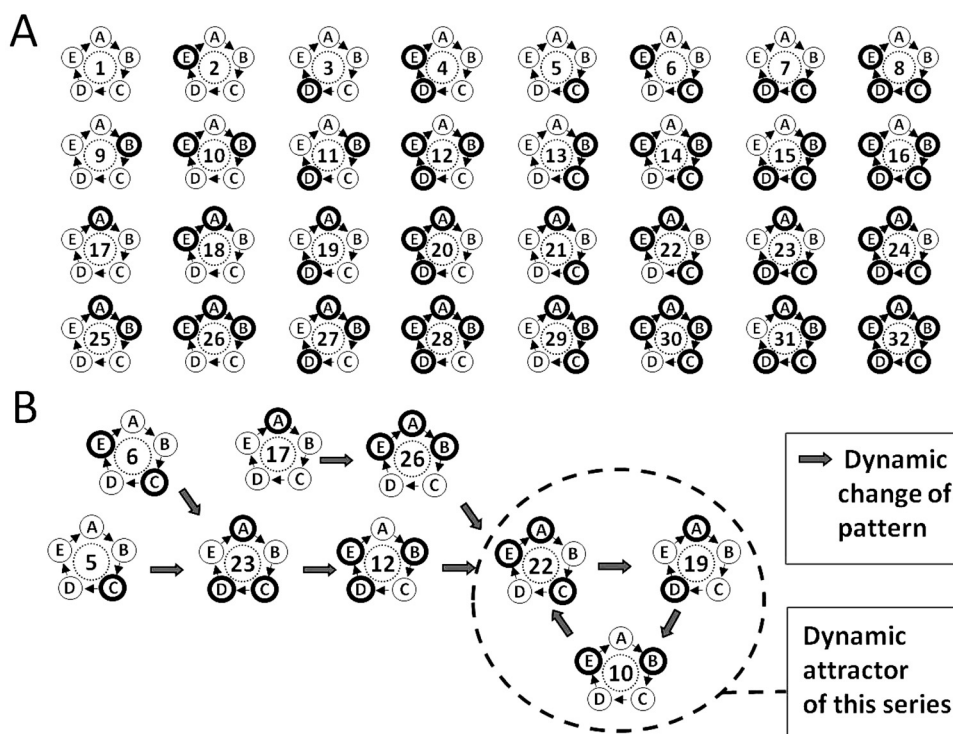
## A Boolean five-element model

As outlined in Fig. 1, the network nodes are interconnected by both stimulatory and inhibitory links, in such a way that we can simulate a perturbation by turning individual nodes on or off, and observe how this affects the behaviour of the network through successive iterations. We can also alter the connections between nodes (e.g., by breaking a link) to simulate a permanent “mutation” of the network’s behaviour. Fig. 1 also illustrates another important feature of natural networks, which is the property of fractal scaling, or self-similarity. Fractal scaling has a number of consequences, including the fact that even small changes in a subcomponent node can propagate through the entire network to become manifest at much higher scales of organization.

Since this model is made up of five nodes, each of which can be in one of two states, the possible patterns – which can be regarded as the “degrees of freedom” of this network – are  $2^5 = 32$ . (Fig. 2). As shown in Fig. 2A, each of these 32 patterns can be assigned a number, so as to represent all the possible combinations, and we can then use these numbers to track the succession of states that the system steps through, as it undergoes repeated cycles of transformation in an iterative process that simulates physiological changes. Observing this network at each time-step (or iteration) enables us to trace how its states (patterns) evolve through successive iteration cycles, starting from any arbitrarily chosen initial pattern. Fig. 2B illustrates the case where patterns five and six are the selected starting points. The system deterministically steps from one pattern to the next at each iteration. Eventually, since the possible combinations are not infinite, it will end up revisiting one of the previously formed patterns, and so from there repeat a previously-executed cycle of transformations. For example, in Fig. 2B, pattern 22 changes into pattern 19, which changes into pattern 10, which in its turn changes back to 22 again. All the patterns represented in Fig. 2B are thus “linked” in a chain which leads the system – after a certain number of steps – to be “attracted” towards a final state where it repeatedly cycles through the 22-19-10-22 pattern sequence. Such finishing states (or cycles of states) which networks attain over the course of time are called *dynamic attractors*, and each Boolean network will sooner or later reach one of these attractors and stay there. This model



**Fig. 1** A five-node dynamic Boolean network as a paradigm of complexity in physiology and pathology. A Boolean network consists of a set of processing units (nodes) connected to each other by a set of communication links that can change the state of their target nodes, in an analogous manner to synaptic connections in the nervous system. In the simplest form, the nodes are simple computing elements that acts as switches: when the sum of the incoming signals exceeds a given threshold, the node fires a signal towards another node. Each node contains the rule to follow in the case where the same input is received from both regulating nodes (i.e., both are in the OFF or ON state). The magnification of pattern "B" shows how each network can in its turn be thought of as composed of other self-similar networks in a fractal way.



**Fig. 2** Degrees of freedom and dynamic attractor of the Boolean network model described in Fig. 1. The possible patterns are represented as combinations of ON/OFF nodes connected by arrows (for sake of simplicity, only stimulatory connections are represented) (A) all the possible patterns (degrees of freedom) of the five-node network described in Fig. 1. (B) The subset of relationships that develop as the dynamics proceed and settle into a dynamic attractor of the Boolean network (no. 22-19-10), towards which different initial patterns (nos. 5 and 6) converge. For simplicity, all state transitions are synchronized, meaning that at each iteration step all nodes transition to the next state simultaneously. The simulation of dynamic changes through successive iterations was done using the "Model Maker" software for Windows (Cherwell Scientific Publications, Oxford, UK). Nodes in the ON state are shown in bold.

