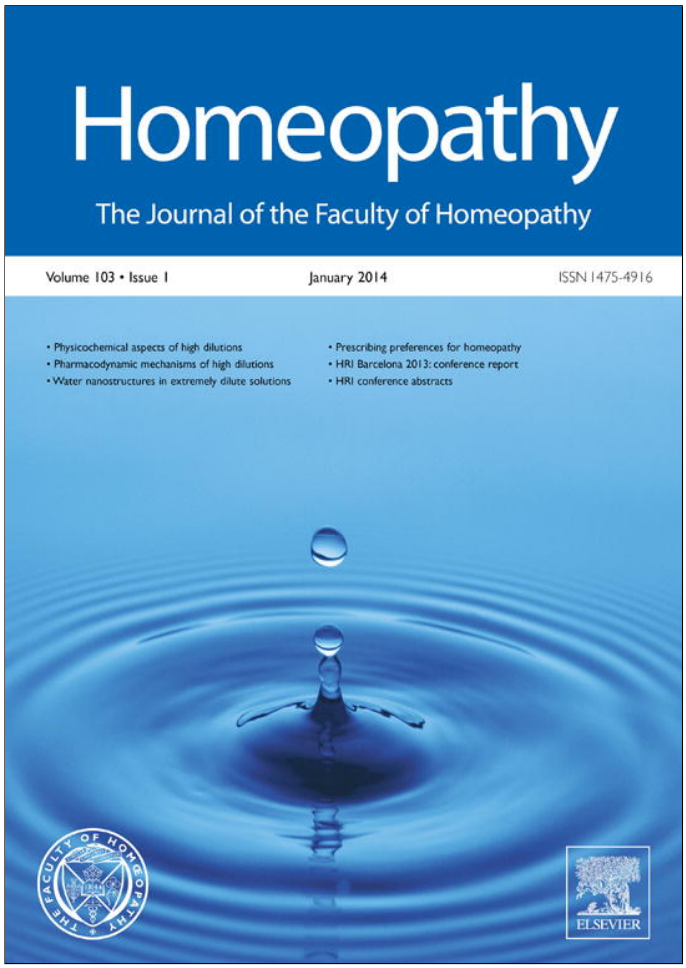

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REVIEW

High-dilution effects revisited. 1. Physicochemical aspects

Paolo Bellavite[1,*], Marta Marzotto[1], Debora Olioso[1], Elisabetta Moratti[1] and Anita Conforti[2]

[1]*Department of Pathology and Diagnostics, University of Verona, Strada Le Grazie 8, 37134 Verona, Italy*
[2]*Department of Public Health and Community Medicine, University of Verona, Piazza L.A. Scuro 10, 37134 Verona, Italy*

Several lines of evidence suggest that homeopathic high dilutions (HDs) can effectively have a pharmacological action, and so cannot be considered merely placebos. However, until now there has been no unified explanation for these observations within the dominant paradigm of the dose–response effect. Here the possible scenarios for the physicochemical nature of HDs are reviewed. A number of theoretical and experimental approaches, including quantum physics, conductometric and spectroscopic measurements, thermoluminescence, and model simulations investigated the peculiar features of diluted/succussed solutions. The heterogeneous composition of water could be affected by interactive phenomena such as coherence, epitaxy and formation of colloidal nanobubbles containing gaseous inclusions of oxygen, nitrogen, carbon dioxide, silica and, possibly, the original material of the remedy. It is likely that the molecules of active substance act as nucleation centres, amplifying the formation of supramolecular structures and imparting order to the solvent. Three major models for how this happens are currently being investigated: the water clusters or clathrates, the coherent domains postulated by quantum electrodynamics, and the formation of nanoparticles from the original solute plus solvent components. Other theoretical approaches based on quantum entanglement and on fractal-type self-organization of water clusters are more speculative and hypothetical. The problem of the physicochemical nature of HDs is still far from to be clarified but current evidence strongly supports the notion that the structuring of water and its solutes at the nanoscale can play a key role. *Homeopathy* (2013) **103**, 4–21.

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

Introduction

Central to the controversy surrounding homeopathy is the need of a plausible mechanism of action for the very high dilutions (HDs) often used in homeopathy.[1,2] The idea of using extremely low doses of diluted and succussed substances was originally proposed by Hahnemann in the eighteenth century: "*The homeopathic system of medicine develops for its special use, to a hitherto unheard degree, the inner spirit-like medicinal powers of the crude substances by means of a process peculiar to it and which has hitherto never been tried, whereby only they all become immeasurably and penetratingly efficacious (…). This process is called dynamizing, potentizing (development of medicinal power) and the products are dynamizations or potencies in different degrees.*" (Organon, par. 269, 295).[3] These paradoxical claims have always elicited great skepticism,[4] because homeopathic medicines undergo a process of serial dilution whereby the final remedy contains extremely low (often non-measurable) amounts of the active substance. However, not only has homeopathy 'survived' these attacks, becoming an increasingly popular medical discipline in western countries, but the study of drugs in HDs is today a rising new interdisciplinary field with more and more

*Correspondence: Paolo Bellavite, Department of Pathology and Diagnostics, University of Verona, Strada Le Grazie 8, 37134 Verona, Italy.
E-mail: paolo.bellavite@univr.it
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publications in mainstream scientific journals.[5] Currently, we have reached a stage of research where the investigation of HDs can no longer be presumed to be 'implausible',[6,7] as there exists a solid body of interdisciplinary work in favor of such effects which were initially described by homeopathic tradition.

Homeopathy is a complex method of diagnosis and of healing, which has various aspects dealing with peculiar traditional and philosophical background and other aspects dealing with the scientific and rational bases of medicine (Figure 1). These latters are exploited by rigorous scientific research, whose commitments may be divided in two main topics: (1) clinical, veterinary and field research, trying to answer to the question: "*does homeopathy work*?", i.e. the problem of efficacy and effectiveness; (2) basic research, trying to answer to the question: "*how does it work*?", i.e. the problem of the nature of the remedy and its putative action mechanisms. These great questions may be investigated utilizing different experimental models, made either of human subjects, of animals, of cells and of chemical solutions. The literature in all these fields is rapidly growing. Point 2a of the scheme presented in Figure 1 is the object of this review, while point 2b is the object of a subsequent work.

Even if the clinical evidence of homeopathic remedies' efficacy is still a matter of discussion for a number of methodological problems,[1,2,8–11] the results from laboratory models[12–18] suggest that highly diluted drugs are endowed with authentic pharmacological activity and are not mere 'placebos'. That said, there is still a need for more consistent and detailed experimental evidence, in both clinical and laboratory settings, and for working hypotheses that can help us construct unified and consistent theories explaining the physicochemical nature of HDs and how they exert an action on living organisms. Since this paper deals with physicochemical studies and theories which may be difficult to readers unfamiliar with the specific terminology of the various disciplines, we have provided in Table 1 a glossary of terms, with their definitions.

