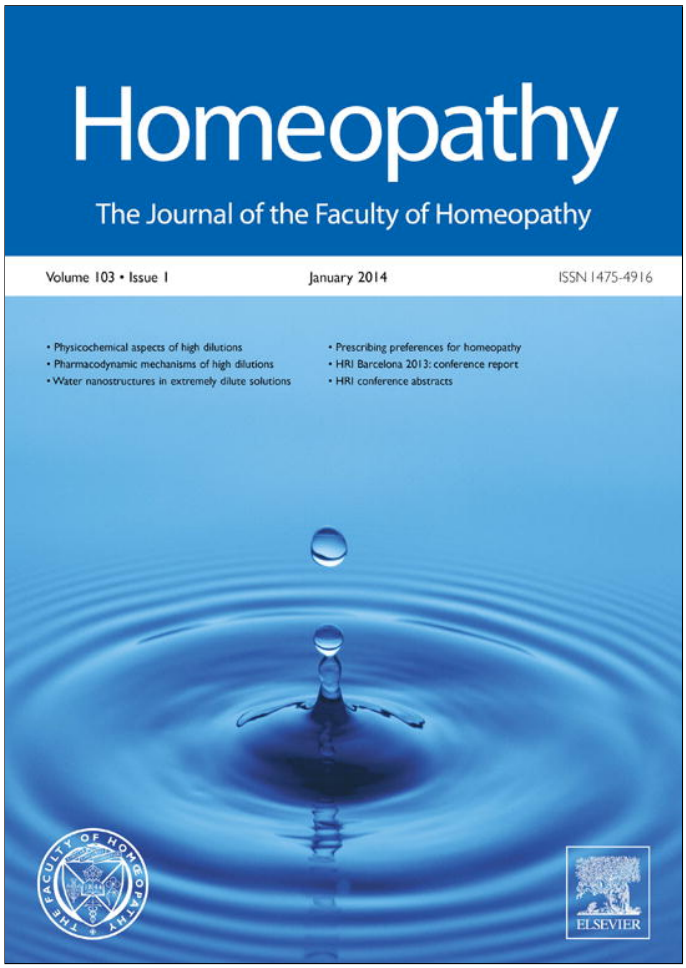

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REVIEW

High-dilution effects revisited. 2. Pharmacodynamic mechanisms

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The pharmacodynamics aspects of homeopathic remedies are appraised by laboratory studies on the biological effects at various levels (cellular, molecular and systemic). The major question is how these medicines may work in the body. The possible answers concern the identification of biological targets, the means of drug–receptor interactions, the mechanisms of signal transmission and amplification, and the models of inversion of effects according to the traditional 'simile' rule. These problems are handled by two experimental and theoretical lines, according to the doses or dilutions considered (low-medium *versus* high dilutions). Homeopathic formulations in low-medium dilutions, containing molecules in the range of ultra-low doses, exploit the extreme sensitivity of biological systems to exogenous and endogenous signals. Their effects are interpreted in the framework of hormesis theories and paradoxical pharmacology. The hypotheses regarding the action mechanisms of highly diluted/dynamized solutions (beyond Avogadro–Loschmidt limit) variously invoke sensitivity to bioelectromagnetic information, participation of water chains in signalling, and regulation of bifurcation points of systemic networks. High-dilution pharmacology is emerging as a pioneering subject in the domain of nanomedicine and is providing greater plausibility to the puzzling claims of homeopathy. *Homeopathy* (2013) **103**, 22–43.

Keywords: High dilutions; Homeopathic potencies; Hormesis; Nanopharmacology; Biophysics; Systems biology; Water clusters; Water coherence domains; Similia rule

Introduction

Homeopathy is progressively receiving scientific validation but a series of theoretical and technical questions need still to be clarified, since several problems appear to distinguish this discipline from conventional pharmacology. The physicochemical nature of the homeopathic remedies, which are produced according to a peculiar method of serial dilution followed by 'dynamization', was dealt with in a previous paper.[1] Here the recent advances concerning the possible mechanism of actions of these drugs in the body are reviewed. Pharmacokinetics is the branch of pharmacology dedicated to the determination of the fate of substances administered to a living organism up to the point at which they are completely eliminated from the body. This approach is often studied in conjunction with pharmacodynamics, the study of effects on the body. Highly diluted medications, including those produced according to the homeopathic pharmacopoeia, are hardly suitable to pharmacokinetic investigation, due to the lack of analytical methods having sufficient sensitivity. On the other hand, experimental evidence from clinical and laboratory studies is providing a remarkable contribution to pharmacodynamics of this class of remedies. The question of how these medicines may work concerns the identification of biological targets at various levels (cellular, molecular and systemic), the ways of drug–receptor interactions, the mechanisms of signal transmission and amplification, and the 'simile' rule (see Table 1). All these problems have several aspects, that can be considered according to the different doses and/or dilutions employed.

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Table 1 Aspects of homeopathic pharmacodynamics

Aspect		*Medium potencies (ultra-low doses)*	*High potencies (high dilutions)*
Nature of the medicine[a]		Very low concentrations of active molecules Nanoparticles	Nanoparticles Water clusters Coherence domains
Biological targets	Local	Molecular interactions: - Cell receptors - Enzyme activation/regulation - Gene expression	Nonlinear dynamics (bifurcation points): - Cell receptors - Enzyme activation/regulation - Gene expression
	Systemic	Neuroimmunologic networks	Neuroimmunologic networks Disease dynamics (attractors-miasms) Bioelectricity (ECG, EEG)
Amplification mechanisms		Cell responsiveness: - Receptor priming - Signal transduction - Stochastic resonance Enzyme activity: - Allosteric activation - Silica nanostructures	Neuroimmunologic networks Nonlinearity-chaos Grotthus-type water chains
Information transfer		Molecular interactions Water chains	Frequency-coded signals Water chains Water nanoparticles Bioelectromagnetics
Inversion of effects (the 'Simile')		Hormesis Dual receptors Gating by cAMP Hsps Paradoxical pharmacology	Rebound in time Systems biology theories Coherent response to stress

[a] This aspect was the subject of the preceding paper.[1]

Pharmacologic activity of mother tinctures and of low potencies (e.g., 2C–3C, containing relatively high doses of active principles) poses no problems of interpretation and requires analysis of the components and identification of their targets in the organism, in a way not dissimilar from that of herbal products, snake toxins, or mineral oligoelements. The action of medium potencies, that contain ultra-low doses of active principles (ULDs, namely from 4C–5C to approximately 12C, close to the Avogadro–Loschmidt limit) entails high sensitivity of living organisms and inversion of drug effects, in the framework of models not much distant from modern pharmacology, like hormetic mechanisms. The action of high dilutions (HDs, namely homeopathic dilutions beyond the Avogadro–Loschmidt constant) requires the identification of possible 'non-molecular' or 'meta-molecular' information transfer mechanisms. Finally, the 'holistic' approach of homeopathy as healing system goes far beyond the identification of specific information transfer mechanisms or molecular targets and should be understood in the light of systems biology.

Biological targets

The specificity of any drug effect is based on the interaction or active principles with their biological targets and the same can be conceived for homeopathic drugs. In the latter case, the identification of these interactions is complicated by several factors, including the different nature of remedies in low and high potencies, the presence of many active principles in most compounds of vegetal or animal sources, and the different sensitivities that presumably exist in healthy and sick organisms. In spite of these problems, experimental evidence gathered in laboratory studies has identified a representative number of cell and molecular targets of homeopathic drugs.

Local targets

The cornerstone of homeopathy that the whole clinical picture is considered on an individual basis is not in dispute, but laboratory models show that mechanism(s) of action of the drug can be investigated in animals, cells, tissues, and even at the molecular level. Pharmacodynamic effects of homeopathic remedies have been proven in several dozens of animal and '*in vitro*' laboratory studies. Apart from reviews on this topic,[2–5] some recent demonstrations of these effects merit to be mentioned. One of the most interesting lines of research regarded histamine and other compounds (*Lung histamine* and *Apis mellifica*), which have pro-inflammatory effects when used at high doses but trigger anti-inflammatory mechanisms when employed at ULDs and HDs. The effect of *Lung histamine* (5C and 15C) and *Apis mellifica* (9C), traditional remedies used for the treatment of allergic diseases, was assessed on *in vitro* human basophil degranulation.[6] After this early study, several independent laboratories reported a significant inhibition of basophil functions by HDs of histamine. Most studies were positive[7–14] with few exceptions.[15,16] The effect was inhibited by histamine H2 receptor antagonists cimetidine,[17] supporting the hypothesis that HDs of histamine exert their inhibitory power at the level of H2 receptors of basophilic cells. That homeopathic drugs may act through modulation of cell receptors and protein synthesis is supported also by studies from the laboratory of Khuda-Bukhsh.[18] In a model of chemically induced murine papilloma, where a known set of proteins involved in the tumor development were altered, the researchers found a significant remodulation toward normal condition after treatment with the potentized drug *Secale cornutum* 30C, driven by

the downregulation of aryl hydrocarbon receptor, as evaluated by western blot analysis.