**Table 1** Glossary of terms used.

Subject/term	Definition
Attractor	An attractor is a set towards which a variable, moving according to the dictates of a dynamical system, evolves over time. An attractor can be a point, a finite set of points, a curve, a manifold, or even a complicated set with a fractal structure known as a strange attractor
Attractor basin	A subdivision of the space-state (see below) containing all the network patterns that converge towards the same attractor. In this basin, points that get sufficiently close to the attractor will remain close even if slightly disturbed
Boolean network	A Boolean network (after George Boole, who first defined an algebraic system of logic in the 19th century) consists of a discrete set of variables, each of which has a function assigned to it which takes inputs from a subset of those variables and whose output determines the state of the variable it is assigned to. The Boolean or logical data type is a variable which can have one of two values (usually denoted true and false, or ON and OFF), used to represent the outcomes of conditional statements (e.g., IF, AND, OR) for branching between different actions. The set of functions of the Boolean network defines a topology (web of interconnections) for its constituent variables, which thus become nodes in a network. Usually, the system's dynamics is expressed as a discrete time series where the state of the entire network at time $t + 1$ is determined by each variable's function on the state of the network at time $t$
Complex adaptive system	Special cases of complex systems, formed in order to adapt to the changing environment and increase survivability. They are complex in that they are dynamic networks of interactions, and their relationships are not aggregations of the individual static entities. They are adaptive in that the individual and collective behaviour mutates and self-organizes in response to changes in events
Emergence	The way complex systems and patterns arise out of a multiplicity of relatively simple interactions. Emergent systems can have qualities not directly traceable to the system's components, but rather to how those components interact (the whole is more than the sum of its parts). A typical example of emergent properties can be found in the biological organization of life, ranging from the subatomic level to the entire biosphere. Individual atoms can be combined to form molecules such as polypeptide chains, which in turn fold and refold to form proteins, which in turn create even more complex structures and eventually an organism
Epigenetics	It refers to functionally relevant modifications to the genome that do not involve a change in the nucleotide sequence. Examples of such modifications are DNA methylation and histone modification, both of which serve to regulate gene expression without altering the underlying DNA sequence. These changes may persist through cell divisions for the remainder of the cell's life and may also last for multiple generations
Fractal scaling	A fractal is a mathematical or geometrical entity that is endowed with a fractional dimension (from the Latin <i>fractus</i> , meaning "broken") and a repetitive configuration when viewed on different scales, i.e., self-similarity between details and the general pattern. Several natural objects (e.g., trees, arteries, mountains) and rhythms (e.g., heart frequency, financial oscillations) show fractal scaling. Also, the Chinese medical system, wherein the whole body is represented in a single organ (tongue, ear), adopts a fractal structure
Grounded theory	Grounded theory is a social sciences methodology that involves discovering a theory through the analysis of data. Rather than starting with a hypothesis, the first step is to collect data through a variety of methods. The collected data is then used to group key points into similar concepts, to make them more amenable to analysis. These concepts are then used to form categories, which become the basis for formulating a theory. This process is the reverse of the traditional research methodology, in which researchers first choose a theoretical framework, and afterward apply the chosen model to whatever phenomenon is being studied
Homeodynamics	From the Greek <i>homoiōs</i> (similar) and <i>dynamis</i> (energy), denotes the cooperative mechanisms of preserving and restoring of the structural integrity and functional efficiency of living systems. A more appropriate synonym of the traditional term homeostasis
Hormesis	Phenomenon whereby low doses have a stimulatory effect while high doses have an inhibitory effect, resulting in either a J-shaped or an inverted U-shaped dose–response curve
Idiotypic network	A theory of how the adaptive immune system works, developed mainly by Jerne and Hoffmann. The theory states that the immune system is an interacting network of lymphocytes and molecules that have variable ( <i>V</i> ) regions (idiotypes). These <i>V</i> regions bind not only to foreign things but also to other <i>V</i> regions within the system. The immune system is therefore treated as a network, whose components are connected to each other by <i>V–V</i> interactions

Table 1 (Continued)

Subject/term	Definition
Iteration	The act of repeating a process or a mathematical function with the aim of approaching a desired goal, target or result. Each repetition of the process is also called an "iteration," and the results of one iteration are used as the starting point for the next iteration
Mutation	In genetics, a mutation is a change in the nucleotide sequence of the genome. Here, the term is used to denote a change in the basic structure of the network that prevents the system from functioning properly
Nanoparticle	A small particle composed of one or more compounds, including linked water, measuring 100 nm or less. Nanoparticulate matter has different properties from its bulk form in terms of mechanical, optical, electrical, magnetic, chemical, biological, and quantum behaviours
Perturbation	An alteration, stimulation or inhibition of the function of a biological system, induced by external or internal factors
State-dependency	This term, usually applied to learning ability, is used here with the meaning that the response of a biological system to a stimulus depends on its present state, incorporating memory of previous experience
State-space	Also called the space of states, is a virtual space determined by the types of variables considered. If the evolving variable of an attractor is two- or three-dimensional, the attractor of the dynamic process can be represented geometrically in a space of two or three dimensions
Trait anxiety	There are two types of anxiety, "state" anxiety (excess anxiety experienced by a subject at a particular time in presence of a stimulus) and "trait" anxiety (an intrinsic feature of the subject that does not vary from moment to moment)
Vicious circle	A vicious circle (also referred to as a vicious cycle) refers to a complex chain of events, in which each iteration of the cycle reinforces the previous one through a feedback loop (positive feedback), with detrimental results. These cycles will continue in the direction of their momentum until an external factor intervenes and breaks the cycle
Water cluster	Aggregate of water molecules linked by hydrogen or other weak bonds. Water molecules can align themselves in pentagonal or hexagonal clusters by effect of their stereochemical structure. Clusters may be created when water molecules set themselves in a grid-like arrangement around an internal niche or cavity, upon agitation or sonication of the liquid in the presence or absence of a solute

of network attractors essentially describes the dynamics of living beings. For example, applying a similar concept to systems with a larger number of nodes and different types of connections has made it possible to approximate various interesting experimental observed phenomena occurring in cell differentiation,<sup>13,14</sup> cytokines,<sup>15</sup> neural networks,<sup>16,17</sup> and also cancer.<sup>18</sup>