Homeopathic drugs are used in a wide range of dilutions/dynamizations (also referred to as potencies). The low dilutions – i.e. between 3C and 5C which, depending on the concentration of active principles in the Mother Tincture (MT), correspond to concentrations between 10^{-6} and 10^{-10} mol/L (moles/litre) – can act 'conventionally' upon specific molecular and biochemical targets by simply exploiting the high sensitivity of biological systems. Activity of higher dilutions (extremely low doses) – i.e. between 6C and 10C, corresponding to approximately 10^{-12} mol/L (picomoles) to 10^{-18} mol/L (attomoles) – has been often reported in the scientific literature, even in work unrelatedly to studies on homeopathic drugs.

We evaluated through Pubmed the size of the body of knowledge concerning ultra-low doses and related topics. The estreme lower limit of a molecular concentration is the yoctomole, that is 10^{-24} moles/L, corresponding to approximately one molecule per litre of solution. This means a probability of 1/1000 of finding a single molecule in 1 ml of solution. We searched Pubmed using a number of keywords of molar concentrations from picomole(s) to yoctomole(s) and other entries (Table 2). This simple evaluation showed that there are hundreds of scientific papers where ultra-low doses of substances have been analytically measured and/or their effects have been ascertained. As expected, the number of non-homeopathic papers on HDs tends to zero near the Avogadro–Loschmidt constant

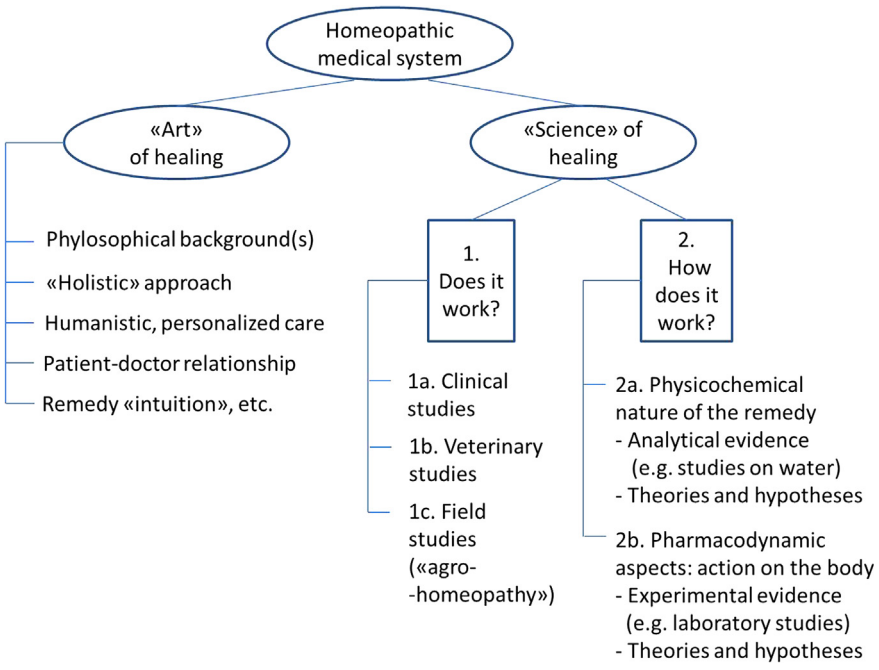

Figure 1 Schematic representation of the main areas of investigation of homeopathic medicine. As every field of medicine, homeopathy is characterized by aspects which belong to the 'art' of healing and by aspects which are belong to scientific domains. The two wings are not necessarily in contrast and should be taken into account for a whole evaluation of the medical system.

Table 1 Glossary of the terms utilized

Subject/term	*Definition*
Autothixotropy	A weak macroscopic phenomenon that is observed in water that has remained at rest for a certain time (in tens of hours or days) and is manifested by mechanical resistance to the immersed body in water with a tendency of changing its position. The autothixotropy of water can be explained by a hypothesis of a cluster formation by H_2O molecules in standing water containing very low salt concentration
Clathrates	The term, from the Latin 'clathrus' (=lattice or grating), denotes hollow formations in which the guest molecule is in a cage formed by the host molecule or by a lattice of host molecules. The cage is held together by very weak forces like hydrogen bonding, ion pairing, dipole–dipole interaction and van der Waals attraction
CDs	Groups of millions of water molecules in spherical domains of nanometre size whose electric dipoles may oscillate in phase with a common electromagnetic field. By this property they may undergo to long-range interactions with environmental waves through resonance mechanism
Cyclotron resonance	A type of interaction of external forces with charged particles experiencing a magnetic field, thus moving on a circular path. It is named after the cyclotron, a cyclic particle accelerator using this resonance to add kinetic energy to charged particles. Ion cyclotron resonance is a phenomenon related to the acceleration of movement of ions in a magnetic field. Each ion has a particular frequency of resonance
Dissipative structure	A system that exists far from thermodynamic equilibrium, hence efficiently dissipates the energy to change itself into higher levels of orderliness by self-organization
Dynamization	In homeopathic pharmacopoeia, the dilution process is followed by vigorous shaking (see 'succussion') which is believed to provide the remedy with higher pharmacological power
Entanglement	Quantum physics theory of 'non-local' interaction between two correlated objects that share a common quantum entity. In the special communication between the correlated objects the measurement of one, instantaneously affects the other, even when they are in the condition of complete mutual isolation at enormous distance
Epitaxy	Refers to the deposition of a crystalline overlayer of one mineral on a crystalline surface that serves as template, inducing a specific structure in overlayer that grows in registry with the substrate
Fractal	Mathematical or geometrical entity that is endowed with a fractional dimension (from the Latin fractus, meaning 'broken') and a repetitive configuration when viewed on different scales, i.e. self-similarity between details and the general pattern. Fractal shapes can be generated on a computer using algorithms based on mathematical functions that are iterated (i.e. repeated for the desired number of times, each time using the result of the previous calculation as the basis for the following one)
Fullerenes	Carbon allotropes, are clathrates of carbon cages that encapsulate atomic or molecular species. The hollow cage structures are made up of hexagonal and pentagonal homo-atomic shells of carbon reaching the final form of a hollow sphere, ellipsoid or tubes
Hormetic dose–response	Phenomenon characterized by a low dose stimulation, high dose inhibition, resulting in either a J-shaped or an inverted U-shaped dose response
Nanobubbles	Stable tiny gas bubbles with a <200 nm diameter formed at the solid–liquid interface of a particle or a surface
Nanoparticle	A small particle composed by one or more compounds, including linked water, measuring 100 nm or less. Nanoparticulate matter has different properties from its bulk form in terms of mechanical, optical, electrical, magnetic, chemical, biological, and quantum behaviours. Nanoparticles cross membranes easily and act as highly reactive and catalytic agents
Nanoscopic	Having a scale expressed in nanometres (10^{-9} m)
QED	Classical electrodynamics studies electromagnetic phenomena whenever the relevant length scales and field strengths are large enough that quantum mechanical effects are negligible. QED represents the quantum counterpart of classical electromagnetism. In essence, it describes all phenomena involving electrically charged particles interacting by means of exchange of photons, giving a complete account of matter and light interaction
Schumann resonant waves	A set of spectrum peaks in the extremely low frequency (ELF) portion of the Earth's electromagnetic field spectrum, excited by lightning discharges in the cavity formed by the Earth's surface and the ionosphere
Succussion	A process of vigorous shaking, usually by 10–100 hard strikes against an elastic body, by which homeopaths mix and imprint 'dynamization' or 'potentization' to a substance diluted in alcohol or distilled water. It can be done also by automatic machineries or by sonication
Vicinal water	Water surrounding a solid surface or macromolecules over a distance from 5 to 200 molecular diameters is influenced by them
Water cluster	Aggregate of water molecules linked by hydrogen or other weak bonds. Water molecules can align themselves in pentagonal or hexagonal clusters by effect of their stereochemical structure. Cluster may be created when water molecules set themselves in a grid-like arrangement around an internal niche or cavity, upon agitation or sonication of the liquid in the presence or absence of a solute

