A computer model of the 'five elements' theory of traditional Chinese medicine

P. Bellavite[1], M. Semizzi[1], S. Lussignoli[1], G. Andrioli[1], U. Bartocci[2],
[1]University of Verona, [2]University of Perugia, Italy

SUMMARY. In this article, a model is presented of a network whose structure was inspired by the 'five elements law' of Chinese medicine. Computer simulations illustrate the dynamic behavior of this system, that can be set in different attractors of Boolean type and can be differentially modified by delays and perturbations. We suggest that this model may contribute to the understanding of the 'logic' of the regulation of biological systems by means of small and carefully selected perturbations, a major line of thought of complementary therapies.

INTRODUCTION

The answer to the question of the usefulness of any therapeutic approach depends both on the clinical proof of its efficacy and on the rational explanation and understanding of its mechanism. Living organisms, from whole bodies to single cells, are dynamic evolving systems, not merely anatomical structures. They are composed of many elements the interaction of which results in behaviour that, in general, cannot be deduced from knowledge of the individual components, a typical feature of complex systems.[1-6]

'Thinking in complexity' has a number of implications in both conventional and complementary medicine. In this contribution we will focus mainly on the latter. Medical traditions like those of oriental origin and homeopathy were founded right from the outset on holistic and vitalistic paradigms, which may be interpreted, at least in part, according to a conceptual framework provided by the theory of dynamic systems and of complexity.

A useful concept helping in the description of living matter is to consider its structure as a network.[7-11] Networks are complex structures because the state and the changes of each element depend, directly or indirectly, on the state and the changes of all the other elements. Therefore, the network behaves as a coherent system, whose health state is governed and restored thanks to the connectedness of internal and external processes. Communication and coherence are guaranteed by the value of original information, the capacity of signaling harmful modifications, and the efficiency by which energy is channeled towards the purpose of reconstructing the original conformation of the system.

In order to deal with puzzling issues like those of self-organization or the regulation of biological healing, one may take advantage of cybernetic models that utilize the language of mathematics and computer simulations.[9,12-15] On the basis of these models, analogies can be drawn with physiological and pharmacological phenomena. What is meant by analogy is that similarity between two distinct systems may serve to explain one of them better on the basis of knowledge already gained about the other. Analogy can therefore be used to construct more advanced models compared to those in current use and to make forecasts about unknown systems starting from known systems (usually physico-chemical or mathematical) which act as archetypes, i.e. as reference systems. Therefore, analogic reasoning, when coupled with testable hypotheses, is an integral part of the scientific process as applied to describing and understanding complex systems.

Classical dynamic and systemic thinking has been followed by Chinese medicine. According to this tradition, life energy is rhythmically channeled through a network of reciprocal influences between the different organs and the different elements which form the body. Basically, the 'law of five elements' regulates the natural interactions between wood (Mu), fire (Huo), earth (Tu), metal (Jin), water (Shui) and between the corresponding organs of the body (liver, heart, spleen/pancreas, lung

P. Bellavite, Istituto di Chimica e Microscopia Clinica, University of Verona, Ospedale Policlinico, Laboratorio, Verona 37134, Italy

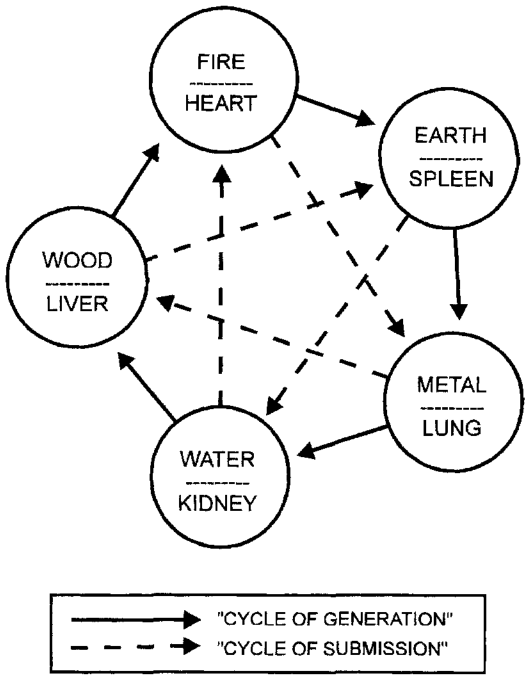

Fig. 1 Schematic (and simplified) representation of the Chinese 'law of five elements'.

and kidney respectively). These elements are connected by circular influences consisting either of activation (also called 'generation') of an element towards the nearest one, or of inhibition (also called 'submission') of an element towards the element which follows the activated one (Fig. 1).