### The state-space of energy

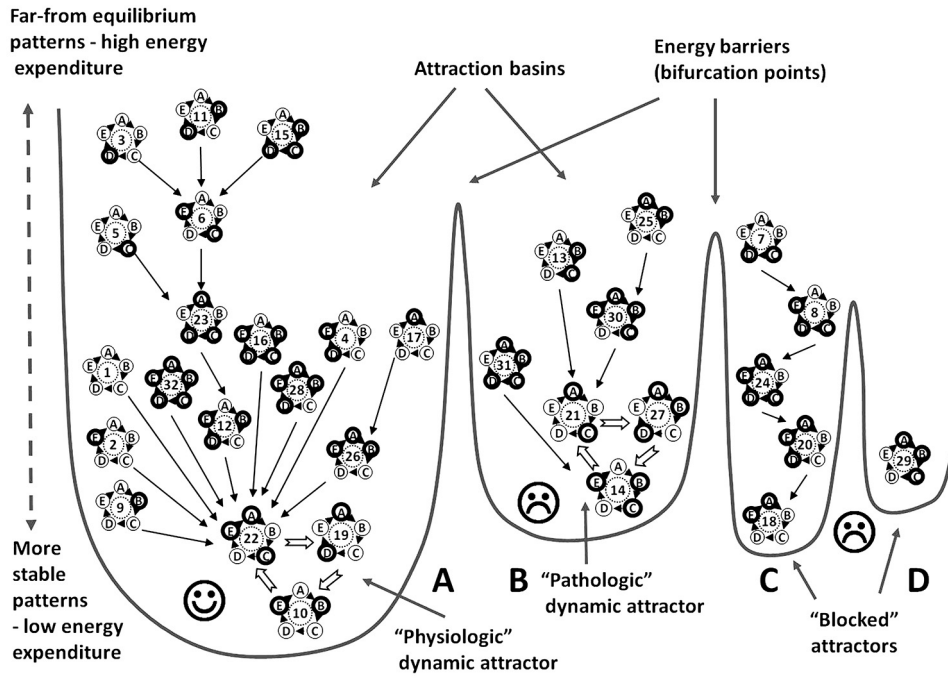
The state of a dynamic system at any given transformation step can be regarded as a point in its phase space, i.e., in the space delineated by the variables of the system itself. A phase space can have two or more dimensions, depending on the number of variables that characterize the system. If we plot energy expenditure along the vertical axis, as in Fig. 3, we obtain what can be described as an energy state-space, meaning that higher states (far from equilibrium) are unstable and have the tendency to descend towards more stable states, where energy expenditure is lower. Depending on the external and internal conditions (number of components and communication pathways, temperature, chemical concentrations, rates of change and so on), a network system may belong to different sub-spaces, or attraction basins, which lead it to naturally settle on different *attractors*. These

attractors are expression of the spontaneous emergence of ordered states from a variety of possible behaviours, and often have great stability because they are situated in a local minimum within their energy state-space. Cellular life can be viewed as one of many physical natural systems that extract free energy from their environments in the most efficient way. Therefore, the "healthy" state is characterized by a metabolic cycle whose functions are optimally organized in a way that minimizes energy expenditure and allows the individual to adapt and respond to unavoidable perturbations.<sup>19</sup>

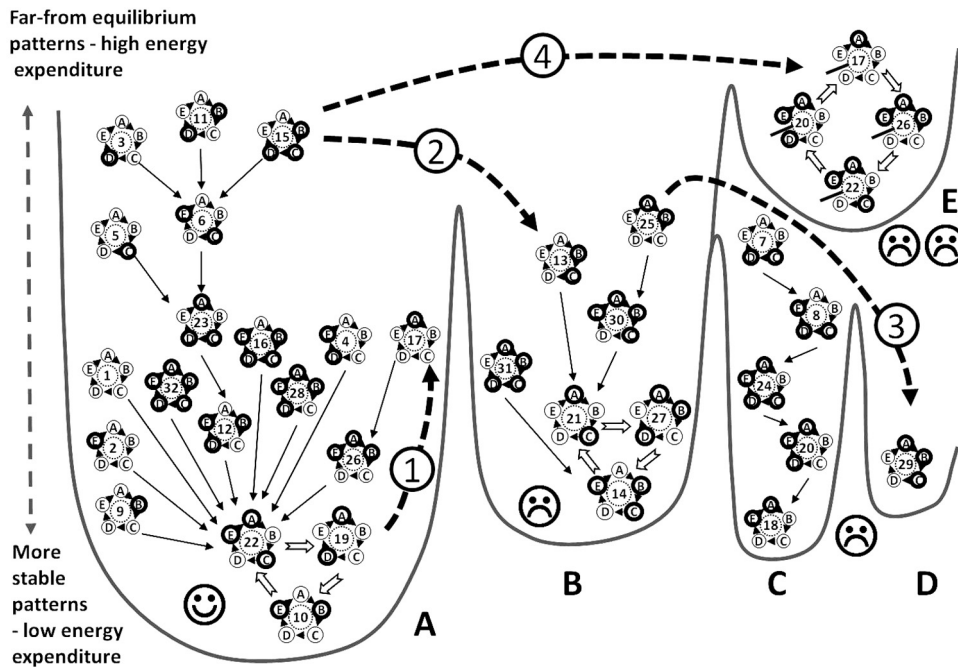
### A dynamic vision of pathology

The concept of disease is central to any medical approach because it unavoidably determines (consciously or unconsciously) the diagnostic methods and therapeutic interventions employed. Understanding the nature of the homeopathic approach to treatment requires adopting the framework of a non-reductionist view of pathology, regarded not as a rupture of a single mechanism but as a disturbance of biological networks. Fig. 4 illustrates the changes in the energy space when the network undergoes external perturbations or mutations that alter the communication links.





**Fig. 3** The full energy landscape of the four possible attractors of the system described in Fig. 1. The state-space provides a useful representation of the possible locations of a dynamic system within its so-called energy landscape. This landscape features valleys and hills that divide it into various sub-spaces (basins) that the different possible system configurations can occupy. Energy expenditure is plotted along the vertical axis, meaning that higher states are unstable and have the tendency to shift down towards more stable states (attractors) where the energy expenditure is lower. Attractor A is considered to be the normal one since it is the most populated; it is positioned at a more stable level, with lower energy expenditure, and can thus be regarded as the ‘‘physiological’’ one. Attractors B, C, D are arbitrarily positioned further from equilibrium, at higher energy expenditure levels.



**Fig. 4** Effects of ‘‘pathological’’ perturbations of nodes and changes of attractors on the Boolean network. (1) Perturbation ‘‘node D → OFF’’. (2) Perturbation ‘‘node D → OFF’’. (3) Perturbation ‘‘node C → ON’’. (4) Mutation ‘‘node D//node E’’ (blocking of communication). In this view, the chronic pathology is represented by certain networks becoming ‘‘stuck’’ in semi-stable states, referred to as local minima, that will not spontaneously reverse because exiting requires more expenditure from the organism’s energy balance than does remaining.