(yoctomoles). A preliminary inspection to papers reporting the study of attomolar doses – corresponding to about one molecule per cubic millimeter – shows that these papers concern mostly the analytical detection of substances in the body or in chemical systems by using high sensitive probes or instruments. A significant minority of studies showed that attomolar concentration may have biological activities, suggesting that extremely powerful systems of amplification, transmission and transduction of information exist in the body. The issue of "*dilution and dynamization*" or "*dilution and succussion*" has been reported very little and this may be due to superimposition with homeopathic issues and to lack of consensus on terminology.

HD effects carry us outside the realm of classical pharmacology, to confront phenomena that may appear inexplicable. The theories of Amedeo Avogadro, first published as a hypothesis in 1811, confirmed by Johann Loschmidt in 1865 and then experimentally verified in 1909, establish that one mole of any substance contains 6.02254×10^{23} units of molecules or atoms. Consequently, if the MT of a given substance is supplied as a molar solution (1 mol/L, also denoted 1 M), a simple calculation shows that after

Table 2 Number of items in Pubmed related to very low doses and HDs, measured June 25, 2013

Molar concentration	*Exponent*	*Number of molecules/ liter*	*Number of molecules/ μl (mm³)*	*Approximate decimal dilution*[a]	*Approximate centesimal dilution*[a]	*Number of papers in Pubmed*[b]
Nanomoles	−9	1, E + 15	1, E + 09	9	4−5	3679
Picomoles	−12	1, E + 12	1, E + 06	12	6	2931
Femtomoles	−15	1, E + 09	1, E + 03	15	7−8	1787
Attomoles	−18	1, E + 06	1	18	9	644
Zeptomoles	−21	1000	1 every 1000	21	10−11	229
Yoctomoles	−24	1	1 every million	24	12	26
Very low dose(s)	–					1974
Ultra-low dose(s)	–					400
Extremely low dose(s)	–					209
HD(s)	–					863
Dilution and dynamization	–					9
Dilution and succussion	–					17

[a] Assuming a starting MT with concentration of 1 mole/L.
[b] e.g.: <nanomoles or nanomole or nanomol or nmoles or nmole or nmol>, <'ultra-low dose' or 'ultra-low doses'>, etc.

24 decimal or 12 centesimal dilutions we will have one molecule per litre of solution, and that at higher dilutions it will be increasingly unlikely to find even a single molecule or atom of the original substance. If the MT instead contains a concentration of active substance between 0.1 and 1 mM (10^{-4}−10^{-3} mol/L), as is much more frequently the case for most of the substances used in homeopathy, the Avogadro limit shifts to around 20D or 10C dilutions. This problem has long plagued the world of homeopathy and can be addressed in various ways, both by careful laboratory research and by physical−chemical analysis.

Many authors have tried to formulate explanations concerning the physical−chemical nature of homeopathic remedies when used in HDs (beyond the Avogadro limit). Very concisely, the majority of views converge on the idea that there is non-molecular (or rather, 'meta-molecular') information imprinted on the structure of the solvent (water, or mixture of water and alcohol) which can interact through resonance with the biophysical regulation systems of the target organism.

Some remarkable features of aqueous solutions

The study of water is an important chapter of physics. In spite of much work, many of the properties of water are puzzling. Although our understanding of this substance is far from complete,[19] what we do know allows us to at least not rule out that it can act as a repository and transmitter of biologically significant information. Water, despite the simplicity of its molecule, exhibits typically complex behaviour during phase transitions and in the liquid state, when it finds itself in an 'open' system which exchanges energy with the environment. Interpretations of the behaviour of water in the liquid state are generally formulated in terms of short-range interactions, such as hydrogen bonds and van der Waals forces, which somehow link the water molecules together into a kind of network. Since the hydrogen−oxygen bonds are polar covalent bonds, in which the hydrogen is more electropositive than the oxygen, the attraction between the negative region surrounding the oxygen atom and the positive region associated with the hydrogen atom of another molecule causes different water molecules to link together into chains or irregular networks. Moreover, the water molecule is not linear, because the negatively charged oxygen atom forms an angle of 104.5° with the two positively charged hydrogen atoms. This means the molecule also has a dipole moment which plays a role in coherence phenomena (see below). The middling strength of the connecting hydrogen bonds seems ideally suited to life processes, being easily formed but not too difficult to break.

When a given molecule is dissolved or immersed in water, the water's structure will change in a manner dependent on the properties of the added molecule. In addition, at the interface between the macromolecules and solvent, an enormous structural reorganization of the water takes place, as a result of which the water takes on entirely new configurations even at a considerable distance from the solute molecule. In this process, cooperative effects undoubtedly play a very important part. In this connection, various investigators speak of 'vicinal water', by which they mean water which is near solid surfaces or macromolecules and is influenced by them.[20−23] For instance, a protein chain with alternating positive (NH) and negative (CO) chemical groups should polarize the surrounding water, reducing the rotation and translation movements, and giving rise to the formation of many ordered states of water molecules. These types of alterations of the structure of water extend, according to various investigators, over distances ranging from 5 to 200 molecular diameters from the surface in question.[21]

Analytical evidence

The existence of some form of structural or dynamic permanent change in HDs has been experimentally demonstrated in several laboratory approaches, although these experiments were often carried out with samples which were not representative of the real homeopathic drug manufacturing and with inappropriate controls (untreated solvent), which is questionable in the field of homeopathy where shaking is needed (shaking might generate the observed physicochemical changes).

An extensive thermodynamic study was carried out on aqueous solutions prepared by successive 1/100 dilution and succussion of certain solutes to obtain an extremely diluted final solutions.[24–26] The heats of mixing of these 'extremely diluted solutions' (EDSs) with acid or base solutions, and their electrical conductivity and pH, were measured and compared with the corresponding heats of mixing, electrical conductivity and pH of the solvent. Despite the extreme dilution of the solutions, in approximately 92% of cases these showed an excess exothermic heat of mixing, compared to the corresponding heat of mixing for the untreated solvent. The authors concluded that successive dilutions and succussions may permanently alter the physical–chemical properties of the solvent water.[25] More recently the same group reported an intriguing observation of a conductometric and calorimetric study on the the supramolecular structure of the solvent water.[27] They stored samples of EDSs of fullerene and carbon nanotube and samples of twice-distilled water, over a 541-day period in alternate rows of EDS and water spaced 0.5 cm apart. These two aqueous systems showed similar variations of the considered parameters over time, suggesting that there was a kind of transmission between them, *via* electromagnetic fields.