We have tried to simulate the dynamic properties of a typical network system by using a computer program. In this paper, we explicate the structure and the behaviour of this system, the dynamic of which may vary during time, utilizing as a model a Boolean network of five elements tied together in a communicating system. Here, we have decided to utilize a network of five nodes interconnected according the rules formulated in the 'law of five elements'. This is an arbitrary choice, suggested by the consideration that this medical tradition was based right from the outset on a dynamic and holistic paradigm. This model is not intended as an explanation of the action of acupuncture but, instead, as a contribution to the re-thinking of the self-organization and regulation of biological systems. We suggest that any theory of acupuncture or of low-dose effects can make use of such concepts.

HOMEOSTASIS AND SELF-ORGANIZATION

In living organisms, physiological systems cooperate to keep most functions within normal limits of variation (so-called homeostasis), and stressful experiences are followed by coordinated and integrated response patterns designed to prevent injury and to promote repair and healing. The physiological patterns are designed to enhance blood supply to the muscles and brain; provide immediately available sources of energy to organs according to need; mount a response to specific antigens and so on. Signals carried by nerves and blood carry out the task of integrating behavior and physiology in specific ways. The regulation of the production of signals is remarkably complex; most of the peptide hormones released by a single gland (e.g. the pituitary gland) are under multiple negative, positive, and mixed feedback control. Furthermore, each is frequency-modulated and functions in a rhythmic manner over time. The subsystems of the organism that generate the fluctuating signals are in constant communication with each other. Because the organism is also in continuous communication with its environment, the subsystems appropriately respond to external perturbations.

According to the external and internal conditions (temperature, chemical concentrations, mathematical parameters), a network system may assume different states, or attractors. An attractor is the state or the series of states (pattern) to which the behaviour of a system is attracted. It therefore possesses an important property – stability. In a system subjected to perturbations, movement tends to be towards the attractor. The theory of dynamic systems shows that the attractor may be a single point, as, for example, in the trajectory of a pendulum when it reaches the stationary state, or a finite number of points reflecting a periodic-type behaviour (orbit), or an infinite system of points generating a figure in the form of an orbit which never repeats itself identically, as may happen in chaotic systems ('strange attractors').

The choice between one state (or attractor) and another possible state (or attractor) often depends on the experience to which the system is exposed. The modifications which the system has undergone, are stored in the space-time as specific permanent and semi-permanent structures, whose existence influences further development and subsequent responses of the system itself. Unlike what happens in a system in a state of reversible equilibrium on changing the external or internal parameters, in a complex system a situation can be reached in which there is a symmetry breaking, or an irreversible change. While it is true that random fluctuations and perturbations can usually be damped, beyond certain threshold values, or in the presence of appropriate environmental conditions, these effects are not annulled, but with the system acting as an amplifier, a reaction is triggered which removes the system from the reference state.

Systems with mixed feedbacks (both positive and negative feedback) and multiple feedbacks with different time constant are sources of abrupt changes and also of deterministic chaos.[16,17] This is the case of the whole organism and of the whole cell, which can be described as dynamic systems where the 'equilibrium' is a special case of an attractor, that is, the integration of a number of attractors. As a consequence, healthy and pathological states become interpretable as different types of attractors, which may be converted from each other by bifurcations or critical perturbations. Rapid state changes and bifurcation are characteristic of networks that are sensitive to very weak initial conditions that lead to widespread changes in the whole system.

Changes of attractor represent a potential problem for the healing process because by this way a certain specific behaviour or structural modification can become fixed in a pathological and repeated pattern, losing the possibility of spontaneous and fully reversible modifications. This kind of pathological modification of a dynamic system can be considered a 'erroneous adaptation', where the system finds a fixed point or a periodically oscillating behaviour outside the normal, original, range of variation. In a particular sub-set of the space-time, i.e. locally or for a short period, this new attractor may appear as the most convenient in terms of energy expenditure, but for the system as a whole and for the future prospects of development of the system itself, an erroneous adaptation can be highly deleterious. Something like this process can be envisaged in the transformation of an acute inflammation into a chronic reaction, or in the heart and blood vessel hypertrophy in chronic hypertension, or in the receptor adaptation that justifies the hyperglycemia in hyperinsulinemic type II diabetic patients. Also, the tissue protein or lipid deposits that can be found in amyloid diseases (including Alzheimer's disease) and in arteriosclerosis may be seen as an adaptation of tissue homeostasis to a chronic load of pathologic precursors of these deposit moieties.