A large series of studies by an Austrian group[19–21] showed the influence of highly diluted thyroxine (30D) on the spontaneous tendency of juvenile frogs, at the end of metamorphosis, to leave the water and climb onto land. Climbing activity diminished under the influence of dilution thyroxine 30D, with statistical significance. These results show that HDs of thyroid hormones, that at physiologic doses stimulate growth and metamorphosis, transmitted inhibitory information to the same test system, even though the molarity was beyond Avogadro's constant. This effect was confirmed by independent laboratories, with various experimental approaches.[22–24]

Evidence from laboratory,[25] animal,[26] and clinical[27] studies showed that the immune system, inflammation mechanisms and leukocytes are among the targets of homeopathic effects. Low potency formulations composed by *Arnica montana* 4D, *Calendula officinalis* 4D, *Hypericum perforatum* 4D and *Symphytum officinale* 6D, clinically used for wound healing, exerted *in vitro* stimulation of fibroblasts, which are the cells responsible of connective tissue repair.[28] Another low potency formulation containing *Arnica montana* and other plant extracts and minerals was tested on an animal model of traumatic inflammation.[29] The decrease of paw oedema, associated with the process of healing, was more rapid in verum-treated than in placebo-treated rats and the therapeutic effect was associated with a significant decrease of interleukin-6. The efficacy of the complete formulation was higher than the combination of a selection of active components, suggesting that its effect cannot be considered as the 'sum' of its active components and probably a synergistic interaction occurs to determine the final effect. The effects of *Arnica montana* 6C on the modulation of acute inflammation kinetics in rats were evaluated by another group.[30] Medium (6C) and high (12C, 30C, 200C) potencies of *Mercurius solubilis* added to mice's drinking water for 7 days (*in vivo* treatment) modulated macrophage functions.[31] Similar effects were observed also when the same drug was added to the cell culture, suggesting that the observed '*in vivo*' effect was due to a direct interaction with macrophages. Interestingly, another group used *Mercurius solubilis* in a rat model of wound healing, showing that rats treated for 21 days with a 12C potency had less wound infections than placebo-treated rats.[32] In animal models, also *Silica*, which is a stimulant of macrophages and fibrous tissue formation at high doses, stimulates tissue healing and macrophage activation also at extremely low (homeopathic) doses.[33,34]

Ignatia, *Gelsemium*, *Chamomilla* (in homeopathic dilutions/potencies) have consistently shown to act on the nervous system and specifically to modulate anxiety-like behaviours in rodents.[4] In the traditional Materia Medica and homeopathic literature, *Gelsemium* is described as a remedy for a variety of anxiety-like psychological and behavioural symptoms.[35–38] All parts of the plant contain the major active principle gelsemine as well as other toxic strychnine-related alkaloids, such as gelseminine and sempervirine.[39,40] The anxiolytic, antidepressant and/or analgesic action of *Gelsemium* extracts and of gelsemine has been recently demonstrated in animal models.[4,41–44] A hypothetical target of *Gelsemium* has been suggested by studies showing that gelsemine stimulates the biosynthesis of allopregnanolone (an anti-stress neurosteroid) in the rat brain,[45,46] but probably other mechanisms of the pharmacodynamic action may exist.[4] The effects of *Gelsemium* are not restricted to the nervous system, as shown by other reports indicating that this plant species may exhibit anticancer and immunomodulation activities.[47–50] The '*Gelsemium* model' – encompassing experimental studies *in vitro* and *in vivo* from different laboratories and with different methods, including significant effects of its major active principle gelsemine – may play a pivotal rule for investigating the pharmacodynamics mechanisms of homeopathic remedies.

Effects on gene expression

The ability of high diluted compounds to modulate gene expression in human and unicellular organisms has been object of investigations. In early studies with the isopathic model of arsenicum-intoxicated mice, the failure to express the protective effect of *Arsenicum album* 30C and 200C in the presence of the transcription blocker Actinomycin D[51] suggested that potentized homeopathic drug acted through active gene transcription. Then, in experiments conducted in biological models (arsenite or UV treated *E. coli* and *Saccharomyces* culture) the treatment with *Arsenicum album* 30C or *Arnica montana* 30C modified the expression of specific genes that are target respectively of the arsenite and UV irradiation injure.[52,53] In recent studies, the same group evidenced the anti-tumorigenic effects of mother tincture drugs (quercetin, gingerol and *Hydrastis canadensis*), as demonstrated by the modulation of the expression of specific mRNA markers of apoptosis and by cell viability tests. Moreover, they demonstrated a direct interaction between the cell DNA and the drug itself, as observed by circular dichroism (CD) spectropolarimetric study and DNA melting analysis.[50,54,55] These findings support the hypothesis that homeopathic remedies could turn on or off some relevant genes, initiating a cascade of gene actions to correct the gene expression that went wrong to produce the disorder or disease. In this hypothesis the target relevant gene should be sensitive to similar stimuli and exert a pleiotropic transcriptional regulation on a battery of genes with correlated functions.

The analysis of gene expression was performed on large-scale by some authors, using the microarray technique. This method is based on microscopic arrays of immobilized nucleic acids (about 15–30,000 genes depending on the type of platform), that function as probes for sequence-specific nucleic acid hybridization. de Oliveira *et al.*[56] investigated the effects of a complex homeopathic medication (*Aconitum* 11D, *Thuja* 19D, *Bryonia* 18D, *Arsenicum* 19D and *Lachesis* 18D) on cytokine production and gene expression from mice macrophages. They found that the verum-treated group differentially expressed 147

genes (45 upregulated and 102 downregulated) when compared to the placebo-treated group. These genes are mainly involved in transcription/translation, cell structure and dynamics, immune response, cytoprotection, enzymatic process, and receptors/ligands.

Bigagli *et al.* evaluated the effects of extremely low copper concentrations (from 10^{-6} to 10^{-17} M) on gene expression profiles of a line of human prostate epithelial cells.[57] Microarray data demonstrated that copper added to the medium varied gene expression at all concentrations tested. Unfortunately, the authors did not declare if the solutions were succussed after dilution and if can be considered as homeopathic preparations. However, an interesting indication is that the effect was not dose-dependent, but followed a sinusoidal behaviour, since about 12.5%, 14%, 5.5%, 15% and 7.5% of the genes were modulated by copper 10^{-6} M, 10^{-9} M, 10^{-12} M, 10^{-13} M and 10^{-17} M, respectively. Moreover, there were clusters of genes overexpressed or downregulated at all concentration and other clusters that were upregulated only in the low or high range on copper dilutions.

A recent study proved the effects of homeopathic medicines (*Ruta* 200C, *Carcinosinum* 200C, *Hydrastis* 200C, *Thuja* 200C) on Dalton's lymphoma tumor cells.[58] In particular they measured the apoptosis and the expression of specific genes, by reverse transcription polymerase chain reaction (RT-PCR) and microarray. In these experiments dynamized preparations showed significant cytotoxic action against cancer cell lines, and at times, the activity was higher for 200C potency than for the mother tincture. By the RT-PCR method, the expression of the apoptotic genes p53, Bcl-2, and caspase 3 after incubation with the ultradiluted remedies was investigated. Not all the potentized drugs induce expression of all the marker genes, but only *Carcinosinum* 200C induced p53 gene expression. Moreover, microarray analysis showed a direct action of ultradiluted solutions on gene expression: about 100 genes were differentially expressed with the potentized drugs, while about 600 with *Thuja* 1M, compared to controls. A comparison of potentiated drugs with their mother tincture indicated that the potentiated drugs have biological activity similar to that of their mother tincture in spite of ultradilution.

Our preliminary results reveal the extremely high sensitivity of human neurocytes gene network to ULDs and HDs of *Gelsemium*.[59] As observed by microarray technique, the drug modulates the expression of a series of genes involved in neuronal function compared to the control vehicle solution. 24 h exposure to the *Gelsemium* s. 2C dilution (the lowest potency employed, corresponding to a gelsemine concentration of 6.5×10^{-9} M) significantly changed the expression of 56 genes, of which 49 were downregulated and seven were overexpressed. Several of the downregulated genes belonged to G-protein coupled receptor signalling pathways, calcium homeostasis, inflammatory response, and neuropeptide receptors. Several genes significantly decreased their expression even after treatment with higher dilution/dynamization (3C, 4C, 5C, 9C and even 30C), although with smaller changes (Marzotto *et al.*, in preparation).

Systemic targets

The existence of specific cell and molecular targets for drugs does not mean that the homeopathic effects can be explained by local interactions only. Although homeopathy is thought to have been born as an empirical approach, it is actually based on a systemic and dynamic view of health and disease, that can be better appreciated inside the new paradigm of complex systems,[60–65] whose key features are:

(a) *nonlinearity*: output is not proportional to input, occurrence of paradoxical responses;
(b) *deterministic chaos*: apparently unpredictable behaviour, sensitivity to initial values and perturbations, fractals, self-similarity;
(c) *emergence*: self-organization, pattern formation, coherence, oscillations, dynamic attractors;
(d) *adaptation*: evolution, plasticity, memory and learning, hysteresis, sensitization/desensitization, tolerance. These concepts of nonlinear dynamics offer a different perspective for understanding homeodynamics and disease,[66–68] and nonlinear system theories are starting to be applied to help interpret, explain, and predict biological phenomena.[69]

When a stimulus is applied to complex networks in the immune, endocrine and nervous systems, the entire network responds and undergoes an adaptation. Such a system is deterministic but extremely sensitive to even small perturbations. The triggers that cause the immune response to go in a certain direction depend not just on a single signal, but rather on a multiplicity of elements acting on each other synergistically, antagonistically and through feedback loops.[70] These features can also be used for the control of chaos and this may open up an avenue for therapy, but further models still need to be refined and developed.

There is some evidence that HDs applied on the tongue trigger rapid electrophysiological responses in central nervous system.[71,72] Rats kept on a high-salt diet were anesthetized and a microelectrode, connected up to an oscilloscope, was implanted in the lateral hypothalamic area to record the discharge frequency in that area. After a suitable period recording the basal tracing, a few drops of *Natrum muriaticum* (sodium chloride or common sea salt) 30C or 200C were deposited on the tongues of the rats. The application caused marked changes (reductions) in the discharge frequency of the nerve centre. This experiment suggests both that the action of the drug can be mediated by the hypothalamic nerve centres and that preconditioning with a high-salt diet makes the animal more sensitive to the remedy *Natrum muriaticum*. Rapid (few seconds) hypothalamic electrophysiological responses to *Nux vomica* 200C and 1000C in ethanol-intoxicated rats were also reported.[72]

Frequency-coded signals

In biology, information transfer does not depend only on the dose of a signal molecule, but also on the 'way'

molecules relate to the receiver systems. For example, cells are capable of distinguishing the kinetics by which a signal is received, i.e., whether it is a sudden signal or one with a slow onset, whether the concentration is stable or oscillating, whether the signal occurs on its own or is accompanied by other concomitant or preceding signals, whether it is the first prompting or a repetition of something previously experienced. Thus, the information is not merely quantitative, but inherently spatiotemporal. Calcium and other intracellular messengers perform their regulating functions by means of oscillations of concentration which constitute a kind of 'digital code' for the various systems sensitive to them. Such digitally encoded signals could more precisely regulate cell responses also through rhythmic changes in hormone concentrations.