Low-temperature thermoluminescence has been used in an attempt to understand the particular structure of HDs.[28,29] The technique involves frozing the solution in crystal state and bathing the chilled sample with radiation. When the irradiated sample is warmed up, the stored energy is released as light in a pattern that reflects the atomic structure of the sample. When ultra-dilute lithium and sodium chloride solutions (diluted down to a notional 10^{-30} g per cubic centimetre) were compared with pure water that had been through the same process, there was found to still be a difference in their thermoluminescence peaks compared to those of pure water. This thermoluminescence study suggests that the networks of hydrogen bonds in the ultra-diluted samples differed from those of pure water, even though neither contained any salt. The author noted that his findings were consistent with the HD remedy retaining the physical chemistry 'fingerprint' properties of the parent source material substance. Significantly, the phenomenon of thermoluminescence of HDs has been confirmed by an independent laboratory.[30]

Using nuclear magnetic resonance (NMR) methods, some authors have reported evidence of supramolecular organization of water in ultra-diluted samples,[31–34] however other experimental approaches have been inconclusive.[35–37] Due to technical difficulties in performing this type of analysis and frequent lack of adequate controls, experiments should be repeated using stricter methodology and standardization before they are accepted as indications of special features of homeopathic potencies.[31] Recently accurate NMR measurements showed increase in relaxation time ratio T1/T2 in samples of silica-lactose, histamine, and manganese-lactose prepared by iterative centesimal dilution with vigorous agitation, even beyond Avogadro limit.[38] The author suggested the existence of superstructures that originate stereospecifically around the solute in HDs, after an initial destructuring of the solvent in the low dilutions. It is likely that, during the dilution and dynamisation steps, the molecules of active substance act as nucleation centres, amplifying the formation of supramolecular structures, involving nanobubbles of atmospheric gases and imparting order to the solvent.

According to some authors, it appears possible that ultraviolet and Raman spectroscopy could serve as simple and useful tools for identifying the differences between HDs of homeopathic remedies and the pure solvent with which these are made.[39–42] Differences in O–H vibrational bands (v2) from homeopathic dilutions and their diluents media have been described also using infrared spectroscopy,[40,43] suggesting a difference in the number of hydrogen-bonded water species and their hydrogen-bonding strength. Interestingly, it was reported that such differences are retained in potassium bromide powder, soaked with homeopathic solutions, dried and pressed into pellets.[44] On the other hand, using Fourier-transformed Infrared (FT-IR) spectroscopy others,[41] were not able to confirm those findings.

X-ray emission spectroscopy and X-ray Raman scattering have provided evidence that density fluctuations are present in water at ambient temperature on a length scale of approximately 1 nm; these may be due to fluctuations between tetrahedral-like and hydrogen-bond distorted structures, corresponding respectively to low and high density water.[45]

Magnetic field and effects of dilution

Magnetic fields can affect the structure of pure water, provided that it contains dissolved oxygen, generating quasi-stable clathrate-like structures, increasing the electrolytic potential, and inhibiting metal corrosion.[46,47] Magnetic treatment of irrigation water of peas (*Pisum sativum*, *Cicer arietinum* L.) (magnetic induction: 3.5–136 mT) led to a significant increase in emergence rate index, of shoot dry weight and contents of mineral salts compared to control seedlings.[48–50] Permanent changes in the structure of water are reported following exposure to resonant resistance–inductance–capacitance circuits.[51]

Next, experiments showed that the activity of highly dilute agonists was abolished by an oscillating magnetic field which had no comparable effect on the genuine molecules.[52–54] This suggested that the activity seen at HD was due to an electromagnetic field. Furthermore, several experiments have confirmed ability to transfer to water, using an electronic amplifier,[55,56] the specific molecular activity of more than 50 substances, such as physiological and pharmacological agonists, antibodies (purified or in whole serum), antigens and even the specific signal of bacteria. Benveniste referred that they digitally recorded (sampling 44 kHz) specific biological activities on a computer, then 'replayed' to water, plasma, target organs, cells, or to an antigen–antibody reaction, the recorded signal induces an effect characteristic of the original substance.[53] Indeed, these advances illustrate the reality of the HD phenomenon and allow for the transmission and detection at a distance of any normal or pathological molecular activity.

The impact of repeated strong shaking and fluid dynamics (turbulence, vortices) in inter-molecular solvent–solute and solvent–particle interactions has been recently reviewed.[57] It is argued that thanks to the shearing forces exerted by dynamization, the particle aggregates, by serving as templates inducing specific adsorption layer structures, transmit their structural information to the solvent, inducing conformational changes of molecular organization. This is a well known phenomenon in material sciences, called 'epitaxy'.[58,59] Although the hydrogen bonds that give rise to clathrates form and break in fractions of picoseconds, if we posit the existence of dynamic supramolecular structures (that likewise continually form and break up), such structures might 'take shape' from the molecular chaos of the liquid, 'guided' precisely by the information of the structures that at that time coexist in solution. Moreover, shock waves of succussion cause increased gas dissolution, nanobubbles, dissolution of silicate from glass tubes and possibly give rise to small amount of hydrogen peroxide formation which can take part in further reactions with other reactive species such as molecular oxygen and dissolved ozone.[60,61] Analysis of serially succussed and diluted solutions showed that boron, silicon, and sodium were present at micromolar concentrations, leaching from glass containers (not plastic containers). These doses were too low to account for any *in vivo* efficacy *per se*, but could potentially influence biological activity of nanoclusters.[62] It is important to note that research in other areas of nanomedicine suggest that precisely because of the increased biological reactivity and actions of nanomaterials, the low doses may actually have more possibility of *in vivo* significance than seemed likely at the time. For instance, nanosilica is sometimes used as an immune adjuvant and can stimulate heightened responses to another agent.[63,64] Other nanoparticles in vaccines have lowered the necessary amount of concomitant antigen needed to trigger a vigorous immune response as low as 2.5 ng.[65] The amount of material needed for nanoscale forms of vaccine[66] or of natural antidepressants[67] has already been shown to be reduced by at least 10–100 times. In synthesis, it is becoming clear that at the nanoscale, the doses of these more reactive nano-forms needed to elicit effects even at low dilutions containing some bulk form materials are going to be lower than for ordinary bulk form materials.

An interesting study concerning the effect of dilution in water found that some molecules form larger clusters on dilution. While studying the particle size of water-soluble fullerene–cyclodextrin conjugates, the authors observed that these conjugates form clusters whose size increased steadily with decreasing concentration of the fullerene compound, rather than the smaller clusters thermodynamically expected.[68] Cluster aggregation phenomena on increasing dilutions have been described also in aqueous solutions of sodium chloride, sodium guanosine monophosphate, and a DNA oligonucleotide. This inverse relationship between the cluster size and concentration could be of general importance with profound implications on the understanding of diverse phenomena involving dilution and dilute solutions. Just the presence of one such large micrometer-sized particles in the 'diluted' solutions could give rise to the noticed biological action, while preparations without such clustered particles may be without action. The exact nature of the interactions involved in cluster formation is not clearly known. It could be attributed, depending on the nature of the species involved (both solute and solvent), to electrostatic, hydrophilic, or hydrophobic interactions.[68]

Water models

The physical basis for the puzzling properties of water and HDs is at present a matter of wide debate. An important concept, often overlooked, is that liquid water is not homogeneous at the nanoscopic level.[69] There are two main theoretical models of 'water memory', namely, hydrogen-bonded clusters and quantum electrodynamic (QED) superradiance (Figure 2).