## Stress and acute disease

As a first case, by turning off node D in pattern 19, situated in attraction basin A, the system is pushed far from equilibrium and reaches pattern 17. By analogy with pathophysiological phenomena, we can consider this pattern as the effect of a stressful change. This may be analogous to a normal reaction (e.g., a small temperature increase, a subcutaneous wheal, a state of anxiety triggered by sudden fright), but it can also lead to "acute disease" if the reaction elicits severe symptoms. However, the spontaneous system dynamics will lead the network from state 17 to state 26, which in turn leads to state 22, thereby returning to the original attractor ("healing"). This type of spontaneous return occurs for various different perturbations of the network inside the same attraction basin. Examples of pathologies that exhibit this type of dynamic include abscesses, thrombi, acute allergy attacks, transitory ischemia, panic attacks and influenza infection. Although those conditions may cause severe complications, the function of homeodynamic systems is ordinarily well-maintained, so that the expected reversal to a previous healthy state is possible. For example, influenza and allergy attacks habitually heal even without treatment; after natural pus discharge, an abscess can disappear and tissue integrity can be restored; a thrombus formed in a blood vessel can be eliminated by the endogenous fibrinolytic system; transitory ischemia may be compensated and reversed by endothelium-dependent muscle relaxation and local vasodilation; and so on.

Of course, the severity of an acute illness will depend on the strength of the cause that provoked it, and on the extent to which it is controlled by normal defence systems and the reinstatement of homeodynamics. Damaging reactions and vicious circles can develop in a manner detrimental to the welfare of organism as a whole. In particular cases, especially when acute disease strikes a system already affected by serious inherited predispositions, other chronic conditions, or use of toxic substances (alcohol, drugs), the local damage may be so serious as to threaten the life of the subject.

## Chronicization

A markedly different outcome occurs if we apply the same perturbation ( $D \rightarrow \text{OFF}$ ) to pattern 15, because in this case the system transitions to pattern 13 (see trajectory no. 2 in Fig. 4). Since pattern 13 belongs to a different attraction basin, the ensuing behaviour of the system will cause it to ultimately reach attractor 21-27-14. From this position, the system consolidates its "pathological behaviour" and is thus unable to "find its way back" to its primary healthy behaviour. An even more awkward situation is the transition from attraction basin B to E, elicited by applying perturbation  $C \rightarrow \text{ON}$  to pattern 25, which leads it to become pattern 29, i.e., to enter a blocked state.

This kind of pathological alteration of a dynamic system can be viewed as an "erroneous adaptation" that causes the system to settle on a fixed point or periodically oscillating behaviour falling outside its original, normal range of variation. Such erroneous adaptations can be triggered by even minor perturbations in an organism that is

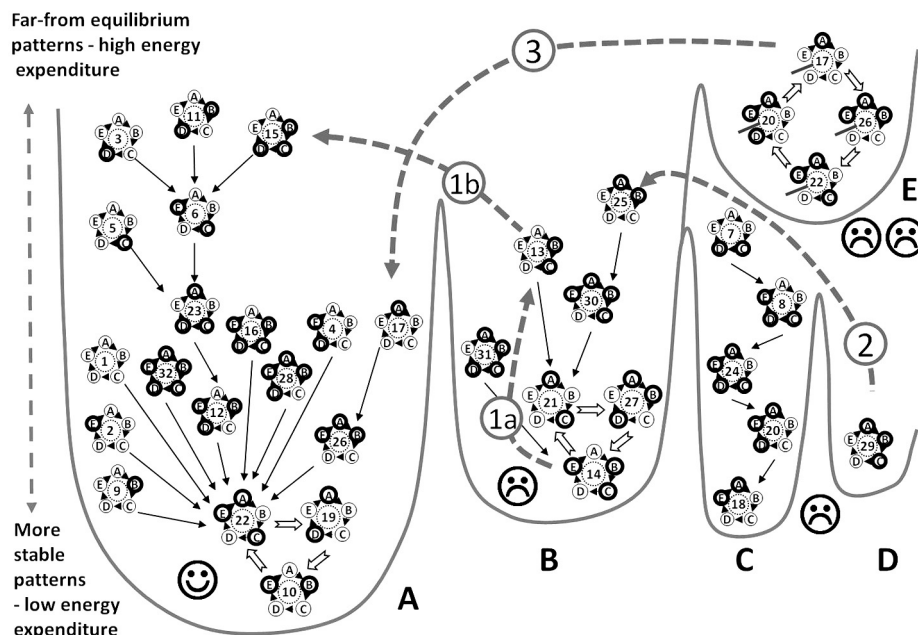
already far from equilibrium. A typical example occurring in pathology is the onset of rheumatic disease following an infection to the oral cavity. While in most cases streptococcal infections heal without consequences, in certain individuals a molecular mimicry mechanism can, for reasons that are largely unknown, induce a serious disruption of the immune system with autoimmune reactions. Similar events can occur in a number of other pathologies with complex underlying mechanisms, and are often also associated with adverse reactions to vaccination. Asthma, and many other chronic diseases of the immune system, can be interpreted as "stuck" states of a network. Interactions among lymphocytes at the idotype network level are very important for regulating processes that control both the quantity and quality of the immune response. Malfunctioning of the idotype network has a role in the mechanisms that cause the onset of autoimmunity: since a certain amount of autoimmune reaction is also present in the healthy body, it is the idotype networks (and more specifically their "connectivity") that govern the transition from innocent to aggressive autoimmunity.<sup>20,21</sup> Similar considerations can be made for permanent or semi-permanent pathophysiological alterations of the cardiovascular system (e.g., hypertension) or nervous system (e.g., trait anxiety).

In previous work we have shown how a feed-back regulatory system retains a memory of the past history that modified the sensitivity of specific receptors.<sup>3</sup> These dynamic changes in sensitivity are not considered here for the sake of brevity, but could be incorporated into the network model to take into account finer and individual variations in the evolution of pathology and/or in drug sensitivity, which may in turn be genetically determined or induced by the disease process itself.