Biological communication is so important that nature has gone out of its way to devise a wide variety of forms of communication. To those previously mentioned we can add others, first and foremost among which are the sense organs endowed with photoreceptors, chemoreceptors, baroreceptors, and others. Bioelectrical signals, encoded in spatiotemporal changes of membrane potential, regulate cell proliferation, migration, differentiation, and morphogenesis.[73] Sensitization to chemical toxins includes bioelectric disorders and autonomic changes that can be revealed by spectral electroencephalography (EEG), blood pressure, heart rate, and plasma beta-endorphin.[74]

In order to create a scientific basis of homeopathy and other complementary medicine applications like acupuncture, it is certainly necessary to add a more non-local approach. A possible framework involves oscillatory electromagnetic (EM) interactions as regulatory and − in case of disease − deregulatory impulses of the organisms.[75] For instance: a homeopathic stimulus (*Strophantus hispidus* 30C) changed the power spectrum of heart rate variability in healthy human subjects during 24-h long intervals.[76] Subsequently the same group used EEG to experimentally investigate the effects of HDs in laboratory rats.[77–79] They tested the effects of *Coffea cruda* 30C and 200C *versus* placebo on the sleep patterns of rats assessed using EEG readings in the Delta band, 0.5−2.5 Hz, from the parietal region. Treatments were administered orally at the beginning of the sleeping period. In synthesis, the spectral power of Delta band was significantly higher than baseline for *Coffea* 30C and caffeine (15.5 mg/kg). *Coffea* 30C and caffeine have similar effects on sleep pattern, enhancing delta power; *Coffea* 200C appeared to affect only the synchronization. Another interesting study regarded histamine.[80] Besides being an inflammation mediator, histamine is a central neurotransmitter, it increases arousal *via* H1 receptors. HDs of histamine (30C) decreased the mean Delta band spectral density and the effect was very rapid. Subsequently the same group tested different potencies and found highly nonlinear patterns, with peaks of activity at 15C, 21C and 30C dilutions.[81]

Following those animal studies, remedy-related sleep stage alterations and EEG changes were detected in human subjects. In patients with fibromyalgia, the clinical response to homeopathic remedies at a systemic level is associated with changes in prefrontal electroencephalographic alpha frequency cordance (EEG-C, a correlate of functional brain activity).[82] In a recent experimental trial, college students with a history of coffee-related insomnia took one bedtime dose of a homeopathic remedy (*Coffea cruda* or *Nux vomica* 30C) and those remedies significantly altered short-term nonlinear dynamic parameters of slow wave sleep.[65] These observations suggest EEG-C as an early biomarker of individualized homeopathic medicine effects. Recently, the same group used EEG to evaluate psychophysiological effects of two homeopathic remedies (*Sulphur* or *Pulsatilla*) after an olfactory activation protocol on healthy young adults.[83]

The data showing significant interactions of remedies for EEG parameters encourage additional research on nonlinear psychophysiological and bioelectric effects of homeopathic remedies.

Disease dynamics and bifurcation points

The ability of extremely diluted drugs to change the behaviour of cells, animals and humans can be ascribed to the high sensitivity of the targets involved and to the existence of subtle bifurcation points in the disease dynamics. For example, we have shown that HDs of *Gelsemium s.* may modulate anxiety in mice, because behavioral tests are designed to put the animal in a situation of uncertainty, regarding the trajectory of movements in an open space.[84] In this situation, an extremely small pharmacological influence on emotional state of the animal can determine the choice of which direction to move, e.g., of whether the animal moves toward the open space or along the walls of the test platform. The sensitivity of laboratory tests (and humans in clinical settings) to minimal factors is also, conceivably, one reason for the high variability of responses in the various experiments and of the experienced difficulties in full replicability in different laboratories.

Far from equilibrium states and bifurcation points are found at each level of the disorganization of living organisms, from molecules to cells, and lead, when not corrected, to progression of disease. Here we will outline some characterizing bifurcation points in the dynamic progression of diseases, summarizing and updating a theory that was extensively reported elsewhere.[85–87] According to conventional diagnostic criteria, what usually appears as the 'disease' is actually the *last phase*, consisting of particular biochemical and anatomical abnormalities. Prior to this, however, there are at least three other phases. We have the very *first phase* in which an initial disorder, largely non-apparent apart from a few very indistinct symptoms or variations in very subtle parameters, makes the body susceptible to perturbation-induced external agents. This stage could for example include people who are subject to overwork (stress) or to an unbalanced diet, or those who smoke, are exposed to low doses of ionizing radiation, or present particular genetic characteristics that make them 'at risk'. Clearly, at this level the balance between normal and pathological is extremely precarious, and the ensuing course of the disease

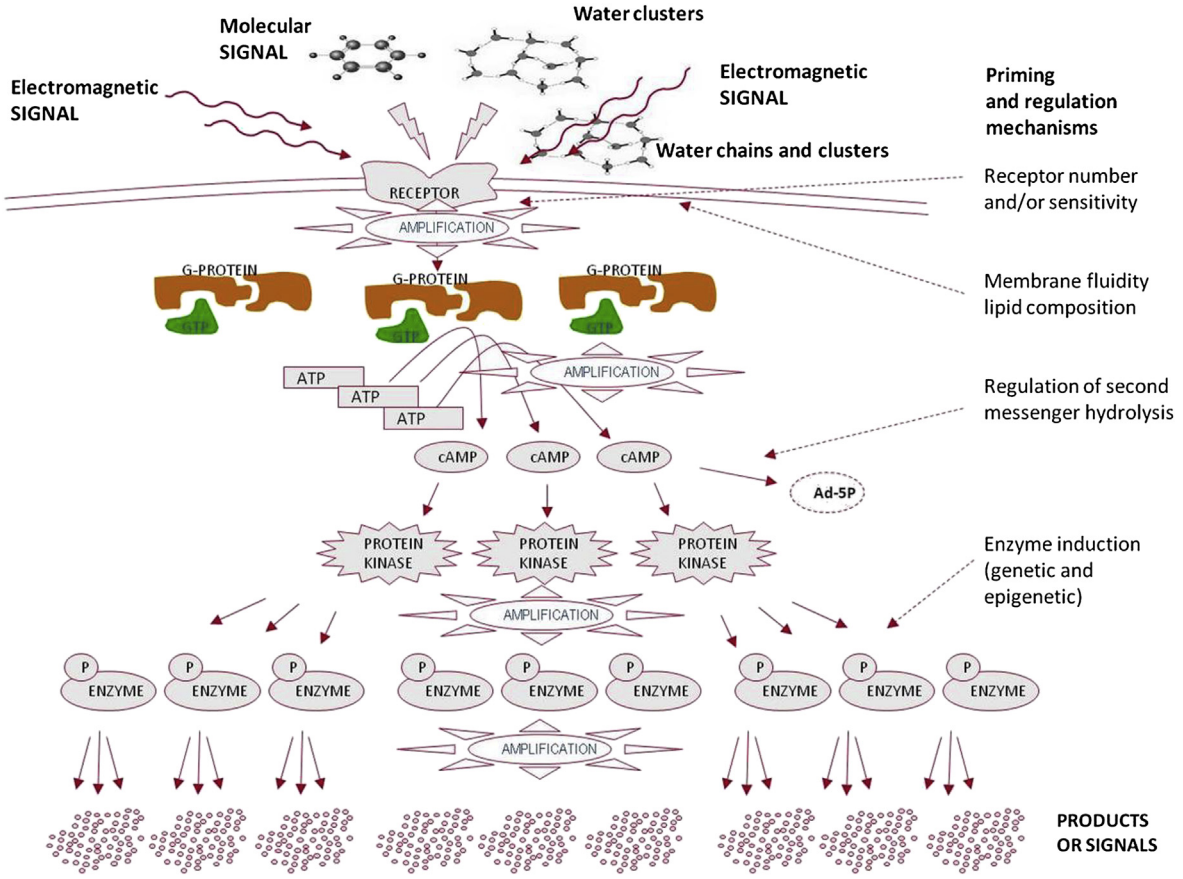

Figure 1 Example of possible signal amplification mechanisms at the cell level. It is not necessary to involve many receptors to have a strong effect, nor is it necessary for the signal to be of a molecular type. Receptor triggering or modulation could also be physicochemical (heat, radiation, vibration, sound waves, or particular structures of water or solvent). cAMP: cyclic adenosine monophosphate (activator of protein kinase A), Ad-5P: adenosine-5phosphate (hydrolysis product of cAMP).

can come down on one side or the other, according to shifts in minor factors.

A second bifurcation can be found in the *reactive phase* of homeodynamic biological systems (haemostasis, inflammation, tissue regeneration, etc.). These systems are 'two-faced', in the sense that they bring about healing but may also cause damage, because they can either attack or disorder the host itself. To what extent, in each individual case, the damage done prevails over the reinstatement of health, or *vice versa*, depends on subtle variations in the behaviour of the homeostatic system itself. In particular, the fate of the reaction depends on the choice that the system has to make between the 'price to pay', in terms of toxicity and suffering, and the guarantee of success of the operation in terms of survival of the body. A choice of this type depends both on the local elements involved (receptors, concentration of mediators, presence of exogenous chemical substances) and on the type of centralised control system that coordinates and regulates the various responses. Thus, at the level of this bifurcation, the outcome of the reaction may depend on subtle factors that are significant for the coordination of the reactions.

A *third phase* in the disease process, which represents another critical decision point, is when the reactive systems fail to cope with the situation and to restore the original state. At this point a pathological *adaptation* may set in, meaning a semi-permanent modification which shifts the receptor sensitivity thresholds and induces further biochemical and anatomical changes. Chronic pathology ('miasms' in homeopathic terms) is a dangerous form of adaptation, which makes it possible to 'live with' the homeodynamic disorder, but also opens up the way to progression. In fact, a chronically disordered system requires high energy consumption and is more susceptible to further damage due to lack of coordination in various defence and healing systems. Also, the choice between reaction and adaptation is very complex, as it is determined by a multiplicity of subtle endogenous and exogenous factors.