In synthesis complex systems are dynamic (i.e. they change in time), self-organized and open to external regulation. Self-organization is based on the existence of multiple elements (ions, molecules, molecular aggregates, cells, organs), that are linked by multiple and reciprocal interrelations by which continuous quantitative and qualitative changes occur. Besides being endowed with self-regulating properties, it can be seen also as an open system, i.e. a system that can be profoundly influenced by external perturbations, coming from its environment. Thus, self-organization does not mean that such an admirable capacity of increasing and maintaining complex forms and functions can occur independently of external help. On the contrary, the thermodynamic stability of a system is guaranteed by the continuous exchange with the environment. Life in general and healing in particular can occur only because living systems are open systems (also called dissipative structures).

DESCRIPTION OF THE MODEL

Having summarized a few essential issues regarding biological complexity, we present a new model of a network of five interconnected elements which allows a qualitative simulation of the behaviour of homeostatic systems. Using this model, the change of attractor induced by pathological perturbations can be observed and the reversal of change (healing) can be induced by a similar perturbation.

To describe the behaviour of a great network composed of many elements coupled together, each of which may be in an active or an inactive state, we resort to the use of models based on Boolean networks (after the logician George Boole). Artificial networks consist of a set of processing units (nodes) which are interconnected via a set of weights (analogous to synaptic connections in the nervous system) in a way which allows signals to travel through the network in parallel as well as serially.[10] The nodes are simple computing elements behaving like a switch: when the sum of incoming signals exceeds a threshold, the node fires a signal toward another node.

In such a network, formed by a number of nodes N, the behaviour of each node (active or inactive) is determined by the input variables which connect or disjoin it from the behaviour of the other nodes. Each node can have a number of inputs according to choice. If the number of inputs is K, the possible combinations of N variables will be N^K. Clearly, there are infinite possible structures of networks that could be taken into consideration to simulate the behaviour of complex homeostatic systems. Either the number of nodes (here referred also as elements), or the number of inputs for each element, or the Boolean rules (Boolean operators, such as, for example 'AND', 'OR', 'NOR' and positive or negative influences between the nodes) can be set.

Figure 2 shows the example of a simple network of five nodes which are interconnected in a way by which each node activates the node that immediately follows (in alphabetical order) and inactivates the node two ahead. Therefore, each node receives two inputs, one activating and another inactivating and is regulated by them accordingly: it may be either active (ON) or inactive (OFF), according to the state of its regulating nodes. In the case that both regulatory nodes are in the same state, the regulated node is set either ON or OFF in an arbitrary way as an initial option that characterizes the system. Table 1 shows the definition of the model described in Figure 2. Since we have five elements with two states, the possible combinations of states ('patterns') are 2^5=32. To every one of the possible 32 different patterns, a number has been assigned. This has been done in order to make easier the monitoring of the change of patterns during time when the behaviour of the system is followed during subsequent cycles of transformation.

Using a program (in this case, 'Model Maker' software for Windows from Cherwell Scientific Publications, Oxford, UK) it is possible to perform various simulations by varying the initial conditions of each node. Since the elements are connected by influences of either stimulatory or inhibitory nature, by activating or inactivating each element in the

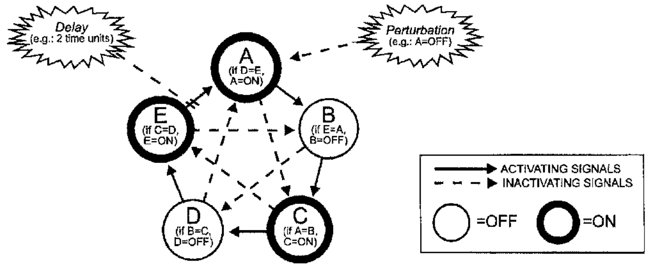

Fig. 2 Model of a network of five elements linked by activating and inactivating influences. The definition of the Boolean functions of this model are reported also in Table 1. For other explanations, see text.

Table 1 Definition of the patterns of the model described in Figure 2.