## Blocking of communication

Let us now consider what happens when an arbitrary mutation is made to the network structure, simulating damage to one or more of its connections. For example, in Fig. 4, trajectory no. 4 represents the situation where node E no longer receives any inputs from node D, and instead depends only on the activity of node C. This broken link introduces a dramatic change that disrupts the dynamics of the whole network, causing a new, anomalous and unprecedented attractor (17-26-22-20) to emerge. The system adapts to the new structure and continues to iterate through a sequence of patterns, but because it is now trapped inside an attractor, there is no possibility of spontaneously restoring the normal homeodynamic reactions. Loss of connectivity and of communication constitutes a sort of initial dis-integration of the complex network, and is deleterious because the homeodynamic function itself is damaged and spontaneous recovery is hindered.

A typical example of such a pathology is diabetes, where either insulin as a communication system is lacking (Type I) or insulin receptors are down-regulated (Type II). In both situations, the metabolism can for a short time arrange a new equilibrium of hyperglycaemia, through hypoinsulinaemia or hyperinsulinaemia, respectively. However, this is pathological because vascular pathology or acute metabolic impairments will very frequently occur in the



**Fig. 5** “Therapeutic” effects of perturbations and changes of attractors in the Boolean network. (1a) Perturbation  $E \rightarrow \text{OFF}$ . (1b) Perturbation  $D \rightarrow \text{ON}$ . (2) Perturbation  $C \rightarrow \text{OFF}$ . (3) Restoring communication between D and E by including or facilitating suitable connecting information in the system.

long term. Common diseases such as atherosclerosis, cancer, schizophrenia, obesity, endocrinological disturbances, etc. exhibit various mechanisms that can be interpreted as a loss of communication between the nodes of a network, occurring due to genetic or external factors like viruses, toxic substances, and alcohol. Overtreatment, too, can lead to impairment of homeodynamics. Resistance to steroids and central resistance to cytokines may become an important pathogenetic mechanism in conditions such as AIDS, allergy, melancholic depression, aging, and vascular disorders.

In summary, from a dynamic-systems based perspective, *chronic disease* can be regarded as the formation of a new, far-from-equilibrium dynamic attractor (pathological adaptation) which may (or may not) be associated with a blocking of network connectivity, leading to a progressive “dis-integration” of the system. This self-perpetuation of disease, as an organization of pathological attractors in a complex system, can be interpreted as an updating of the “miasm” concept of classic homeopathy.<sup>22–24</sup> Modern epigenetics, too, appears to be casting new light on the traditional homeopathic tenets, as for example in the recent findings suggesting the transgenerational transmission of altered brain chemistry and behaviour after a single nonlethal exposure to a fungicide chemical in the original male animal.<sup>25</sup> Such data lend general credence to the homeopathic construct that disease tendencies can be inherited as a result of the stressors and illnesses experienced by the parents and grandparents of the current patient.

### Healing dynamics and “the similia”

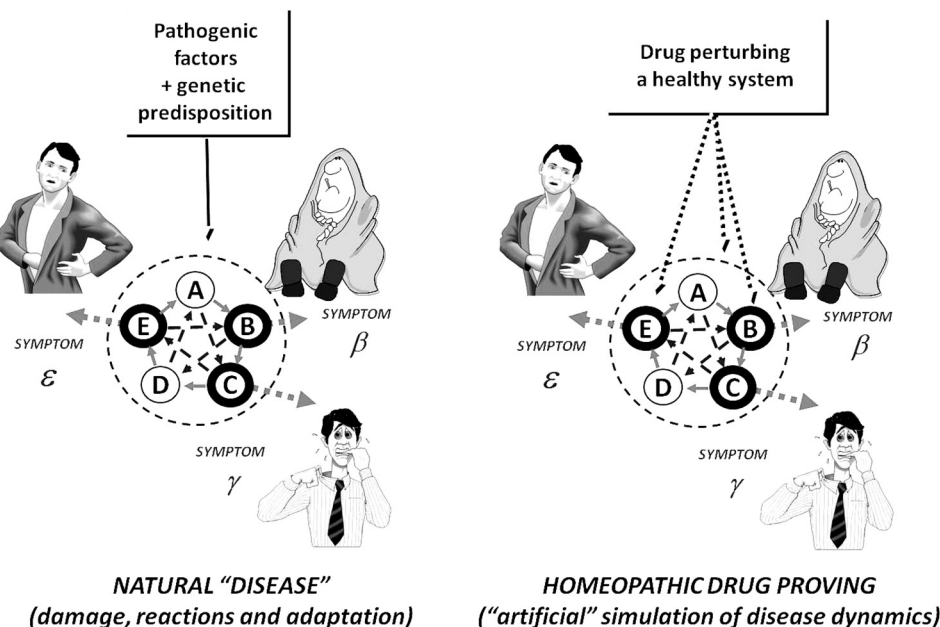
Given this Boolean network model, the question becomes how to stimulate the recovery of homeodynamic

communication, once the system has fallen into an erroneous adaptation and/or there is a blockage of the normal response to the stressor. Fig. 5 illustrates the attempts to reinstate the normal system dynamics, starting from the “pathological” attractor 21-27-14. Here we see some examples of how the network dynamics can be altered by small changes to individual nodes. In some cases, altering the state of a node shifts the system into a different attractor basin, where the energy consumption is fundamentally lower, which in our theoretical representation is analogous to a healing process.

Starting from pattern 14, one way to attain this desirable goal is indicated by trajectories 1a and 1b: a perturbation ( $E \rightarrow \text{OFF}$ ) displaces the system’s equilibrium, causing it to change to pattern 13. From there, a second perturbation ( $D \rightarrow \text{ON}$ ) has the effect of shifting the system towards pattern 15, i.e., the state from which the previous perturbation had triggered the chronic pathology. From pattern 15, the intrinsic and spontaneous dynamics of the system restore the normal function represented by the 22-19-10 attractor. However, it should be noted that if perturbation “ $E \rightarrow \text{OFF}$ ” is not immediately followed by “ $D \rightarrow \text{ON}$ ”, the system instead spontaneously returns to the original pathological attractor, passing from pattern 13 to 21. Even starting from a blocked attractor (pattern 29 in attractor D), it is possible to reverse the “pathology” and move to a pattern belonging to an attractor closer to the healthy state (pattern 25 of attractor B) with a single targeted modification ( $A \rightarrow \text{OFF}$ ).