Amplification mechanisms

The 'biological power' of a drug depends on the affinity between the binding site and the molecule itself, as well as on the response of the treated system. Note that conventional drugs normally act at concentrations between 10^{-6} M (micromolar) and 10^{-9} M (nanomolar), whereas the more modern ones such as cytokines are also active at concentrations from 10^{-12} M (picomolar) to 10^{-15} M (femtomolar). In the scientific literature, there are many publications showing a clear biological effects (meaning

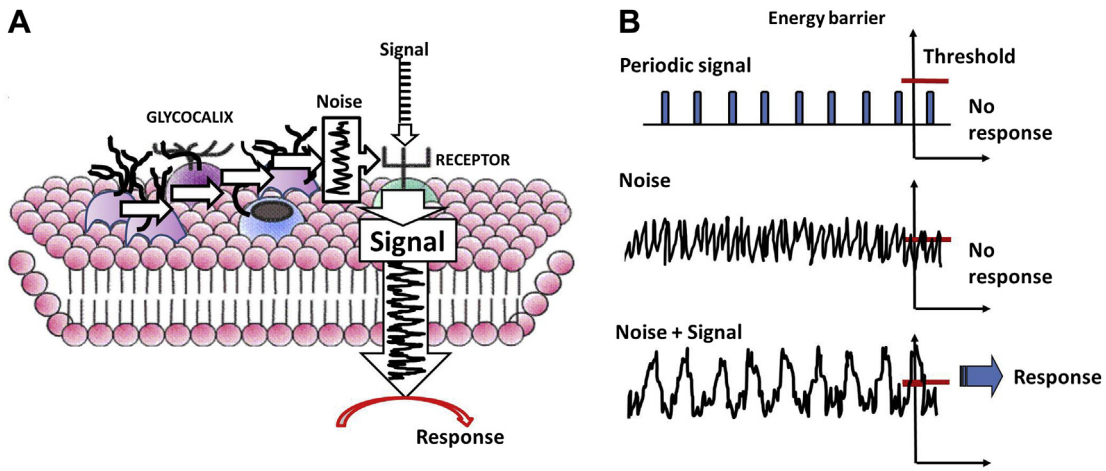

Figure 2 An intuitive illustration of stochastic resonance in plasma membrane. (A) The glycocalyx introduces a noise as an amplifier of signal–receptor interaction and increases the periodic signal passed to the transduction systems. (B) Upper diagram: A small periodic signal, with energy under the activation threshold of receptor, produces no response. Intermediate diagram: Noise contains no specific information and the receptor is not activated. Lower diagram: When the noise is added to the signal, the activation energy exceeds the threshold and the system receives an information with a frequency component equal to the periodic signal, but stronger than the pure incoming signal.

that there are demonstrable effects in laboratory systems) of substances diluted by as much as 10^{-18} M (attomolar), corresponding approximately to the 9C homeopathic dilution.[1] The typical physiological levels of the endogenous hormones are extremely low: 10–900 pg/ml for estradiol, 300–10,000 pg/ml for testosterone, and 8–27 pg/ml for T4. When the circulating levels in blood are corrected for the low fraction of the hormones that are not bound to serum binding proteins, the free concentrations that actually bring about effects in cells are even lower, for example 0.1–9 pg/ml for estradiol.[88]

A simple calculation illustrates how these doses pose a challenge to current theories: in fact, a concentration of 10^{-15} M (approximately 5C–7C in homeopathic drugs, depending on the starting concentration) corresponds to 10^{9} (one billion) molecules per litre, which is also equivalent to 10^{6} (one million) molecules per cubic centimetre, or 1000 molecule per cubic millimetre. Taking blood as a reference substance, it contains around 7000 leukocytes per cubic millimetre, meaning that in this case, a 10^{-15} M solution would contain one molecule for every seven cells. It is clear that the action of ULDs, which contain very low doses of active substances, poses a challenge to pharmacology and claims the existence of amplification mechanisms at some stage of the signal transmission chain, from molecules in water environment to signal–receptor interaction and the wide range of transduction pathways. A simplified scheme of some amplification steps at the level of receptors and signal transduction inside the cell is depicted in Figure 1.

Receptors for signal molecules or for other types of messengers (light, EM signals, stretching, action potentials) are highly plastic: the cells are capable of increasing (hypersensitivity, priming) or decreasing (desensitization, tolerance, adaptation, downregulation) the number of receptors according to their needs, as well as of regulating their activity by modifying the affinity for the signal molecule. On occasion, the cells may present more than one receptor for the same molecule, but with different affinities and different intracellular effects.

The intracellular transduction systems couple receptor activation with production of signals or activation of effector mechanisms; they are associated with enzyme activities, variations of intracellular second messengers, modifications of membrane lipids and proteins, and the opening of ion channels. Small changes of concentration and/or of oscillations frequency in second messengers like free calcium, protons (H+), cyclic adenosine monophosphate (AMP) and phospholipid derivatives can induce allosteric modifications of enzyme functions, chain reactions and cascades of intracellular signals, and eventually gene expression. The multiform characteristics of the receptor and transduction systems are too vast to be dealt with here. What is beyond doubt, however, is that the level of responsiveness is controlled at various levels in the cell, that the sensitivity to external messages is modified during the course of disease, and that all these mechanisms are susceptible to pharmacological modulation as well as by diet (e.g., the change of membrane lipid composition, the role of antioxidants, the epigenetic effects of food components).

In summary, a few extracellular molecules or even a single molecule, or extremely low magnetic fields can trigger (or regulate) a series of chain reactions that lead to the activation (or downgrading) of the specific cell function related to that particular signal. According to this model, interaction between a potentized homeopathic solution and the cell surface causes the membrane proteins, or their glycosylated parts, to produce a cascade of biochemical events inside the cell resulting from contact with the drug itself. Such events could be enormously amplified at the receptor and post-receptor level, to even affect gene expression.[18,89] We[90,91] and others[92–94] have previously illustrated how receptor sensitization and desensitization, and in general the postconditioning of cells by various types of treatments, may support the beneficial effect of low dose

stress compounds that are applied according to the similia principle.

In the previous paper we cited the findings that silica nanostructures are formed during succussion in glass containers which are usually employed in the preparation of homeopathic drugs.[95] Recently Ives *et al.*[96] showed that boron, silicon, and sodium leaching from glass containers are present at micromolar levels and have enzyme activity stabilizing effects. Moreover, the increased enzyme stability could be mimicked in a dose-dependent manner by the addition of silicates to the enzyme assay. This finding suggests a further mechanism of amplification of biologic effects of homeopathic drugs.

Stochastic resonance

A further point linked to the ULD effects concerns resonance phenomena,[97,98] which are involved in both information transfer and signal amplification. Stochastic resonance is a seemingly paradoxical concept, according to which background noise (random fluctuations of energy and molecular vibrations that disturb any natural system) may increase, rather than decrease, the perception of signals (see Figure 2). So, by this process, a system may become sensitive to stimulations so small that they would not otherwise be perceived. In recent years, a series of experiments have shown that this phenomenon occurs in lasers, superconductors, electronic circuits, neurons, and biological membranes.[99,100]

Stochastic resonance requires a physical system capable of making transitions between two or more states (oscillations), and of being perturbed by an input which can consist of an aperiodic 'noise' and of a periodic signal that is weak with respect to the noise. For example, stochastic resonance may involve the membrane glycocalix which may introduce a noise as an amplifier of signal–receptor interaction. When the noise of glycocalix oscillations is added to a (small) periodic signal, the periodic oscillation is amplified, and at its output the system emits a signal with a frequency component equal to the periodic signal, but stronger than the same incoming signal.

The membrane potential is a source of EM noise generated by continuous vibrations of charges and molecular bonds, and by fluctuations in the dynamics of ion channels. The lipid–water interfaces are transition regions with a very refined electrical structure, and highly sensitive to electric fields so that even the slightest change in their electrical properties has an impact on the structure and the oligomerization state (aggregation function) of proteins in the same membrane.[101] Thus there is a nonlinear relationship between the incoming signal (input) and the transmitted signal (output): when the input drops below a given threshold value, there is no output at all. On the other hand, a very weak signal can be elevated above the threshold when it encounters the right amount of noise, and enters into resonance with it; i.e., the signal encounters a resonance that can amplify it to an appropriate level for the transmission. Intracellular events such as calcium oscillations, are increased by background metabolic noise.[102]

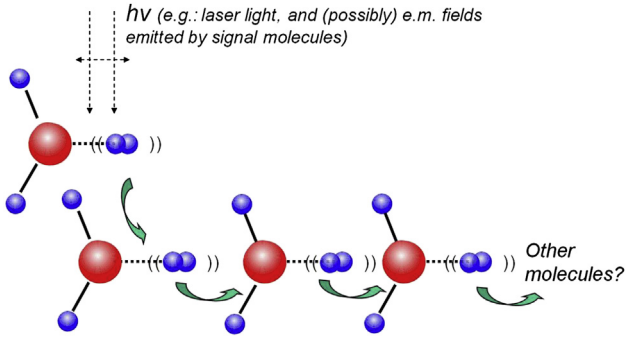

Figure 3 Schematic representation of ultra-fast inter-molecular energy transfer in water by excitation of O–H bond. Free adaptation of evidence provided by Nitzan and Woutersen.[104,105]

The role of water

Membrane proteins interact not only with signal molecules but also with water molecules and clusters, a phenomenon that leads to protein conformational change and transient proton transfer.[103] This leads to the hypothesis that biological effects of HDs can also be mediated by transmission of EM energy (and information) through water, using the ultra-fast and extremely efficient transfer of energy, as exemplified in Figure 3.