The former postulates the permanence of biologically useful information in structures made up of many molecules of water (or water + ethanol) linked by hydrogen

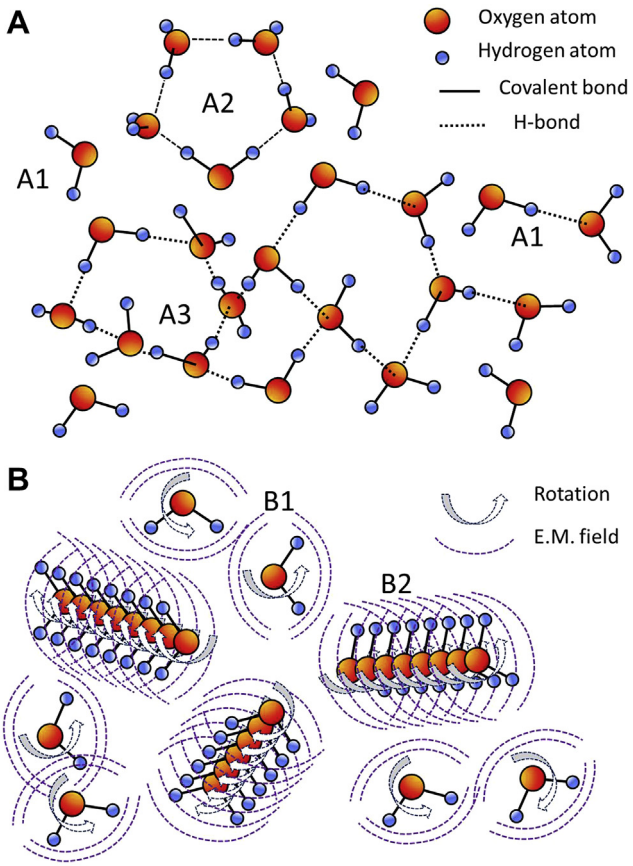

Figure 2 Illustration of two proposed models of supramolecular water structure. (A) Hydrogen-bond network structure: A1 free or partially bound molecules, A2 regular (pentagonal) water cluster, A3 irregular water cluster. Note that the theory postulates the possible formation of clusters made of hundreds of molecules in geometrical shapes (see text). (B) Two phases of water according to QED theory: B1 Water molecules in gas-like phase produced by thermal fluctuations, B2 CDs of rotationally excited water molecules. Note that the theory postulates the involvement of millions of molecules in spherical domains of nanometre size.

bonds. The latter postulates the formation of coherent domains of water whose electric dipoles may oscillate in phase.

Clathrates and clusters

Early theories of the 'memory of water' were proposed by some investigators[70–72] based on the formation of aggregates of water molecules in the form of clathrates. Under certain conditions (agitation or sonication of the liquid), various polygonal conformations can form complex, internally hollow geometrical figures. In addition, varieties of chemical bonds other than hydrogen bonds may be involved, such as dipoles between hydrogen and hydroxyl ions. According to this model, a certain number of molecules of the original compound are thought to be surrounded, once they are dissolved in water, by a larger number of water molecules which form a kind of shell or niche. Such a niche could possess stability even when the original compound is expelled from the niche itself. Thus, after repeated dilutions and succussions, empty clathrates would begin to form and in their turn become the nuclei for the formation of other clathrates, all with the same original pattern.

A point of interest of the clathrate model is that provides a mechanism whereby 'aggregates' of water molecules become a pathway for transmitting information, though there is still no consensus on how such aggregates can *persist* in stable form for sufficiently long periods to justify their medicinal use as suggested by homeopaths. The micro-cavities formed within clathrates should be able to take on a wide variety of three-dimensional shapes, including dodecahedral forms capable of binding together in a manner similar to helicoidal chains joined by their pentagonal faces. Such chains could then be the locus for coherent interactions between water and the magnetic field of a current that might cause synchronized 'hopping' from one proton (hydrogen atom) to another linking adjacent oxygen atoms.[72]

The clathrate model is very speculative, but the presence of clusters in water is well established both by computer simulations and analytical evidence. The possibility that clusters may form nanoscale cages (see Figure 3) in liquid water is universally accepted: infrared spectroscopy and X-ray diffraction have confirmed that clusters of dozens or even hundreds of water molecules exist in nature.[61,73–76] The model of water clusters implies that water may store and transmit information, concerning solutes, by means of its hydrogen-bonded network. As shown in Figure 3D–E, the clusters formed can interconvert between lower and higher density forms by bending, but not breaking, some of the hydrogen bonds. This structuring accommodates explanation of many of the anomalous properties of water including its temperature–density and pressure–viscosity behaviour, the radial distribution pattern, the presence of both cyclic pentamers and hexamers, the change in properties on supercooling and the solvation and hydration properties of ions, hydrophobic molecules, carbohydrates and macromolecules.[76]

Due to the complexity of these phenomena we still lack a well-established theory for dealing with them, though computer simulations seem to offer be a promising approach.[77,78] Water nanoclusters are shown from calculations to possess vibrational modes in the 1–6 THz range, corresponding to O–O–O 'bending', 'squashing', and 'twisting' 'surface' distortions of the clusters.[79] The author suggested that these