In short, when pathology is considered as an alteration in the self-organization of a complex network, it is theoretically possible to restore normal, healthy behaviour through targeted perturbations of the system that exhibits the pathology. Such modifications can enable the system to become “unstuck” from its pathological behaviour, by





**Fig. 6** Schematic view of homeopathic concepts based on similarity of symptoms. In a “healthy” regulating system network, an exogenous pharmacological signal can trigger multiple signs that mimic the natural disease. The disease (left) produces an internal disruption of the homeodynamic networks which is manifested in the form of symptoms and can be (also) characterized by a symptom pattern unique to the disease and to the individual patient. The homeopathic proving methodology (right) characterizes drugs according to their ability to induce perturbations, manifested as symptoms, in healthy subjects.

pushing it back towards a point in its energy-space trajectory that preceded the chronicization of disease. This approach is fundamentally different from trying to suppress the symptoms of disease, and may even cause symptoms to be temporarily exacerbated, because the changes induced by the perturbation carry the system far from equilibrium, thus requiring increased energy. This conception of healing as a process of becoming “unstuck” has been analysed and characterized, in its various aspects and modifying factors, using techniques borrowed from phenomenology and grounded theory.<sup>26</sup> Interviews of patients with chronic illnesses, including cancer and multiple nonmalignant conditions, who were treated with different packages of care clearly indicated experiential differences between stuckness, unsticking, and unstuckness (or “transformation”). These results offer some preliminary conceptualizations and descriptions of the impact that whole system interventions can have on individuals’ life courses.

The procedure for “healing” by reinstating a communication link, illustrated in Fig. 5, is obviously a simplification. The most significant difficulty inherent in this approach is the fact that a complex network can have a number of different attractors, and that not all perturbations lead to recovery of the original homeodynamics. To nudge the behaviour of a complex system in the desired direction, we need to know how the system is configured at a certain point of its trajectory (i.e., its state at the time of intervention), where it will be optimally sensitive to our intervention and, especially, the outcome towards which our perturbation will redirect the system. Provided that this information is known, we can take advantage of the self-organizing properties of the system, and achieve large and permanent change even with small and brief perturbations.

This type of knowledge can – at least in theory – be acquired through the homeopathic methodology. The traditional “law of similia” presupposes that the intrinsic tendency to self-recovery can be supplemented and actively assisted by applying suitable and coherent stimuli to a system when it is in a particular sensitive state. In brief, there are two steps: (a) the remedy pushes the system out of its pathological adaptation, i.e., away from an attractor positioned higher in the energy consumption landscape, (b) the system settles into a new self-organizing state of equilibrium, more proximal to the healthy state, thus reaching a positive adaptation, at a lower position in the energy landscape. Homeopathic remedies may thus induce adaptive changes in the organism, serving as low level danger signals to the biological stress response networks. It has been suggested that regulation of stress response effectors, including heat shock proteins, inflammasomes, cytokines and neuroendocrine pathways, and sensory neurons, initiates beneficial compensatory reactions across the interconnected networks of the organism as a complex adaptive system.<sup>7,27</sup>

### The logic of symptoms

The traditional homeopathic method is based on the analysis of “symptoms”, either provoked by the drug on healthy subjects (proving) or taken from patient interviews and observation. This phenomenological approach can in part be ascribed to lack of scientific knowledge in this field, but mainly derives from the fact that most homeopathic clinical experimentations and provings were conducted at a time when knowledge of “disease” was based essentially on the

outward signs of body-mind disorders. Though symptoms are not the disease, they are nevertheless the “external” manifestation of internal changes affecting networks at different levels of biological organization.

From this perspective, the most suitable regulatory drug is the one capable of directing the recovery of homeodynamic equilibrium through simulation of behaviour patterns (“symptoms”) which are “similar” to those of the disease that is being cured. When a homeopathic drug produces a similar pattern of symptoms to those caused by the disease, that drug is the correct one to use, because it has the ability to interact with the specific target systems involved in the disease (see Fig. 6). If the network has lost some internal connections, the drug may reactivate the blocked nodes and eventually recruit internal coherent signals, by conveying pattern-specific information. Thus, according to homeopathic principles, because most symptoms have informational value as evidence of network alterations, it should somehow be possible to affect those same networks by using a substance that provokes similar symptoms in healthy and sensitive subjects.

To eliminate some possible misunderstandings, it is important to note that the “artificial” perturbation induced by homeopathic proving is not a “disease” in the common and nosological sense (as are, e.g., cancer, multiple sclerosis, Alzheimer’s disease, and liver cirrhosis), but rather a set of modifications that simulate an illness whose symptoms match various reactions of an individual during the disease. Symptoms (e.g., headache, fever, cough, nasal discharge, skin spots, decrease of libido, anxiety and other psychological changes) are the expression of the reaction of homeodynamic systems and offer a very accurate way to characterize the disorder of these systems as well as their dynamics over time.

It is important to note that symptoms are emergent properties of the global, individual, network. The external signs and internal sensations represent a unitary phenomenon, which is due to the unitary alterations of the internal homeodynamics. There are numerous ways (“modalities”) through which a body expresses its needs, and each one has its own language of symptoms. It will be necessary to look at the patient’s history and its manifestations in the somatic and psychic domains, the characteristics of past diseases, behaviour, environment, susceptibility to weather and foods, without neglecting anything (the process of individualization). All this with a view to investigating the particular “terrain” characteristic of that patient, of which the pathological manifestations are an expression. In short, the homeopathic doctor does not prescribe a remedy by considering the disease, but rather by considering the whole patient who is suffering from the disease.

## Conclusions and perspectives

According to the view expressed here, healing necessarily implies restoring the integrity of homeodynamics and, therefore, reinstating the health of the whole organism. This concept has two important corollaries, which predict the dynamics of healing and can be verified experimentally:

- (a) This model predicts that the more “interesting” symptoms, for the purpose of identifying towards which pattern the system should be pushed through homeopathic stimulation, are those pertaining to a previous stage of the disease dynamics. It is also possible that the “old” symptoms, reflecting the patient’s basic characteristics and reactivity, may be obliterated in the more advanced phases of the disease. Administering a medicine that produces a similar symptom pattern in healthy individuals may direct the patient’s homeodynamics towards a state situated in a previous, healthier attraction basin.
- (b) Conversely, in every “real” healing process, the sequence of health deterioration of the particular patient’s disease history will be retraced. This means that old, long-forgotten disease symptoms may suddenly flare up again in the form of a “healing crisis”. During healing, especially of chronic long-lasting conditions, the manifestations of body reactivity and compensation (changes of attractors) will appear in reverse chronological order with respect to how the symptoms initially appeared. The individual will thus re-experience all the preceding changes, both physiological and psychological, including skin reactions, gastro-intestinal upsets, unconscious feelings, grief, fear, anger, or pain.
- (c) This temporary exacerbation of symptoms is referred to in homeopathy as “homeopathic aggravation” or “healing reaction”, and should be regarded as a positive event. The healing reaction concept highlights the different perceptions that conventional and homeopathic medicine have of the healing process. For example, a moderate inflammation can be regarded as an important tool for healing and tissue repair, since it increases blood flow, increases lymph fluid to wash away toxic compounds, and recruits phagocytes and immune cells. It is well known among homeopaths that, if a cutaneous inflammatory reaction occurs during treatment of a chronic disease, the phenomenon is a positive sign that the therapy is working and should not be suppressed by anti-inflammatory drugs.