Chains of water molecules facilitate proton transfer within hydrophobic proteins. Since this occurs at an intermediate conformation only, the rearrangement of protein-bound water molecules, from inactive positions in the ground state to an active chain in an intermediate state, appears to provide insight into proton-transfer mechanisms and functions of ubiquitous membrane spanning proteins.[103] The Grotthus mechanism also works in so-called 'water wires' that enable hopping of protons through trans-membrane proteins such as bacteriorhodopsin that function as a proton pump.[108]

Such 'supramolecular' organization of water in chains is similar to the proton 'hopping' mechanism proposed by Grotthus,[106] and may account for amplification of effects of drug molecules dissolved in water. An indirect confirmation that this may account for some activity of HDs is the increase of electrical conductivity of highly diluted/succussed solutions reported by Elia.[107] When an H+ ion encounters a water molecule in a favourable geometrical position, it forms a bond with the water molecule which in its turn releases an H+ ion. Thus, it is effectively as if ions that encounter a water molecule (which enables this 'hop') diffuse faster than ions which do not meet a water molecule in this favourable geometrical position. Variations in the supramolecular structure of water may augment the contribution of the hopping mechanism and hence the resultant diffusion of ions, thereby also increasing specific conductivity.

Information transfer

The transmission of drug information from remedies of low and medium potency (ULDs) to body target systems can occur through molecular interactions, regulated by

affinity and concentration, as in conventional drugs. Compounds can interact with local receptors (e.g., in the mouth or on the skin) or be absorbed by mouth or intestine and transported to their targets through biologic fluids like blood and lymph. On the other hand, it is conceivable that HDs can use different pathways of signal transmission, like body water, nerve impulses, solitons, or even EM pathways. We call these pathways of signal transmission as 'meta-molecular' since they may require molecular movements and changes, but are not restricted to them. Use of HDs is a tentative approach to the bioenergetic regulation of the human body on a physical–biochemical interface, made possible by the extreme sensitivity of biological systems to this type of regulation.

Biophysical interactions

There is no single unitary explanation for the action of HDs on the organism, however an accumulation of evidence from various fields of science is building up a conceivable and plausible picture, in which biophysics is integrated with molecular biology and system biology. If the problem is couched in physical and not merely in chemical terms, it is very likely that any such explanation must necessarily take into account the sensitivity of living systems to small energies like those carried by EM fields.[109,110] In this context, the emerging bioelectromagnetic paradigm will have an important role because it re-evaluates an important form of long-range communication, not only at intermolecular but also at supramolecular levels of organization of biological systems.

Cells are able to detect and respond to weak electric and magnetic fields, possibly through glycoprotein bound to ionic channels.[111] Several molecular systems have been shown to be sensitive to EM fields, even of very low intensity: photoreceptors (eye and skin), chlorophyll, G-Protein-coupled trans-membrane receptors, cAMP-dependent protein kinase, heat-shock proteins (hsps), chromosomes, Na+/K+ ATPase, lysozyme, membrane ionic channels and even water itself. Cells are detectors of very weak periodic magnetic fields at around 10^{-3} V/cm intensity, but in specific frequency 'windows', i.e., where certain responses occur only within a restricted frequency band, the minimum intensity, necessary to trigger the cell response, may be several orders of magnitude lower (10^{-6} V/cm).[112] On the other hand, in living systems there are a number of sources of EM fields: electrical activities of nervous centres and heart, charge movements (ions) in vessels, charge movements (ions, H+) inside cells, membrane polarization/depolarization, electron-transport and proton-transport chains in mitochondria, proton *jumping* in water and proteins, oxidation–reduction metabolic activities, phosphorylation/dephosphorylation processes, enzymes that generate chemiluminescence, release of biophotons by DNA, muscle contraction, piezoelectric activity (on bending) of bone, connective fibres, microtubules, and microfilaments. Although many of these electrical events may be by-products of metabolic activities without any specific function, the widespread EM sensitivity of sensing and transduction systems suggest that they are also utilized as signalling modes for communication and coordination among cells and tissues.

Practically all organisms emit light at a rate from few photons per cell per day to several hundred photons per organism per second. This emission of 'biophotons', as they are called, is distinct from the chemiluminescence of leukocytes or the bioluminescence of fireflies, which is associated with specific organelles. Biophotons emission occurs at very low intensity but is universal to living organisms, where it is thought to represent a long-range form of communication, capable of generating synchronous and coherent phenomena.[113–115] DNA generates a longitudinal wave that propagates in the direction of the magnetic field vector, and frequencies computed from the structure of DNA agree with those of the predicted biophotonic radiation.[116] The authors suggest that such a wave is able to use genetic code chemically stored in the base pairs of the genes and to electrically modulate them, so as to 'piggyback' information from the cell nucleus to another cell. At the receiving end, the reverse process takes place and the transported information is converted back into a chemical structure.

It has been suggested that acupuncture meridians are related to an interconnected cellular network that regulates growth and physiology[117] and meridians can, to a certain extent, be compared with pathways for the propagation of electronic excitation in the body, similar to optical waveguides along which EM pulses propagate as solitons.[118] This theory may explain the high electric conductance of the meridian system, and electrodermal activity may be a valuable physiological marker for the acupuncture phenomenon.[119,120]

A review of the current progress in understanding coherence effects in relation to the mechanisms of homeopathy and acupuncture, and of how bio-information may be stored in water has been published by Smith.[121] The author concludes that living systems interact with external EM fields in such a way that it should be possible to control chemical reactions both *in vitro* and *in vivo* through the interaction of the magnetic vector potential with the chemical potential. EM fields have a long range and then are able to produce recognition at a distance, also in a crowd of non-resonating molecules. Long-range EM communication between molecules may represent the founding theory able to unravel the nature of the molecular signal and the role of perimolecular water in its transmission.[122]

Electronic transfer of information

There is mounting experimental evidence that biological information capable of modulating cellular behaviour and responses can be transferred by electronic means. The results of 'digital biology' suggest a previously unknown EM nature for the molecular signal. This signal, that is 'memorized' and then carried by water, most likely enables *in vivo* transmission of the specific molecular information between two functional biomolecules.[122]

In one study, neutrophils placed on one coil of an oscillator were activated by phorbol ester placed on another

coil, suggesting that molecules emit signals that can be transferred to neutrophils by artificial physical means.[123] Intriguing experiments evaluated cell proliferation rate and morphology in two different cell populations seeded in separate polystyrene culture dishes incubated one above the other: cell activities were different depending on whether there was a disk of black paper to separate the different dishes, suggesting that specific signals emitted by the cells were transmitted through the polystyrene wall.[124] Others reported an electrical transfer phenomenon using a device made by a glass test tube filled with distilled water (intended as receiver) and a quartz test tube with a source compound (*Amanita muscaria* dust, magnesium sulphate).[125] Two solutions were connected by a high voltage field pulse for 15 min, then the exposure of biological systems (cress germinating seeds, *E. Coli* bacteria) to such electrically-treated water caused a growth inhibition of the tested cultures.

The notion that organisms have mechanisms for generating biologically useful electrical signals is not new, but the modern version is that magnetic fields act in conjunction with ion cyclotron resonance (ICR), to regulate and transmit biological and pharmacological information within living systems. ICR predicts effects by small ions involved in biological processes, which occur in definite frequency- and intensity ranges ('windows') of simultaneously impacting magnetic and EM fields.[126,127] According to Liboff, changes in human body impedance are significantly altered during exposure to ICR and sinusoidal magnetic field combinations and protein peptide bonds are broken by ICR fields at ultra-low magnetic intensities (0.05 muT).[128] Investigating the phenomenon of resonant signalling, it has been reported that exposure of human epithelial cell to ICR, generated by a commercial electromedical device tuned to calcium ion at 7 Hz, acts as a cell differentiation factor.[129] Furthermore, it has been observed that specific frequencies modulate cell function and therefore can help restore or maintain health.[130]

The phenomenon of 'digitization' of biological signals was reported by Benveniste's group[123] and recently confirmed,[131–135] with the exception of another group.[136] In brief, Montagnier *et al.* demonstrated the ability of some bacterial DNA sequences to induce EM waves at HDs in water. A solenoid captured the magnetic component of the waves produced by the DNA solution in a plastic tube, converting the signals into an electric current. This current was then amplified and finally analysed on a laptop computer using specific software. Each dilution was followed by strong agitation and this step was found to be critical for the generation of signals. Such signals appear to be a 'resonance phenomenon' triggered by the ambient EM background of very low frequency waves.[132] Interestingly, the genomic DNA of most pathogenic bacteria contains sequences that are able to generate such signals, suggesting that a highly sensitive detection system might be developed for chronic bacterial infections in human and animal diseases. A second paper followed up this suggestion, showing that it is indeed possible to detect the presence of HIV DNA even when the RNA of the virus has disappeared from the blood of HIV-infected people undergoing antiviral therapy.[133]

Recent investigations showed that retinoic acid (a neuronal differentiating agent), placed on one coil attached to an oscillator, induced a decrease in cell growth, metabolic activity, and the protrusion of a neurite-like structure in neuroblastoma cells incubated on another coil connected through an electronic amplifier.[134] If confirmed, these experimental results provide some evidence that the incubation medium could be tuned in a resonant manner through a carrier frequency provided by the oscillator.[135] Taken together, these findings suggest that there are associated molecular signals that can be transferred to target cells by physical means in a fashion that mimics the original molecules.

Water, nanoparticles and molecular interactions

The importance of water to living processes derives not only from its ability to form hydrogen bonds with other water molecules, but especially from its capacity to interact with various types of biological molecules. Because of its polar nature, water readily interacts with other polar and charged molecules such as acids, salts, sugars, and various regions of proteins and DNA. Recent advances in theoretical methods, experimental techniques and brute computing power have made it possible to study how water interacts with DNA, proteins and cells in unprecedented detail. Protein binding to specific DNA sequences is a key element in various biological functions related to processing of genetic information by regulating transcription, replication, and recombination. The mechanism of DNA sequence discrimination, however, is still poorly understood.