Pattern n.	A	B	C	D	E	Pattern n.	A	B	C	D	E
32 for	1	1	1	1	1	16 for	0	1	1	1	1
31 for	1	1	1	1	0	15 for	0	1	1	1	0
30 for	1	1	1	0	1	14 for	0	1	1	0	1
29 for	1	1	1	0	0	13 for	0	1	1	0	0
28 for	1	1	0	1	1	12 for	0	1	0	1	1
27 for	1	1	0	1	0	11 for	0	1	0	1	0
26 for	1	1	0	0	1	10 for	0	1	0	0	1
25 for	1	1	0	0	0	9 for	0	1	0	0	0
24 for	1	0	1	1	1	8 for	0	0	1	1	1
23 for	1	0	1	1	0	7 for	0	0	1	1	0
22 for	1	0	1	0	1	6 for	0	0	1	0	1
21 for	1	0	1	0	0	5 for	0	0	1	0	0
20 for	1	0	0	1	1	4 for	0	0	0	1	1
19 for	1	0	0	1	0	3 for	0	0	0	1	0
18 for	1	0	0	0	1	2 for	0	0	0	0	1
17 for	1	0	0	0	0	1 for	0	0	0	0	0

1 corresponds to "ON" state and 0 corresponds to "OFF" state.

network at each interval time, we can observe the evolution of the states (patterns) of the network in subsequent cycles. For the sake of simplicity, each passage from one state to another is implemented by synchronous modification of all the elements involved.

The system passes from one state to another in a deterministic manner and then, in view of the fact that the possible combinations are not infinite, it will always end up sooner or later by finding itself in a state previously formed, thus resuming the cycle of transformations. This is shown by Figure 3, where the evolution of the same system is followed, starting from a number of different patterns. All the patterns shown in Figure 3 are linked in a chain according to which the system, after a precise number of steps, is 'attracted' towards a cyclic behaviour where three different patterns are repeated.

The cycles of states which Boolean networks pass through in the course of time are called dynamic attractors, and each network, if left to its own devices, will sooner or later finish up in one of these attractors and stay there. The series of different patterns that form repeated cycles can be plotted in a time-course diagram that visually describes the attractor(s) to which each system converges, starting from a given initial condition. Figure 4A reports the trajectory of the attractor starting from pattern number 1 (i.e. a pattern where all the elements are initially set 'OFF'). It can be seen that the system sets itself in the attractor very quickly and subsequent variations appear as an oscillation with period of three time units. Figure 4B demonstrates that the same attractor is rapidly reached also starting from initial conditions where all the elements are set as 'ON'. Plot C, D, and E of Figure 4 demonstrate that the same system can have different attractors.

Of the four different attractors, two have the aspect of periodic attractors (with period of three time units), while two others are point attractors. If

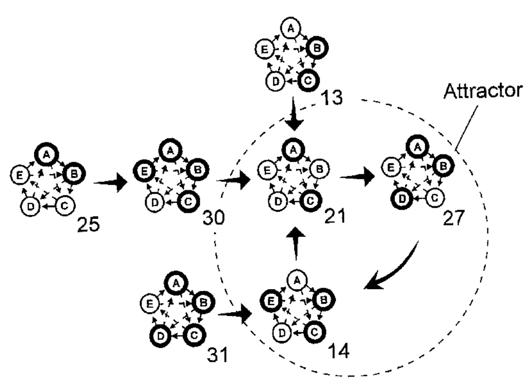

Fig. 3 Dynamic changes of the network of five elements described in Figure 2, starting from several different initial patterns. The symbols correspond to those of Figure 2 and the number of patterns correspond to the classification reported in Table 1.