Like all abstract models, our theory has the benefit of being generally adaptable to various levels of biological function, thus contributing to re-evaluate the role of network dynamics in physiology, pathology and drug effects. However, a noteworthy limitation of the simple Boolean network described here is that its node states are restricted to ON/OFF only. Computer simulations that allow for continuous quantitative changes in node activity could be more flexible, and yield further unexpected insights. Furthermore, the intrinsic limitations of a simple conceptual model such as this could be overcome by using more system-specific working models, with different numbers of nodes and types of connections, to better simulate the specific molecular and cellular mechanisms involved in healing processes. Under this perspective, the homeopathic approach could be integrated with recent developments in complexity theory applied to modern biomedical sciences such as genetics, biochemistry, cell biology, immunology, neurology, and molecular pharmacology.<sup>28–35</sup>

The present work has dealt with the similia principle and does not discuss the controversial issue of doses and

dilutions. As a general concept, we can assume that the more sensitive a system is to a particular regulation, the lower should be the dose (or the energy) required to regulate it in an effective way. The homeopathic approach is intended to detect highly specific and individualized sensitivities triggered by the illness, and therefore homeopathic drugs must also be highly specific. There are a number of known biological mechanisms by which the sensitivity of receptors and the efficiency of signal transduction pathways in cells and whole systems can be amplified.<sup>36,37</sup> It is conceivable that ultra-low doses and high dilutions of drugs may act on the information networks of the body, where putative electromagnetic interactions and water clusters associated with proteins and DNA have a major role in information transfer and as coordination pathways for biochemical reactions, immunological control of body identity, and even of psychological integrity. Interestingly, water itself constitutes a molecular network regulating intracellular events.<sup>35,38,39</sup>

The similia principle provides fertile ground for investigations that are not limited to theoretical models. Several authors have proposed mechanistic explanations of the phenomenon of “inversion of effects” of drug action depending on the dose of drug employed.<sup>37,40–44</sup> Others have pointed out the role of hormesis,<sup>45</sup> nanoparticles,<sup>46–48</sup> stochastic resonance for signal amplification,<sup>49</sup> phenomena requiring interaction with the organism as a complex adaptive system,<sup>50,51</sup> and time-dependent sensitization.<sup>48,52</sup> While we have restricted this paper to describing a model for the healing process, a global theory of homeopathic similia would have to encompass all these important issues.

## Conflict of interest statement

The authors do not have conflicts of interest.

## Acknowledgements

The experimental research carried out by our group is supported by a grant from Boiron Laboratoires to Verona University, and by the Italian Research Ministry.

## References

- Rutten L, Mathie RT, Fisher P, Goossens M, Van WM. Plausibility and evidence: the case of homeopathy. *Med Health Care Philos* 2013;**16**:525–32.
- Bellavite P. Complexity science and homeopathy. A synthetic overview. *Homeopathy* 2003;**92**:203–12.
- Bellavite P, Ortolani R, Pontarollo F, Pitari G, Conforti A. Immunology and homeopathy. 5. The rationale of the ‘simile’. *Evid Based Complement Altern Med* 2007;**4**:149–63.
- Schwartz GE, Russek LG, Bell IR, Riley D. Plausibility of homeopathy and conventional chemical therapy: the systemic memory resonance hypothesis. *Med Hypotheses* 2000;**54**:634–7.
- Torres JL. Homeopathic effect: a network perspective. *Homeopathy* 2002;**91**:89–94.
- Bell IR, Koithan M, Pincus D. Methodological implications of nonlinear dynamical systems models for whole systems of complementary and alternative medicine. *Forsch Komplementmed* 2012;**19**(Suppl 1):15–21.
- Bell IR, Schwartz GE. Adaptive network nanomedicine: an integrated model for homeopathic medicine. *Front Biosci (Schol Ed)* 2013;**5**:685–708.
- Sanday L, Zanin KA, Patti CL, Tufik S, Frussa-Filho R. Role of state-dependency in memory impairment induced by acute administration of midazolam in mice. *Prog Neuropsychopharmacol Biol Psychiatry* 2012;**37**:1–7.
- Silvanto J, Pascual-Leone A. State-dependency of transcranial magnetic stimulation. *Brain Topogr* 2008;**21**:1–10.
- Tayebi MK, Vakili ZA, Zarrindast MR, Djahanguiri B. Effects of ultra-low doses of morphine, naloxone and ethanol on morphine state-dependent memory of passive avoidance in mice. *Behav Pharmacol* 2005;**16**:139–45.
- Watanabe H, Taga G. Initial-state dependency of learning in young infants. *Hum Movement Sci* 2011;**30**:125–42.
- Bellavite P, Semizzi M, Lussignoli S, Andrioli G, Bartocci U. A computer model of the five elements theory of traditional chinese medicine. *Complement Ther Med* 1998;**6**(3):133–40.
- Kauffman S, Peterson C, Samuelsson B, Troein C. Genetic networks with canalizing Boolean rules are always stable. *PNAS* 2004;**101**:17102–7.
- Serra R, Villani M, Barbieri A, Kauffman SA, Colacci A. On the dynamics of random Boolean networks subject to noise: attractors, ergodic sets and cell types. *J Theor Biol* 2010;**265**:185–93.
- Callard R, George AJ, Stark J. Cytokines, chaos, and complexity. *Immunity* 1999;**11**:507–13.
- Yang XS, Huang Y. Complex dynamics in simple Hopfield neural networks. *Chaos* 2006;**16**:033114.
- Sprott JC. Chaotic dynamics on large networks. *Chaos* 2008;**18**:023135.
- Davies PC, Demetrius L, Tuszynski JA. Cancer as a dynamical phase transition. *Theor Biol Med Model* 2011;**8**:30.
- Baverstock K. Life as physics and chemistry: a system view of biology. *Prog Biophys Mol Biol* 2012.
- Varela FJ, Coutinho A. Second generation immune networks. *Immunol Today* 1991;**12**:159–66.
- Madi A, Kenett DY, Bransburg-Zabary S, Merbl Y, Quintana FJ, Boccaletti S, Tauber AI, Cohen IR, Ben-Jacob E. Analyses of antigen dependency networks unveil immune system reorganization between birth and adulthood. *Chaos* 2011;**21**:016109.
- Mathur M. The concept of miasm—evolution and present day perspective. *Homeopathy* 2009;**98**:177–80.
- Milgrom LR. Patient-practitioner-remedy (PPR) entanglement. Part 6. Miasms revisited: non-linear quantum theory as a model for the homeopathic process. *Homeopathy* 2004;**93**:154–8.
- Bellavite P, Pettigrew A. Miasms and modern pathology. *Homeopathy* 2004;**93**:65–6.
- Crews D, Gillette R, Scarpino SV, Manikkam M, Savenkova MI, Skinner MK. Epigenetic transgenerational inheritance of altered stress responses. *PNAS* 2012;**109**:9143–8.
- Koithan M, Verhoef M, Bell IR, White M, Mulkins A, Ritenbaugh C. The process of whole person healing: unstuckness and beyond. *J Altern Complement Med* 2007;**13**:659–68.
- Shahabi S, Kasariyans A, Noorbakhsh F. Like cures like: a neuroimmunological model based on electromagnetic resonance. *Electromagn Biol Med* 2013, <http://dx.doi.org/10.3109/15368378.2012.743911>, in press.
- Park J, Lee DS, Christakis NA, Barabasi AL. The impact of cellular networks on disease comorbidity. *Mol Syst Biol* 2009;**5**:262.
- Hidalgo CA, Blumm N, Barabasi AL, Christakis NA. A dynamic network approach for the study of human phenotypes. *PLoS Comput Biol* 2009;**5**:e1000353.
- Liu YY, Slotine JJ, Barabasi AL. Controllability of complex networks. *Nature* 2011;**473**:167–73.
- Vidal M, Cusick ME, Barabasi AL. Interactome networks and human disease. *Cell* 2011;**144**:986–98.