Water is an essential participant in macromolecular binding and can contribute to recognition in several ways. Complex formation is initiated by interactions between partners of protein−protein or protein−DNA molecules with fully hydrated surfaces. During the process, specific bound waters are expelled from the interface, leading to burial of the contact surfaces. However, a number of water molecules may remain trapped at the interface and serve to mediate interactions between the macromolecules. Interfacial water molecules in specific complexes not only act as linkers, but have also been shown to buffer electrostatic repulsion between negatively charged groups of protein and DNA.[137]

The functioning of enzymes and protein folding is well known to be assisted by the surrounding chaperoning water molecules, which are connected to the proteins *via* noncovalent, dynamically changing chemical bonds. Water clusters have a key role in the light receptors of bacteria: on excitation by light, retinal isomerization leads to a rearrangement of a water cluster that partly disconnects two helices of the receptor. This hydrogen bond network proceeds further in later stages of conformation transitions, altering tertiary structure and establishing the signalling state of the receptor.[138]

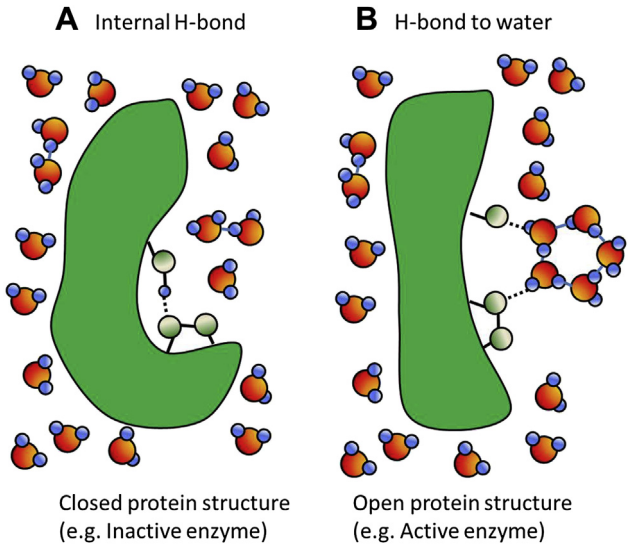

Figure 4 Scheme of how a water cluster may change a protein conformation by breaking internal hydrogen bonds.

High-resolution protein ground-state structures of proton pumps and channels have revealed internal protein-bound water molecules. Their possible active involvement in protein function has recently come into focus. An illustration of the formation of a protonated protein-bound water cluster that is actively involved in proton transfer was described for the membrane protein bacteriorhodopsin.[103] The authors showed that three protein-bound water molecules were rearranged by a protein conformational change that resulted in a transient Grotthus-type proton-transfer chain extending through a hydrophobic protein region. This discovery provides insight into proton-transfer mechanisms through hydrophobic core regions of ubiquitous membrane spanning proteins such as G-protein coupled receptors or cytochrome C oxidase.

The concept of aqueous nanodomains has been introduced to explain high potentization in homeopathy. Simulations show that these long-lived nanodomains may interact with their targets, such as inactive enzymes, converting them into the active form. This simple model omits many of the complexities of a live organism but incorporates the essential elements of homeopathic action.[139] Nanoparticles have unique biological and physicochemical properties, including increased catalytic reactivity, protein and DNA adsorption, bioavailability, dose-sparing, EM, and quantum effects that are different from those of bulk-form materials.[140] Enzyme regulation involves molecular allosteric changes due to interaction with other molecules, phosphorylation/dephosphorylation of specific amino acids, and complex formation. However, all these events occur in a surrounding non-covalent intracellular network

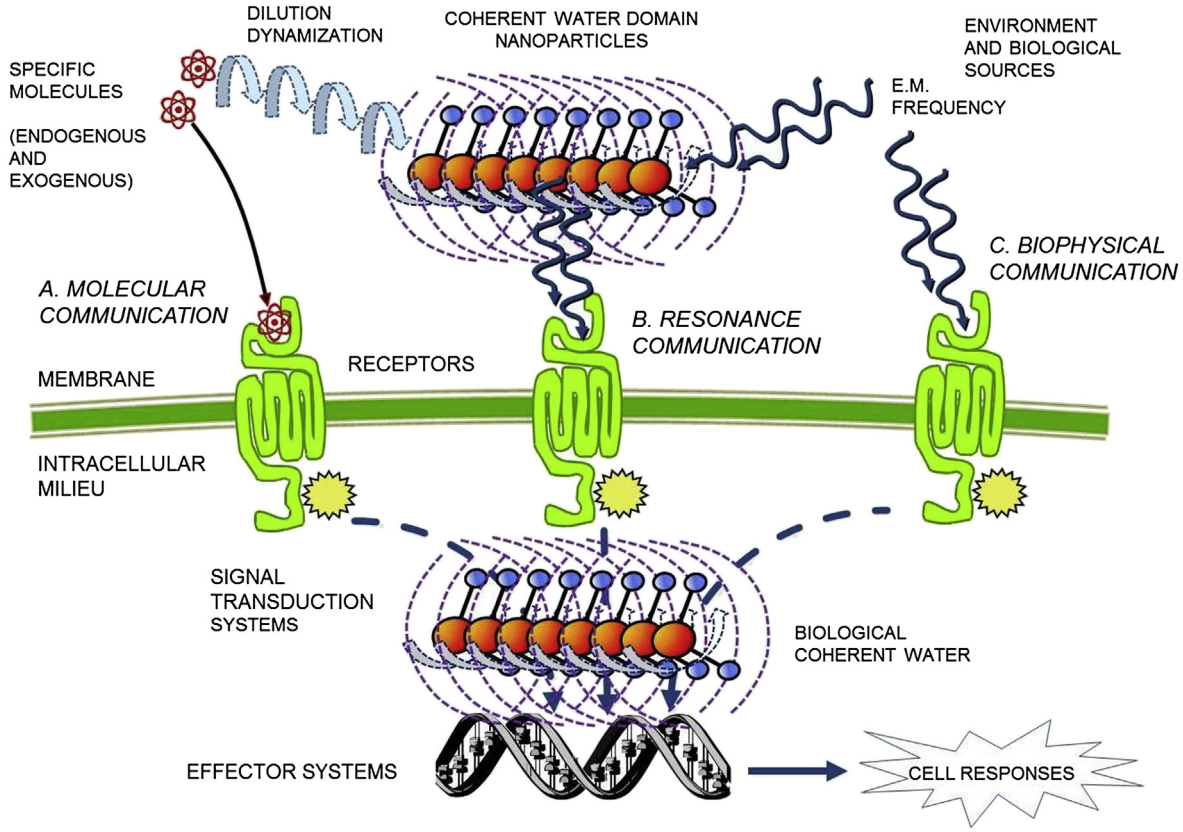

Figure 5 Hypothetical model of various ways of biological communication. (A) Left side: Classic molecule–receptor interactions, (B) Centre: Resonance interaction between water nanodomains and cell membrane receptors and/or DNA, (C) Right side: Classic biophysical regulation of receptor responses. The water nanodomain is formed by water molecules oscillating in phase, where oxygen is represented by red spheres and hydrogen by blue spheres. For details concerning the physicochemical nature of homeopathic remedies see the previous paper (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).[1]

made up of water molecules. These water molecules do not just play a part in solvation, but also function as chaperone catalysts participating in the regulation of chemical changes in living cells. A 'water-regulated cycle' consisting of this type of intracellular network of weak non-covalent connections may be presumed to exist in living cells.[141] An intuitive sketch of how a water cluster could alter the conformation of a target protein is shown in Figure 4.

Water and gene expression

DNA recognition by proteins involves a subtle interplay between direct protein−DNA interaction and the indirect contribution from water and ions. The structure and energetics of water at the protein−DNA interface show that water distributions exhibit sequence-dependent variations, suggesting that interfacial waters can serve as a 'hydration fingerprint' of a given DNA sequence.[137] The double helix structure, the strength of the hydrogen bonds, and even the DNA volume tend to change with increasing water content. The bound water sheath is not just an integral part of such structures. It can also perform a precise switching function, because results indicate that increasing the hydration shell by only two water molecules per phosphate group may cause the DNA structure to 'fold' instantly.[142] High-resolution crystal structures of the DNA duplex sequence reveal a highly-conserved cluster of 11 linked water molecules, positioned in the minor groove. This cluster appears to have a key structural role in stabilizing the non-covalent binding of small molecules and in mediating between ligands and DNA by means of an array of hydrogen bonds.[143]

An interesting view of how coherence domains postulated by quantum electrodynamics theory may interact with biochemical pathways, has been recently proposed.[144] When the energy stored in the EM field of a coherence domain becomes equal to (resonates with) the activation energy of a specific non-aqueous molecule, the coherence domain discharges its energy to perform a specific reaction (coupling of EM and chemical modes).

Resonance and drug effects

A further concept linking homeopathy with a biophysical perspective is that disease may be regarded not only as a functional or molecular-structural abnormality, as in the classical view, but also (and not by way of contrast) as a disturbance of an entire network of EM communication. Such a network is based on long-range interactions between elements (molecules, nerve centres, organs, to mention but a few) which oscillate at frequencies that are coherent and specific, and so capable of resonance. The disease processes, besides causing quantitative and qualitative molecular alterations, involve a disturbance of the bioelectric harmony and coherence of the body, of oscillation frequencies and of the communications associated with them. If this is the case, it should be possible to bring these alterations back to a state of equilibrium by means of 'tuning', i.e., by a change in frequency imposed by resonant interaction with another oscillator. According to this notion, the homeopathic remedy might act upon the patient as an external guiding frequency.