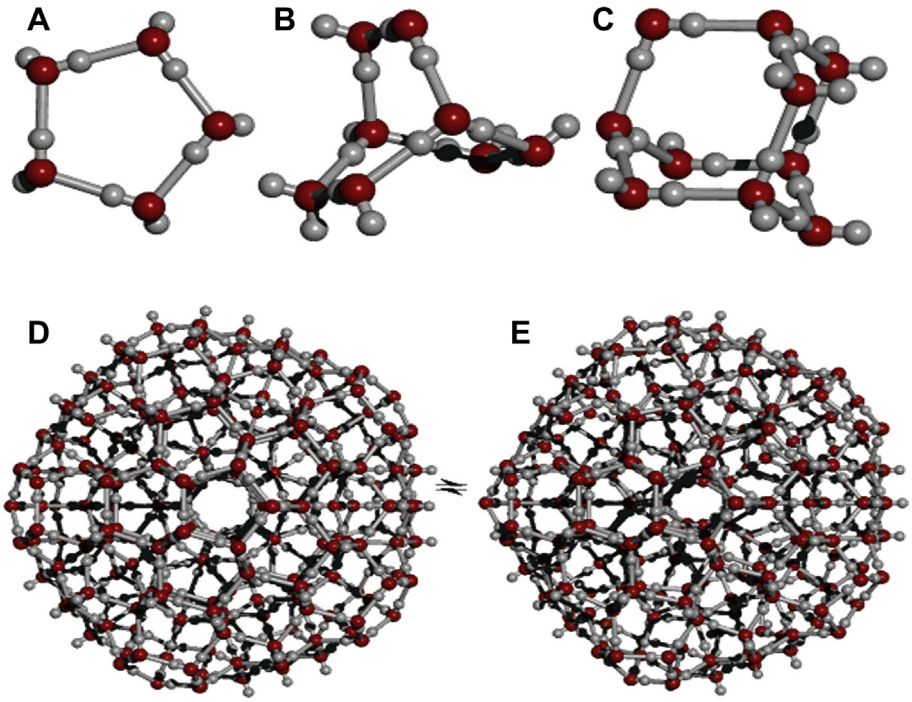

Figure 3 Detailed representation of typical water clusters having different shapes and dimensions. (A) cyclic pentamer, (B) bi-cyclooctamer, (C) tri-cyclodecamer, (D) 280-molecule expanded icosahedral water cluster, (E) icosahedral structure collapsed into the puckered central dodecahedron. Adapted from drawings of Martin Chaplin,[76] with permission.

vibrations may have a role in important biological processes like protein folding and microtubule functions.

Czerlinski and Ypma[80] recently introduced the concept of aqueous nanodomains to explain high potentization in homeopathy. According to these authors, such nanodomains interact with their targets by enhancing the enzyme−substrate interaction. Various simulations showed that homeopathic solutions were able to convert the inactive form of the enzyme to an electronically excited state, which then converted it to an active free enzyme.

Arguments against the 'memory of water' based on water clusters usually concern the extremely short-lived nature of hydrogen bonds (about one picosecond). According to this view, any cluster that might form in liquid water should in any case dissolve within that time span, along with any potentially associated structural information. However, as pointed out by Chaplin,[61,76] such an argument is fallacious because cluster and hydrogen bond lifetimes are independent. In the case of solid water (ice) the hydrogen bonds also break down and reform in an instant, but a crystal of snow can 'remember' its original structure over extended periods. It is also evident that a large population of water molecules may − taken as a whole − maintain a particular structure even if its individual molecules diverge from that behaviour, as in a sea wave whose constituent molecules are continually changing. We would expect some form of self-organization of clusters to play a role in the hypothesis of 'water memory'. In a study on the time-dependent properties of water, Elia *et al.* observed cyclical changes in conductivity occurring in samples stored in closed vials.[27,81] It clearly emerged that pure water is not a stable system, but is instead subject to fluctuations in its chemical−physical parameters in response to even slight perturbations by effect of the formation of dissipative structures, especially if confined to 'small' volumes. The energy for self-organization could be derived initially from succussion, then self-organized structures could be maintained or even increased by dissipation of environmental energies of an electromagnetic (e.g. Schumann resonant waves) or geomagnetic (Earth, Moon) nature. The phenomenon of time-dependent changes of conductivity in water was confirmed by an independent group which pointed out a possible role of traces of ions from container surfaces and hydrophilic surfaces.[82,83] These self-organized aqueous nanostructures (clathrates or clusters) may continue to exist even after their core molecules have been removed during the dilution process, or the hydration-shell structure is exchanged with solvent molecules due to thermal agitation and entropy of the solution itself.[69,81] This model, which has some analogies with crystal growth and fractal geometries, may have implications extending far beyond the physicochemical basis of homeopathic pharmacotherapeutics.

As applied to homeopathy, the 'memory of water' concept should also be extended to the memory of aqueous ethanol preparations, which are also used. Addition of ethanol to water forms solutions in water that are far from ideal and very slow to equilibrate.[76] Such solutions may contain several distinct phases and more generally consist of a complex mixture dominated by water−water and ethanol−ethanol clusters, where hydrogen bonding is longer-lived than in water alone. They also favor nanobubble (that is, nanocavity) formation. Thus, the peculiar behaviour of aqueous solutions is accentuated by the presence of ethanol.

Coherence domains (CDs)

A model of liquid water based on the framework of QED has been applied to the interaction between water molecules and the EM field in several seminal studies by Preparata, Del Giudice *et al*.[84−88] These studies showed that QED interactions in water systems may cause a particular phase transition, denoted 'superradiance', whereby particles oscillate in phase with an EM field. It was found that the dipole moments of these liquid molecules are aligned so that the domains have a polarization vector, the direction of which changes from one domain to another, resulting in a net zero polarization. Some of these findings have been confirmed by independent research groups.[89] Here, we will summarize the main points in a manner that can be grasped intuitively, avoiding the mathematical arguments and technicalities of the theory.

The starting point is the realization that liquid water molecules cannot be assumed to be bound by purely static interactions (H-bonds, electric dipole−dipole interactions). The fundamentally novel insight of the theory is that interactions among the microscopic systems (atoms and molecules) are not restricted to the 'nearest neighbours', but extend over typical domains having the size of the wavelength of the electromagnetic field that vibrates at the common frequency of the matter systems. Such 'CDs' represent the fundamental building blocks of condensed matter, inside which matter (atoms, molecules, electrons and nuclei) oscillates in tune (technically: in phase) with a macroscopic (classical) electromagnetic field, in much the same way as happens in the familiar laser, but with the fundamental difference that the coherent EM radiation is now trapped permanently inside the CDs, its function being to hold the system together against the dispersive assaults of the thermal fluctuations.[90]

In quantum physics, vacuum is able to exchange energy and momentum with matter. As a consequence of Heisenberg's famous uncertainty principle, constant vibrations are a result of the impossibility of pinning down the total energy of a system with absolute precision at any given moment in time. In the case of water, these vibrations stretch the bonds between hydrogen atoms and their host oxygen atoms, enabling them to link up with neighbouring molecules more easily. The fluctuations of the quantum vacuum engender the possibility of tuning together the fluctuations of all the components of a system, thus causing a coherent phase to appear. According to this view, liquid water features two types of molecular interactions (see Figure 2B): (a) 'free' water molecules, that may become linked to others through hydrogen links, (b) CDs in which

all molecules oscillate in unison, in tune with a self-trapped electromagnetic field, at a well-defined frequency.[88] At room temperature, liquid water consists of a mixture of coherent and incoherent water. At 0°C it is 50% coherent and 50% incoherent, and at 30°C it is 40% coherent and 60% incoherent.[91]

A new non-trivial minimum energy state of CD implies a configuration of the system where the water molecules are located in an extended region whose size is the wavelength of the trapped field, about 1000 Å (0.1 μm), with each such region containing about 5.5 million molecules that oscillate in phase.[92] The above results apply to all liquids, but the peculiarity of water is that the coherent oscillation of CDs includes an ensemble of almost free electrons which are able to accept externally supplied energy and transform it into coherent excitations (vortices) whose entropy is much lower than the entropy of the incoming energy. Consequently, water CDs can become dissipative structures, in the sense of the thermodynamics of irreversible processes. In CDs, the dipole moments of the water molecules are aligned and consequently these domains have a polarization vector; due to the rotational invariance of bulk water, the direction of changes from one domain to another, resulting in a net zero polarization.[85,89]

By virtue of its quasi-free electrons, a CD of water has unique properties with respect to all other liquids. It has a rich spectrum of excited states corresponding to vortices of quasi-free electrons. In the presence of external fields, such as the magnetic field of the Earth, these vortices line up and are summed. Since electrons move coherently, they do not collide, which means that the vortices are cold, and in the absence of internal friction caused by collisions, they are very long-lived (weeks, months, years). The CD of water is therefore a structure capable of transforming low-grade (high entropy) incoherent environmental energy into high-grade (low entropy) coherent energy, which can excite specific chemical reactions.[92] Ions close to water CDs are attracted by the electromagnetic field trapped in the domains, and so they are kept orbiting around the domain, moving at a circular speed proportional to the so-called cyclotron frequency.[93] The authors point out that, since DNA and proteins are polyelectrolytes, they are surrounded by a cloud of positive counter-ions with a cyclotron frequency in the interval between 1 and 100 Hz playing an important role.