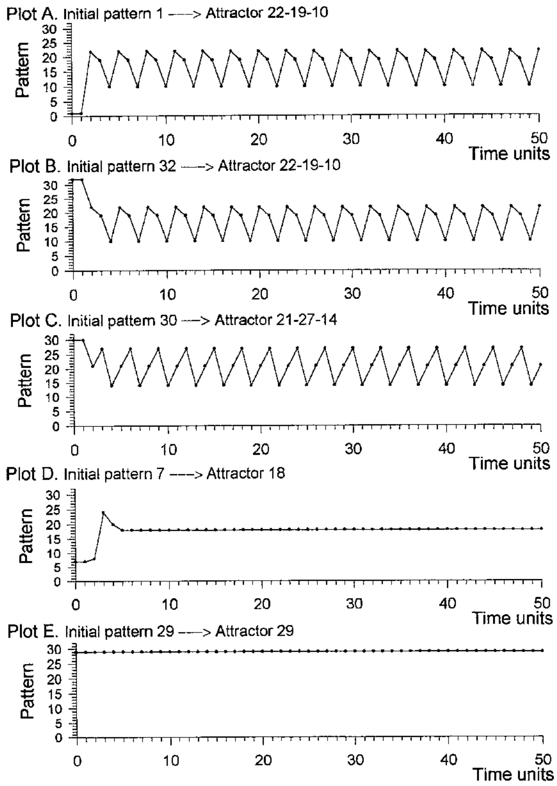

Fig. 4 Plots of the dynamic changes in a time period (attractors) of the network of five elements, starting from different initial patterns. The four possible steady-state behaviours (attractors) of the network described in Figure 2 and Table 1 are reported.

one tests all the possibilities of this system, starting from each of the 32 different possible initial conditions, it is found that 18/32 of the initial patterns end in the attractor 22–19–10, 7/32 end in the attractor 21–27–14, 6/32 end in the point attractor 18, and only one initial pattern (pattern 29) does not modify during time, representing a point attractor from the outset.

In summary, the system-model here described is composed by five elements that have 32 different combinations (patterns) of ON/OFF states. When the system dynamic is started and is left to change during time according to its pre-defined rules, it reaches a steady-state where it makes use of only eight different patterns (namely the 22, 19, 10, 21, 27, 14, 18, and 29), irrespective of the starting point. Moreover, if one considers the dynamic behaviour of the system, that is the repeated schemes that are formed during time (attractors), the possible dynamic states of the same system are reduced to only four. Therefore, starting from 32 degrees of freedom, the existence of rules of behaviour forces the system to only 4 degrees of freedom. In other words, the system utilizes the communication between the different elements in order to create an organization of patterns. This is a simple but meaningful example of self-organization in a dynamic system. The unavoidable tendency to organize in a periodic behaviour, independently of the different starting conditions, is an intrinsic feature of the system itself.

DELAYS AND PERTURBATIONS

As illustrated in Figure 2, it is also possible to vary the delay of the response of each element, i.e. the lag time passed between the receipt of the input signals and the emission of the output signals, and to perform experiments, introducing perturbations, like an arbitrary external modification of the state of an element at a given time.

Figure 5 illustrates how the behaviour of the same system can be changed by delays and by perturbations. Introducing a delay of two time units in the element E (Figure 5A), leads the system to oscillate between different patterns for the first six cycles, then to set in an oscillating, repeated behavior (attractor) with a period of four time units. One can try to make the system much more complex, introducing delays in all the elements. Plot B of Figure 5 shows one of these simulations where the system, starting from pattern 27, ends in a stable periodic attractor only after 40 time units; it can be seen that the system organizes itself by exploring different oscillating cycles (with periods of seven to 10 time

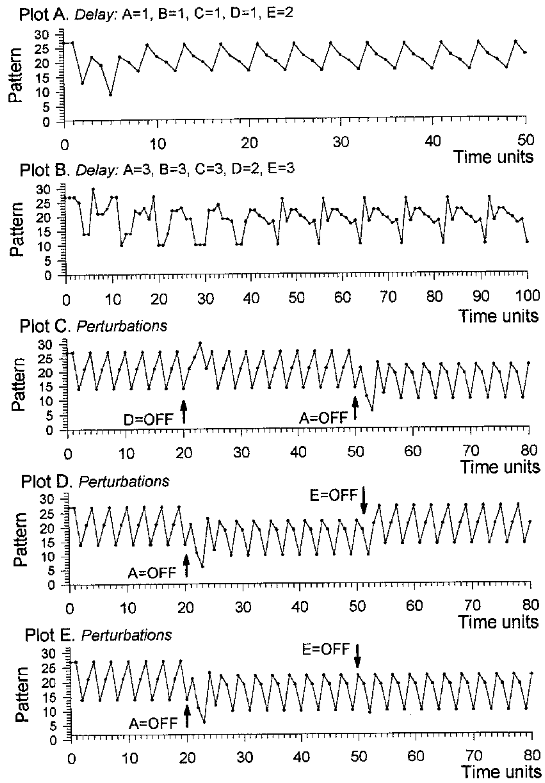

Fig. 5 Plots of the dynamic changes in a time period (attractors) of the network of five elements described in Figure 2. The effects of the introduction of delays in the indicated elements (plots A and B) and of perturbations (plots C, D and E) are shown.

units), until it finds out the right one, which allows it to remain in a repeated cycle, with a period of nine time units.