On this basis, a hypothetical model of the possible action mechanism of homeopathic drugs can be advanced (see Figure 5). A potentized homeopathic drug might be regarded as a small amount of matter containing elements oscillating in phase (coherently), which are capable of transmitting these oscillatory frequencies, *via* a process of resonance, to biological fluids (in turn mostly made up of water), but also to complex 'metastable' structures. These structures (macromolecules, a-helixes, membranes, filamentous structures, receptors) are subject to nonlinear behaviour patterns and are capable in their turn of oscillating. There is thus the possibility of a resonance link forming between drug frequencies and oscillators present in the living organism perturbed by disease. The nanoparticulate water clusters or CDs would thus not act by 'conventional' molecular interactions based on mass law, but rather by modulating through resonance interactions the internal EM communications whose energy is provided by the cell metabolism.[145]

The EM hypothesis of homeopathic drug action is very attractive but, at the present state of knowledge, is mainly speculative and is awaiting physical or mathematical formalism. Information transmission phenomena require resonances between oscillators of close frequencies (eventually between harmonics). There are many orders of magnitude between the frequencies of molecular vibrations (>10^{13} Hz) and, for example, the EM signals emitted by HDs of DNA (1000−3000 Hz).[132,133] How can those relatively low frequency waves of DNA solutions modulate high molecular frequencies responsible for specific biochemical reactions remains to be clarified, even if some hypothesis has been put forward by the authors.[131]

The inversion of effects (the simile)

According to the homeopathic law of similia, the remedy able to positively regulate a diseased organism (personalised homeopathic treatment) is the same substance that elicits similar symptoms in a healthy organism. The homeopathic pharmacopoeia was developed through careful testing of hundreds of substances on healthy people to detect their specific and global perturbation power. This was the first systematic application of pharmacological experimentation in the history of medicine, and it continues to this day.

The various theories of the simile have been described in previous papers.[90,91,146,147] The characteristic 'therapeutic similarity' in drug action purported by homeopathy may be fundamentally based on the widespread phenomenon of inversion of biological effects dependent on the following factors: (a) the dose utilized and absorbed, (b) the time or schedule of administration, (c) the physiological state of the receiver/target system. A combination of one or more of these factors and the

Table 2 Examples of inverse effects in laboratory systems

System	*Agent*	*First effect*	*Inverse effect*
Yeast[163]	Heavy metals	Block growth	Low doses increase growth
Leukocytes[164]	Cytostatic agents	Cytotoxicity	Low doses stimulate growth and phagocytosis
Fibroblasts[165–167]	Arsenite Cadmium	Cell toxicity	Low doses protect from toxicity or stimulate DNA synthesis
Neurons[168,169]	Naloxone	Antagonizes morphine	Low doses enhance the effect of morphine
Epithelial cells Tumor cells[170]	Oxidants	Short-term/high doses decrease viability	Long-term/low doses increase viability
Platelets[148,171]	Diclofenac	High doses stimulate adhesion	Low doses inhibit adhesion
Leukocytes[146,172]	Bacterial peptides	Stimulate adherence	Low doses inhibit adherence
Leukocytes[173]	Podophyllotoxin	Cell toxicity	Low doses enhance oxidative metabolism
Wheat germ[174–176]	Arsenite	Cell toxicity	HDs protect from toxicity
Lymphocytes[177,178]	Cadmium	Cell toxicity	HDs protect from cadmium toxicity
Neurons[179,180]	Glutamate, cycloheximide	Neurotoxicity	Extremely low doses and HDs protect from neurotoxicity
Basophils[14]	Histamine	Inflammation	HDs inhibit basophil activation
Basophils[181]	Quercetin	Inhibit cell activation	Low doses enhance formyl-peptide-induced activation

contribution of complexity science give rise to a consistent theory of the homeopathic 'simile' effect.[91,147]

Hormesis

Currently, efficacy is intuitively regarded as being higher when more molecules of drug reach the target (receptor, enzyme), but this approximation is largely incorrect because dose–response curves are often nonlinear and even paradoxical. There is a widespread occurrence of low molecular dose effects that appear to be opposite to those caused by high molecular doses, as seen in hormesis. Moreover, *in vivo* acute and chronic effects of drugs are often opposite in their effects, an observation that some authors have suggested could be exploited using conventional drugs[148–150] or homeopathic remedies.[151]

Various authors have suggested that hormetic phenomena can provide a framework for interpreting homeopathic effects, at least insofar as low dilutions, rather than HDs, are concerned.[91,152–157] Inverse (or 'paradoxical') effects of drugs or of biologically active compounds on specific target systems can be often observed by changing the concentrations or the doses of the compound: for example, low doses of a toxic compound may be stimulatory, high doses may be inhibitory (as we will see later, also the opposite may be possible, according to the experimental systems employed). In general these effects, formerly described in the 'Arndt–Schulz Law',[158,159,160] can be documented by the finding of inverted U-shaped curve of dose–response. Endpoints displaying this curve include growth, fecundity, and longevity. Another possibility is to find a time-course of an intoxication experiment where high dose causes progressive death of biological system, while a low dose causes an initial decrease of viability, followed by a recovery (rebound) and an increase over the basal levels.

Despite the substantial development and publication of highly reproducible toxicological data, the concept of hormetic dose–response relationships was not integrated into the mainstream of toxicological thought until recent years.[161] This phenomenon is now well recognized, with a number of explanation at the molecular level (e.g., different receptors for the same substance having different ligand affinities and triggering transduction pathways) and in immunology, where the systemic and local responses are known to depend on the dose in a complex way (e.g., foreign antigens may sensitize the host but low doses of the same substance may suppress the system if administered by oral route). The term 'postconditioning hormesis' was introduced to indicate the phenomenon where small stimuli exert a beneficial effect when applied to cells or organisms which previously experienced a severe harmful stress.[162] As an example, a low level of hypoxic stress was applied subsequent to myocardial infarction, which reduced the cellular damage.

Tables 2 and 3 summarize several examples of inverse effects according to the dose in laboratory systems and in animal models respectively.

Without going into many details, the paradox of arsenic can be mentioned as an example. This mineral is a well-documented carcinogen that also appears to be a valuable therapeutic tool in cancer treatment.[216] In this context, the research line of the group of Van Wijk *et al.* is worthy of citation.[93,152,152,217] In response to proteotoxicity, cells react with an upregulation of hsps. These proteins function primarily as molecular chaperones, facilitating the folding of other cellular proteins. When cells were damaged with chemical compounds such as arsenic or cadmium and subsequently exposed to low dose conditions of the same compounds, both hsps synthesis as well as defence and survival capacity were enhanced ('homologous' simile). Low doses of arsenic were also able to enhance survival of cells to a heat shock (exposure to temperatures >42.5°C) ('heterologous' simile). This line of research clearly demonstrates the biphasic action of a substance: a small dose can exert a stimulatory effect on the recovery and the development of survival capacity of cells that have been previously disturbed by a high dose of the same substance. It is of interest that this stimulatory effect of low dose stress is dependent on the initial exposure condition: the more severe the initial stress conditions, the smaller the

Table 3 Examples of inverse effects in animal models

System	*Agent*	*First effect*	*Inverse effect*
Tadpoles (frogs) [20,21,182,183]	Thyroxine	Stimulates metamorphosis	HDs inhibit metamorphosis
Rat blood[184–186]	Acetylsalicylic acid	Inhibit platelet aggregation and haemostasis	Very low doses have thrombogenic activity
Dog heart[187]	Ischemia	Causes infarction	Ischemic preconditioning protects from infarction
Mice kidney[188]	Free radicals	Toxicity	Pre-treatment with low doses protect from toxicity
Mouse prostate[189]	Estrogens	Inhibit growth	Low doses promote growth
Mouse and rat immune system[190,191]	Protein antigens	Induce allergy autoimmune disease	Oral administration protects and cures autoimmunity
Mice[192]	Morphine	Antinociceptive effects	Extremely low doses enhance pain sensitivity
Rat arthritis[193]	Naloxone	Hyperalgesia	Low doses have antinociceptive effects
Mice[194,195]	Naloxone	Antagonizes morphine	Analgesic effects in ULDs
Rat, guinea pig[196–201]	Histamine and/or bee venom	Inflammation, oedema	Low doses and HDs reduce inflammation
Rat liver[202,203]	Carbon tetrachloride	Toxicity	Low doses protect from liver toxicity
Rat immune system[204–206]	Mycobacteria in adjuvant	Induce arthritis when injected intra-paw	Intraperitoneal low doses cure arthritis
Mice, guinea pig, rats[207–211]	Arsenic	Liver toxicity, genotoxicity	Protection by ULDs of arsenic and increase of arsenic elimination
Rat[212,213]	Carcinogens (acetaminofluorene, phenobarbital)	Induce cancer	Low doses protect from cancer
Rat[214]	*Bacillus antracis*	Severe inflammation and death	Low doses of bacillus extract protect from toxicity
Mice[215]	*Gelsemium sempervirens*	Causes severe weakness, dizziness, convulsions	HDs are anxiolytic and increase exploration movement

concentration required for stimulating survival and hsps induction.

Our group has given several contributions in this field, like the demonstrations that bacterial peptides (leukocyte receptor agonists with powerful stimulating activity on leukocyte metabolism and adhesiveness) have inhibitory effects on leukocyte adhesion when used at low doses.[172,218] This paradoxical effect of low-dose peptides is probably due to the 'gating' exerted by cAMP at the level of intracellular signal transduction pathways.[146,219] Furthermore, we showed that human platelets are inhibited by low doses and stimulated by high doses of non-steroidal anti-inflammatory drugs[148,171] and that podophyllotoxin inhibits leukocyte metabolism when administered at high doses while it exerts a stimulating role (priming) at low doses.[173] These observations are in the framework of the hormesis concept.

Although the inversion of effects is often observed on changing the doses (or dilution/dynamization steps in homeopathic terms), this is not a general rule. Others have reported that *Ruta*, *Thuja*, *Hydrastis* and *Carcinosinum* have cytotoxic and apoptosis-inducing effects on several cell cultures, even at homeopathic doses.[220,221] In animal models, *Silica* (which is a stimulant of macrophages and fibrous tissue formation at high doses) stimulates tissue healing and macrophage activation also at extremely low (homeopathic) doses.[33,34] We have observed[181] that quercetin, a natural compound contained in fruits and vegetables, exhibits a 'inverted U-shaped' dose–response curve (stimulation at low doses, inhibition at high doses) when human basophils are stimulated by bacterial peptides. However, when the cells are stimulated by anti-IgE antibodies (mimicking an allergic reaction) the inhibition exerted by quercetin is observed both at low and at high doses, the effects being proportional to the dose utilized.