32. Farkas IJ, Korcsmaros T, Kovacs IA, Mihalik A, Palotai R, Simko GI, Szalay KZ, Szalay-Beko M, Vellai T, Wang S, Csermely P. Network-based tools for the identification of novel drug targets. *Sci Signal* 2011;4:t3.
33. Bode C, Kovacs IA, Szalay MS, Palotai R, Korcsmaros T, Csermely P. Network analysis of protein dynamics. *FEBS Lett* 2007;581:2776–82.
34. Szalay MS, Kovacs IA, Korcsmaros T, Bode C, Csermely P. Stress-induced rearrangements of cellular networks: consequences for protection and drug design. *FEBS Lett* 2007;581:3675–80.
35. Kovacs IA, Szalay MS, Csermely P. Water and molecular chaperones act as weak links of protein folding networks: energy landscape and punctuated equilibrium changes point towards a game theory of proteins. *FEBS Lett* 2005;579:2254–60.
36. Bellavite P, Marzotto M, Oliosio D, Moratti E, Conforti A. High-dilution effects revisited. 1. Physicochemical aspects. *Homeopathy* 2013, <http://dx.doi.org/10.1016/j.homp.2013.08.003>, in press.
37. Bellavite P, Marzotto M, Oliosio D, Moratti E, Conforti A. High-dilution effects revisited. 2. Pharmacodynamic aspects. *Homeopathy* 2013 (in press), <http://dx.doi.org/10.1016/j.homp.2013.08.002>.
38. Wei D, Wilson WD, Neidle S. Small-molecule binding to the DNA minor groove is mediated by a conserved water cluster. *J Am Chem Soc* 2013;135:1369–77.
39. Yinnon CA, Yinnon TA. Domains in aqueous solutions: theory and experimental evidence. *Mod Phys Lett B* 2009;23:1959.
40. Wiegant FAC, Van Wijk R. Self-recovery and the similia principle: an experimental model. *Complement Ther Med* 1996;4:90–7.
41. Bellavite P, Signorini A. Physiopathological models of the similia principle. In: *Proceedings of the 51st L.M.H.I. international congress Capri 2–6 October 1996*. 1996. p. 98–106.
42. Van Wijk R, Wiegant FA. Postconditioning hormesis and the similia principle. *Front Biosci (Elite Ed)* 2011;3:1128–38.
43. Boyd LJ. *A study of the simile in medicine*. Philadelphia: Boericke Tafel; 1936.
44. Chattopadhyay S. Proposition of a new system of medicine based on tolerance principle. *Med Hypotheses* 2002;59:191–203.
45. Calabrese EJ. Hormesis and homeopathy: introduction. *Hum Exp Toxicol* 2010;29:527–9.
46. Chikramane PS, Suresh AK, Bellare JR, Kane SG. Extreme homeopathic dilutions retain starting materials: a nanoparticulate perspective. *Homeopathy* 2010;99:231–42.
47. Iavicoli I, Calabrese EJ, Nascarella MA. Exposure to nanoparticles and hormesis. *Dose Response* 2010;8:501–17.
48. Bell IR, Koithan M. A model for homeopathic remedy effects: low dose nanoparticles, allostatic cross-adaptation, and time-dependent sensitization in a complex adaptive system. *BMC Complement Altern Med* 2012;12:191.
49. Torres JL, Ruiz G. Stochastic resonance and the homeopathic effect. *Br Homeopath J* 1996;85:134–40.
50. McDonnell MD, Ward LM. The benefits of noise in neural systems: bridging theory and experiment. *Nat Rev Neurosci* 2011;12:415–26.
51. McDonnell MD, Abbott D. What is stochastic resonance? Definitions, misconceptions, debates, and its relevance to biology. *PLoS Comput Biol* 2009;5:e1000348.
52. Antelman SM, Levine J, Gershon S. Time-dependent sensitization: the odyssey of a scientific heresy from the laboratory to the door of the clinic. *Mol Psychiatry* 2000;5:350–6.