Testing the dynamic behaviour of this system with different initial values revealed that the attractor whose plot is shown in Figure 5B represents the final behaviour of 27/32 of the possible initial patterns. The other attractors for this system are represented by two point attractors and namely by pattern 18 (occurring with 4/32 of the possible initial patterns) and pattern 29 (when the initial pattern is 29). Therefore, we see that by increasing the complexity of the system (with different delays) and of its behaviour (showing a period of nine time units), the degrees of freedom are not increased but, instead, are further reduced. Apart from the two point attractors (that are something like the 'paralysis' of the system), the dynamic behaviour of this system is represented by only one characteristic scheme, independently of the initial conditions. The system 'looks for' its individual scheme/attractor until it finds it (according to the initial pattern, sometimes it employs a few cycles, other times it employs about 50 cycles).

Figure 5C reports the dynamic of the system in the absence of delays, which is represented by attractor 21–27–14. At the time 20, a perturbation is introduced by an arbitrary change of element D, which was set 'OFF' with external manipulation of the system; as a consequence, after one cycle of delay, the pattern changes to a different one (in this case, 25 instead of 27) Subsequent patterns are also modified. However, after a small disorder, the original attractor is restored. This indicates that the system has the power to recover after a perturbation. Using a word from physiology vocabulary, it is as if there was a kind of homeostatic behaviour in the system, and this is one of the main reasons why such networks tend to simulate a number of properties of biological systems.

On the other hand, if another perturbation (element A=OFF) is introduced at time 50, the system changes its behaviour, entering into a different attractor (in this case, 22–19–10). Thus, the latter perturbation is not absorbed, but instead destabilizes the network and forces it towards another attraction 'basin' whence it can no longer return to the previous one. The biological word that corresponds to this effect may be 'adaptation', that is a permanent modification introduced by external stimuli. For simplicity, we can consider this new attractor (22–19–10) as a perturbed system. Although the external change is introduced only once, at time 50, the modification is permanent. This indicates that the dynamic behaviour of this system is sensitive to small perturbations (i.e. only one element of five and only once).

Plots D and E of Figure 5 document a few attempts that have been done in order to restore the original attractor by introducing a further perturbation into the system. A specific perturbation has been found (E=OFF), which, when introduced at a certain point of the cycle (in plot D, at time 51, when the system is in the pattern 19), is able to force the perturbed system into the original attractor (21–27–14). We could draw a medical analogy, by saying that the second perturbation (E=OFF) heals the system, which was permanently affected by the first one (A=OFF). On the other hand, plot E shows that, if the same perturbation is introduced at a different time of the cycle (in this case, at time 50), after a single modification (see the point at time unit 52) the system rapidly goes back to the perturbed system (attractor 22–19–10).

It is worth noting that in our network model system the restoration of the original attractor (Fig. 5, plot D) is obtained using a single perturbation (turning OFF a node for a single time point). However, not all the perturbations cause the recovery of previous homeostasis: only when both the right node (in this case, element E) and the right period of the cycle (in this case, when the system finds itself in pattern 19) are chosen does this occur. In other words, one could speculate that in order to modify in the right direction the behaviour of a complex system, we should know how the system is (i.e. its state at the time of intervention) and when it is sensitive to our intervention. Provided that this information is known, we can take advantage of the self-organizing properties of the system, and obtain large and permanent change even with small and brief perturbations.

IMPLICATIONS FOR MEDICINE

The logical-mathematical model we have described helps in understanding three of the main properties of complex networks, typical of living systems: self-organization, homeostasis and adaptation. Moreover, the system provides a rudimentary and qualitative example of how external perturbations can have both pathological effects (inducing permanent, self-maintained modifications) and therapeutic effects (inducing a modification that allows the system to find the way toward the original state), by inducing specific changes of attractors when suitable conditions are satisfied.

Extrapolating these concepts to medicine, it is possible to envisage that major changes in the homeostatic systems and eventually the healing of the entire body could be obtained through minor but carefully selected stress stimuli such as inserting a needle into an acupoint, administering a low-dose remedy, or even providing the right psychological advice. Signals which are endowed with highly specific information and are capable of specific interactions with the recipient system, could act as regulators.