Combined parallel static and alternating magnetic fields cause a rapid change in the ionic current flowing through an aqueous glutamic acid solution when the alternating field frequency is equal to the cyclotron frequency (from 1 Hz to 10 Hz). Only one resonance peak in the current is observed in this frequency range. Interestingly, the above effect only arises at very small intensity alternating field amplitude in the range from 0.02 to 0.08 μT.[94,95]

It should be noted that the incredible degree of coherence and harmony that electrodynamic interactions establish between matter and field inside a CD permits a completely new mode of interaction of such collective systems with external electromagnetic fields, and in particular an efficient exchange of frequency information between the coherent ground states of different systems. The role of the background low-frequency electro-magnetic field (EMF) is to provide a resonant alternating magnetic field in order to load energy into the water CDs. In higher organisms such as humans, the researchers suggest it is produced by the nervous system. Elementary organisms such as bacteria use environmental fields such as the Schumann modes of the geomagnetic field.[93] These modes are the stationary modes produced by the magnetic activity (lightning, etc.) occurring in the shell whose boundaries are the surface of the Earth and the conductive ionosphere, which acts as a mirror wall for wavelengths greater than several hundreds of meters.

It is the coherent water that has the 'memory' properties. The incoherent water is responsible for the normal thermodynamic properties of water including the heat of mixing. This theory is the only one to give the correct latent heat of evaporation and the correct dielectric constant for water and to account for its anomalous behaviour. External radiation will interact with an entire CD, not with individual molecules. Within a coherent system, the coherence length is the constant parameter and there can be many interacting velocities and proportional frequencies. These coherent oscillations only weakly couple to external electromagnetic fields so that their measurement with conventional instrumentation is difficult.[51]

A recent work discussed the relationship between the theories of dissipative structures, seen as highly complex structures which are able to self-organize, and quantum interaction among elementary objects, through which order is generated by phase correlation of the elementary components.[92] The problem was discussed with reference to a specific instance of an ordered system, the Belousov–Zhabotinsky (BZ)-reaction in a particular layout, which gives rise to the appearance of spatially ordered patterns of lamellar lipid structures, exhibiting a well-defined time evolution. Since this reaction requires the presence of water above a critical threshold (70% of the weight of the lipid) the result was interpreted as a consequence of 'organized' water based on the QED concepts. The possibilities for formation of CDs composed by water molecules together with dipole ions (zwitterions), peptides or even proteins were discussed by others.[96]

Nanoparticles

Other relevant concepts that have been invoked to describe the nanoheterogeneity of the HDs include clusters, nanoparticles, and nanobubbles.[60,61,69,97–100] Pure water does not exist, because even the most purified solution after distillation and ultrafiltration will contain dissolved gas and traces of 'contaminants' which should chemically or physically interact with the medium. Experimentally observed aggregates in aqueous solutions have been analysed, revealing 0.5–6 μm-sized domains composed of solvated strong electrolyte ions, organic- or bio-molecules and clusters of up to 280 water molecules.[101] A related phenomenon in liquid water is the formation of weak gel-like behaviour which develops over time when water is left to stand undisturbed.[102] This effect,

termed autothixotropy, occurs in the presence of very low concentrations of salt ions. Interestingly, it has been argued that active oxygen species in water, due to chain reactions triggered by various initial perturbations in the presence of even minute impurities, may have a role in maintaining non-equilibrium states of an aqueous system.[60] Evidence has been provided by NMR that gases dissolved in water affect the hydrogen-bond network and change the structure of nanobubbles or clathrate nanocavities.[34] The dynamics of small water clusters is markedly affected also by ionization processes.[103]

In this context, it has been suggested that a major role in the formation of water clusters is played by silica released from the glass containers which are usually employed in the preparation of homeopathic drugs.[104] Silica nanostructures formed during succussion in glass and/or biosynthesized by specific plant extract tinctures may also acquire and convey epitaxial information from the remedy source materials into the higher potencies.[105] If this is the case, the process of silica dissolution will become a key factor in the formation of nanoparticles and, possibly, in the effect of the remedy. This may explain why glass is preferred over polypropylene tubes in homeopathic manufacturing. However, many laboratory studies, including ours[106–108] have reported positive results using disposable plasticware, suggesting that using glass is not a direct requirement. Studies designed to compare solutions prepared using vessels made of different materials are warranted. Interestingly, HDs of silica-lactose have represented the first case where a NMR feature (increase of T1 relaxation time) distinct from pure solvent was shown in highly diluted solutions[109,110] and homeopathically diluted silica was shown to have biological effects in laboratory models.[111,112]

There are empirical data showing that nanosilica *per se* can self-assemble networks of nanostructures built upon the templates of organic materials and retain memory of electromagnetic information.[113] Such empirical data could be related to the models for how HDs retain specific information of the remedy in solution. The 3D nanosilica structures built on DNA, proteins, collagen, and living cells can survive drying,[114–116] and, according to a preliminary report by Elia, aqueous nanostructures exist also in solid phase, a novel and totally unexpected phenomenon.[117] This evidence could help address the nagging practical problem whenever homeopathic solutions are medicines absorbed onto globules and are then dissolved in the patient's mouth: the nanoparticles or the water nanoclusters are restored to the liquid phase and under such conditions, they might exert their therapeutic action in contact with the body water and other receptor structures.

Nanoparticles have enhanced bioavailability, adsorptive capabilities, adjuvant reactivity, and electromagnetic and quantum properties compared with bulk forms of the same material.[118] Independently of homeopathic issues, some studies that investigated the biological effects of nanoparticles of toxic substances observed a hormetic dose–response, i.e. lower doses may trigger a beneficial adaptive response.[119]

It is also true that the original Chikramane *et al.* paper[97] showed very small remedy source nanoparticle sizes of 15 nm or smaller for the six metal remedies studied. These would be in the realm of quantum dot sizes for nanoparticles, in which a large percentage of the atoms are stuck at the surface of the nanoparticle. As a result, quantum dots and other very small nanoparticles acquire atom-like properties and can exhibit actual quantum mechanical phenomena at the macro level.[120–122] This might also be related to the arguments around quantum entanglement effects as reported below.