Regarding the effects in animal models, the studies from the group of Doutremepuich deserve citation. Starting from the observation that platelet aggregation on whole blood was stimulated after administration of ultra-low dosage acetylsalicylic acid in healthy volunteers,[222] they extensively investigated these effects in a rat model of thrombus formation.[184–186] A partial occlusion was induced in small mesenteric vessels by an argon laser. The laser induced damage of endothelial cells and thrombi formed within seconds after the laser lesion and grew rapidly. Embolization began during the minute following the laser injury. Compared to placebo, the administration of acetylsalicylic acid at ULDs induced an increase in number of emboli and in the duration of embolization. These findings are highly paradoxical because the 'conventional' pharmacological effect of acetylsalicylic acid would be to inhibit platelet aggregation and thrombus formation. Also paradoxical pro-inflammatory, pro-thrombotic effects associated with chronic use of anti-inflammatory agents have been described.[223] These effects are attributable to compensatory host response rather than direct effects of the drugs.

At Verona University we explored the applications of similia principle in various animal models. The first one showed that HDs of histamine are able of modulating the inflammation caused by high doses of histamine in rats.[198] A second rat model was developed by our group,

showing that injection of low doses of immune adjuvant (based on killed *Mycobacterium butyricum*, Mb) into the peritoneum of rats is capable of preventing and curing the arthritis induced by the injection of high doses of the same adjuvant into the paw.[205] Local injection of low doses of Mb at 3rd and 10th day after adjuvant arthritis induction is correlated with suppression of primary and secondary lesions of disease, decrease of inflammatory cytokines like IL-6, increase of anti-Mb antibodies, increase of nitrite/nitrate serum levels and growth of regulatory peritoneal cells.[206] This kind of immunoregulation by the 'simile' ('isopathic' approach according to the traditional terminology) is coherent with several other lines of evidence obtained in animals and in humans.[91,160,191]

Others have questioned whether there is a direct link between homeopathy and hormesis, arguing that homeopathy is a highly individualized therapeutic system, that homeopathic concentrations are often far below the Avogadro number and that hormetic substances do not require any special preparation.[224] The relationship between hormesis and homeopathy has been recently discussed in a full issue of Human and Experimental Toxicology. As we[90,91] and others[156] have pointed out, hormesis is the name given to experimental evidence of certain apparently paradoxical phenomena, but does not itself constitute any sort of explanatory theory, least of all for homeopathy. Each example of a hormetic curve can be explained by one or more mechanisms, which are today being explored with ever greater detail and thoroughness: transduction of extracellular signals into intracellular messages, cellular and tissue repair systems, control of cell growth and apoptosis, genetic and epigenetic molecular changes. In any case, the traditional hormesis concept applies only to molecular 'doses', that is to concentrations from zero (no effect, taken as a control) upward; homeopathy also employs very HDs/dynamizations that in theory do not contain a single molecule of the original active substance.

Paradoxical pharmacology and rebound effects

Inverse (or 'paradoxical') effects of drugs or of biologically active compounds on specific target systems can be often observed by changing the time or duration of the application of the treatment and the observation period. For example, short treatment may be stimulatory, long lasting application may be inhibitory (also the opposite may be possible, according to the experimental systems employed). This field includes rebound effects (reversal on withdrawal) and paradoxical pharmacology. One possible general hypothesis for why paradoxical pharmacology might work is the difference between the chronic *versus* the acute effect of drugs.[91,149,150] It has been suggested[151,225,226] that even modern drugs can be utilized according to the principle of homeopathic cure, employing the rebound effect as a curative reaction. It would be possible to compile a Materia Medica that would group the symptoms produced by rebound effects of the medications in human individuals, utilizing them, a posteriori, following a partial or total similitude, in minimal or ponderous doses. By doing that, it should be possible to take advantage of the modern pharmacological experimentations either in healthy individuals (phase 1 trials) or in ill people (phase 2−3 trials), thus amplifying the spectrum of homeopathic cure with a wide range of new symptoms and medications.

Finally, inverse effects of drugs, or of biologically active compounds, on specific target systems can be often observed by changing the physiological state or the susceptibility conditions of the system itself: for example, the same compound may cause stimulatory, growth-promoting effects on a healthy/unperturbed system and inhibitory, suppressing effects of the same variable when applied to the diseased/previously perturbed system (also the opposite may be possible, according to the experimental systems employed). This field includes the "*initial value rule of Wilder*"[227,228] and other widely documented pharmacological phenomena.[91]

In summary, the applications of the 'simile' principle − interpreted as inversion of biological and pharmacological effects of active compounds according to the dose and/or the sensitivity of the target system − are widespread and consistent: stimulation or protection by low doses of toxic compounds (typical hormesis effect) on cell and animal models, regulation of specific cellular activities by low doses of stimulating compounds, inhibition or protection of autoimmunity by low doses of antigen, and paradoxical effects of drugs. Within the framework of our current knowledge of living systems and modern investigational techniques, it will be possible to reformulate the ancient principle with the aim of constructing reasonable models that can be tested at different biological levels, from cells to human beings.

Systems biology

In dynamic systems far from thermal equilibrium, minimal variations in the internal or ambient conditions (such as those induced by even a very small oscillatory resonance) may play a decisive part in the ensuing evolution of the system itself. In a variety of systems, the 'butterfly effect'[229] may be used to control chaos, on condition that the parameters to be controlled and changed are well known.[230−233] Systems at any level (e.g., physical, biological, social, ecological) are open to information, energy, and matter to varying degrees, and therefore interact with other systems to varying degrees.[234] The dynamic interaction of systems in mutual recurrent feedback relationships naturally create resonance and synchronizations, such as those between heart and brain.[235] Those interactions over time create memory in homeodynamic systems. The logic of recurrent feedback loops, which applies to all dynamical network systems, leaded to the systemic memory hypothesis, applied to high-dilution therapies.[98]

Based on microarray data, it has been suggested that gene regulatory networks may be regarded as dynamically 'critical' systems poised near the phase transition between order and chaos,[233,236] where extreme sensitivity to initial conditions and small perturbations is well known to occur.

Genetic regulatory networks may be the target of HDs message by virtue of their flexibility in response to environmental stimuli.[236] According to this argument, the highly diluted drug might be regarded as a complex solution endowed with nanoparticulate structures capable of communicating some pharmacological information, through a resonance process, to biological fluids and to critical cell systems such as macromolecules, alpha-helixes, filamentous structures, receptors, and DNA networks. This effect could be mediated by the participation of a dynamic intracellular water network which may be presumed to exist in living cells.[141] Chaotic regimes have been found in a number of physiological systems, including heart and neural systems,[237–240] and this would result in enhanced susceptibility to extremely low energy inputs and to small changes of regulatory factors. The mechanism suggested above is in line with findings that homeopathic effects in humans can be detected through sensitive evaluation of heart rate variability.[76,241]

The working hypothesis is that the homeopathic remedy, containing small amounts of the original substance – or its information imprinted in the solution by dilution and succussion – possesses a high 'information content' targeted for a specific case, by virtue of the similarity between the patient's symptoms and those ascribed to the remedy (law of similarity). This information content, acting on a system in critically sensitive conditions, is able to guide it toward a particular behaviour, somewhat like a 'catalyzer of order' or a 'pacemaker' that moves the system away from a pathological attractor and redirects it toward a physiological attractor.

In short, the remedy selected based on homeopathic principles can be perceived by the various regulation systems—which have a crucial role in the dynamics of the pathology—as an exogenous signal that affects particularly active receptors, enzymes or genetic networks. The 'similarity' enables drug information to interact with endogenous targets that have lost their regulatory capacity due to homeodynamic blockages (pathological adaptations) and changes of attractors (miasms).[242–244] Precisely because it 'touches' extremely sensitive points (bifurcations), the target signal, even with minimal energy, can trigger a homeodynamic reaction that shifts the global imbalance of the sick person toward a new dynamic attractor, closer to the state of health.

The specificity of the information can be ascribed to sensitizing (*priming*) of the receptor system as a result of antecedent biological stress, to the fact that using low doses or HDs only touches certain particular systems, and finally to the complexity of corrective actions at various levels. In acute diseases, homeopathic regulation can be considered a 'regulation' in the sense that it abates the counterproductive excesses of the reactions themselves, while in chronic disease it can be regarded as 'unblocking' pathological adaptations and redirecting the organism toward correct responses. Others have suggested that refocusing attention on the dynamics of the patient as a nonlinear complex system could help account for similar effects of various forms of natural medicine in the healing process of the person as a unified whole.[245–248] Updating the designation from 'homeopathy' to 'system regulation therapy' would most adequately reflect the integration of this historical but controversial medical system with modern scientific theories and findings.

Conclusions

The rational view of the pharmacodynamic activity of homeopathic drugs can thus be set forth as follows:

1. Natural diseases are a consequence of perturbations of molecular and bioelectrodynamic networks at the various levels of biological organization; the healing or progression of a disease depends on the systemic and dynamic rules of the affected networks, which determine the reactions and/or adaptation to those perturbations.
2. ULDs and HDs of drugs may act on the information networks of the body, where EM interactions and water clusters associated with proteins and DNA have a major role in the coordination pathways for biochemical reactions, neuroimmunological control of body identity and integrity, and even of psychological integrity.
3. A number of molecular, cellular and systemic targets of homeopathic drugs have been described in laboratory model systems. These targets are highly sensitive to drug regulation thanks to powerful amplification mechanisms and to the participation of solvent (water) dynamics in information transfer.
4. The medicine that has been chosen according to the similia principle may be perceived by specific regulatory systems – that have a crucial role in the dynamic of the diseases – as specific signal which may trigger a homeodynamic reaction that shifts the global disequilibrium of the ill person toward a new dynamical behaviour, proximal to the healthy state.
5. 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. Frequency information can be imprinted into a water solution by succussion, in the form of coherent domains or nanoparticles. This is what creates a homeopathic HD solution or potency.

Conflict of interest

The authors declare that they have no conflict of interest.

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