We speculate that the changes of attractors enlightened here by our 'perturbation' trials have implications also for the understanding of the action of low doses of drugs selected according to the 'principle of similarity,' traditionally proposed by homeopathic medicine. Several theoretical attempts have been made by us[18–19] and by others[20–22] to construct explanatory models of this principle. A common denominator of all these models, is the activation of homeostasis control systems in immune cells or in nervous centres. This causes the production of regulatory signals to resume and, thus, activate a feedback mechanism related to the spontaneous progression of disease. Homeopathic drugs are thus thought to act as substitutes for an endogenous regulatory signal which, for various reasons, may be inadequate or ineffective because the system is no longer sensitive to it, being 'blocked' in a pathological attractor by the disease itself. The traditional 'similia law' presupposes that the intrinsic tendency to self-recovery can be supplemented and actively assisted by the employment of suitable stimuli to a system, when it is in a specific sensitive state.

This type of logical-mathematical approach has made it possible to gain deeper insights into complex systems and the relationships between the self-organization of order and external influences of negative or positive value. Above all, this kind of approach has been able to demonstrate the phenomenon as self-organization, that specific patterns of attractors may originate from multiple interconnected elements. This phenomenon is of undoubted importance in the interpretation of the properties of living systems and of every therapeutic approach which is aimed at the refined regulation of physiological homeostasis.

REFERENCES

1. Nicolis G, Prigogine Y. Exploring Complexity. An Introduction. Munchen: Piper, 1987.
2. Cramer F. Chaos and Order. The Complex Structure of Living Systems. Weinheim: VCH Verlagsgesellschaft, 1993.
3. Stein, W, Varela, F J (editors). Thinking about biology. Reading, MA: Addison Wesley, 1993.
4. Mainzer K. Thinking in complexity. The complex dynamics of matter, mind, and mankind. Berlin Heidelberg: Springer-Verlag, 1994.
5. Nicolis, G. Introduction to nonlinear science. Cambridge: Cambridge University Press, 1995.
6. Goldberger A L. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. The Lancet 1996; 347: 1312–1314.
7. Roszman T L, Brooks W H. Signaling pathways of the neuroendocrine-immune network. Prog Allergy 1988; 43: 140–159.
8. Perelson A S Immune Network Theory. Imunol. Rev. 1989; 110: 5–36.
9. Varela F J, Coutinho A. Second generation immune networks. Immunol Today 1991; 12: 159–166.
10. Cross S S, Harrison R F, Kennedy R L. Introduction to neural networks. The Lancet 1995; 346: 1075–1079.
11. Capra F. The web of life. New York: Doubleday-Anchor Book, 1996.
12. Peper A, Grimbergen C A, Kraal J W, Engelbart J H. An approach to the modeling of the tolerance mechanism in the drug effect. I: The drug effect as a disturbance of regulations. J Theor Biol 1987; 127: 413–426.
13. Peper A, Grimbergen C A, Kraal J W, Engelbart J H. An approach to the modeling of the tolerance mechanism in

the drug effect. II: On the implications of compensatory regulation. J Theor Biol 1988; 132: 29–41.

14. Kauffman S A. Antichaos and adaptation. Scientific American 1991; 265: 64–72.
15. Kàuffman S A. Origins of Order: Self-Organization and Selection in Evolution Oxford: Oxford University Press, 1993.
16. Denton T A, Diamond G A, Helfant R H et al. Fascinating rhythm: A primer on chaos theory and its application to cardiology. Am Heart J 1990; 120: 1419–1440.
17. Elbert T, Ray W J, Kowalik Z J, et al. Chaos and physiology: deterministic chaos in excitable cell assemblies. Physiol Rev 1994; 74: 1–47.
18. Bellavite P, Lussignoli S, Semizzi M L et al. The similia principle: From cellular models to regulation of homeostasis. Brit Hom J 1997; 86: 73–85.
19. Bellavite P, Andrioli G, Lussignoli S et al. A scientific reappraisal of the "Principle of Similarity". Med Hypoth 1997; 49: 203–212.
20. Wiegant F A C, van Wijk R. Self-recovery and the similia principle: an experimental model. Complem Ther Med 1996; 4: 90–97.
21. Jonas W B, Jacobs J. Healing with homeopathy. The complete guide. New York: Warner Books, 1996.
22. Oberbaum M, Cambar J. Hormesis: dose-dependent reverse effects of low and very low doses. In: Ultra High Dilution (P.C. Endler and J. Schulte). Dordrecht: Kluwer Acad Publ, 1994; 5–18.