Recent physicochemical studies of Chikramane *et al.*[123] detected nanoparticles of the starting raw material (metals) by transmission electron microscopy (TEM) and selected area electron diffraction (SAED) in extremely HDs prepared with traditional homeopathic manufacturing. In their hypothesis nanoparticles are retained even at HD levels by a mechanism that allows the nanoparticles to levitate to the surface and accommodates as a monolayer at the top. Original nanoparticles concentrated on the air–liquid interface of the suspension are preserved and carried almost entirely in the subsequent dilution, thereby forming an asymptotic concentration. They reproduced the phenomenon with gold nanoparticles (AuNP) and observed that it depends on the dynamic formation of air bubbles and nanobubbles during the succussion steps and is stabilized by the interaction with lactose used in the preliminary trituration. In the published experiments, they serially 1:100 diluted the lactose triturated synthetic AuNPs in 90% v/v ethanol for 15 times, i.e. with a dilution factor up to 10^{30}, and estimated the particle concentration in each dilution step by ultrasensitive inductively coupled plasma-atomic mass spectrometry (ICP-MS) in samples obtained from the bulk and from the surface layer of the succussed liquid, after 45 min of stationary store. The dilutions were carefully performed by transferring 1% of the solution volume skimmed from the surface (top 0.6 mm) to a fresh ethanol solution. They observed that wherein the concentration of the bulk decreased with increasing dilution and become undetectable at the third centesimal dilution, the concentration measured in the top layer of the corresponding dilution plateaued to a mean value of 200 ng/ml up to the 14th dilution, indicating that almost the total of the Au particulate matter floated on the top of the liquid and was transferred in the subsequent dilutions. In their experiment they also observed that bare AuNPs, that did not undergo trituration with lactose powder before ethanolic dispersion, did not show the asymptotic concentration. Actually, they demonstrate by TEM and SAED studies the formation of nanoclusters of AuNP embedded within lactose and that lactose primary –OH interact with the metal particles to form hydrogen bonds, as showed in specific stretching/vibrational frequency in FT-IR spectroscopy. The non-covalent interactions with lactose seem to stabilize the nanoparticles, aiding the formation of nanoparticles and their floating mechanism. Upon liquid dispersion and succussion, lactose-particles nanocluster should host on the solid–liquid interface nanobubbles formed by supersaturation of gases, whose solubility increases during turbulence of

liquid mixing. In the author hypothetic mechanism the nanoparticles 'frost' with nanobubbles are not able alone to float on the surface but levitation occurs when the larger air bubbles, formed during turbulent mixing, adhere to the surface-nanobubbles forming a sort of froth flotation. At the contact with air the large bubbles implode and the NPs set as a temporary stable monolayer on air−liquid interface, that may be preserved in the serial dilutions.

The surface monolayer hypothesis is an intriguing theory to understand the extreme dilutions of metal powders and the author validated it in their specific experimental conditions. However, those are different from the ones usually applied in centesimal homeopathic dilutions, where bulk volumes of just shaken liquids rather than the very top layer of stationed solutions are systematically transferred to subsequent stages. Moreover, the preparations that not include the presence of lactose should be explained by a different mechanism and the hypothesis could not be generally applied. Clearly the possible carry-over of significant amount of nanoparticles from a dilution to the subsequent one is very important from a technical standpoint and may represent one of the factors involved in the lack of full reproducibility between different laboratories using different methods of dilution and 'dynamization'. Finally, the findings of Chikramane *et al.*[97,123] may have a great technological impact, helping and help understanding the rationale of various types of homeopathic procedures such as, for example, the 'korsakovian' method, in which the same container is repeatedly emptied and filled with the same aqueous solvent.

Other speculative hypotheses

Physicochemical aspects of homeopathic drugs include also advanced theories based on non-local phenomena of quantum entanglement and on chaos and fractal theories.

Entanglement

In recent years new explanatory hypotheses of the effect of high homeopathic dilutions have been developed, based on a theory of 'non-local' phenomenon, or 'entanglement'.[124−128] A 'local' theory postulates a physical structure of the homeopathic remedy, like those shown here in the 'cluster' or 'CD' models; this 'structure' (chemical or vibrational or both) would be the deposit of molecular information that would be transmitted to another structure by 'local contact' in a manner not substantially different from the views of conventional physicochemical interactions, for example with the receptors of the cell or with the genome, etc. The theory of 'non-locality' relies instead on a particular type of interaction, described by quantum mechanics for the submicroscopic particles, called 'entanglement' (correlation). The latter is one of the most profound achievements of quantum physics, revealed for the first time by the phenomenon of Einstein−Podolsky−Rosen (EPR) at the level of photons. It results in a measurement performed on one of the entities instantaneously providing information on its entangled partners, even if they are out of speed-of-light contact.

Quantum entities behave as one indivisible whole, such that their non-local interaction transcends both space and time. It is a special communication between correlated objects in which the measurement of one, instantaneously affects the other, even when they are in the condition of complete mutual isolation at enormous distance. The quantum entanglement exceeds the distance space−time and instantly connects distant objects in space and time, so scientists had predicted that this 'weirdness' of quantum mechanics would lead to computing systems and communication of unprecedented power.

'Orthodox' quantum theory is confined to the nanoscopic domain of molecules, atoms, and subatomic particles, making theoretically doubtful that entanglement might find application in macroscopic domain of cells and bodies. However, in 2001 a group of researchers in Denmark has succeeded to develop a type of quantum correlation between two samples of a trillion atoms,[129] suggesting that the results for imaging and for the wave-particle duality features, which have been demonstrated in the microscopic case, persist in the macroscopic domain. More recently, quantum teleportation between remote atomic-ensemble quantum memory nodes has been realized as intriguing means to faithfully transfer quantum states and information among distant locations without actual transmission of the physical carriers.[130−132] In this relation, some authors argue today a vision of quantum theory, called 'weak' (weak quantum theory − WQT) according to which the entanglement between macroscopic systems would also occur whenever two variables or observables that describe a system are complementary: one describing a global and one the local aspects of the system.[128,133] In homeopathy, the entanglement would occur at two levels: one between the remedy and the original substance (principle of potentiation), one between the pathophysiological changes of the patient and the pharmacological properties of the remedy (principle of similarity). According to others[134] one should consider a three-way entanglement: remedy−patient, patient−doctor, medical remedy (patient−practitioner−remedy, PPR). Only when these correlations are carried out in an optimal way, homeopathic treatment would take place, and this could be another reason why in this medical approach the human and relational factors have such great importance. It is highly conceivable that, in order to fully comprehend its therapeutic mode of action, homeopathy might require both 'local' biomolecular mechanisms, such as 'memory of water' and 'non-local' macro-entanglement, such as PPR descriptions.[135] However, at this still early stage in its development, PPR entanglement has yet to provide quantitative prediction, so it cannot be considered a full-blown model. For the time being therefore, it is probably best considered a metaphor.

Fractals and homeopathic drugs

As stated above − notably for its nanoheterogeneous structure − an aqueous solution is a typical example of a

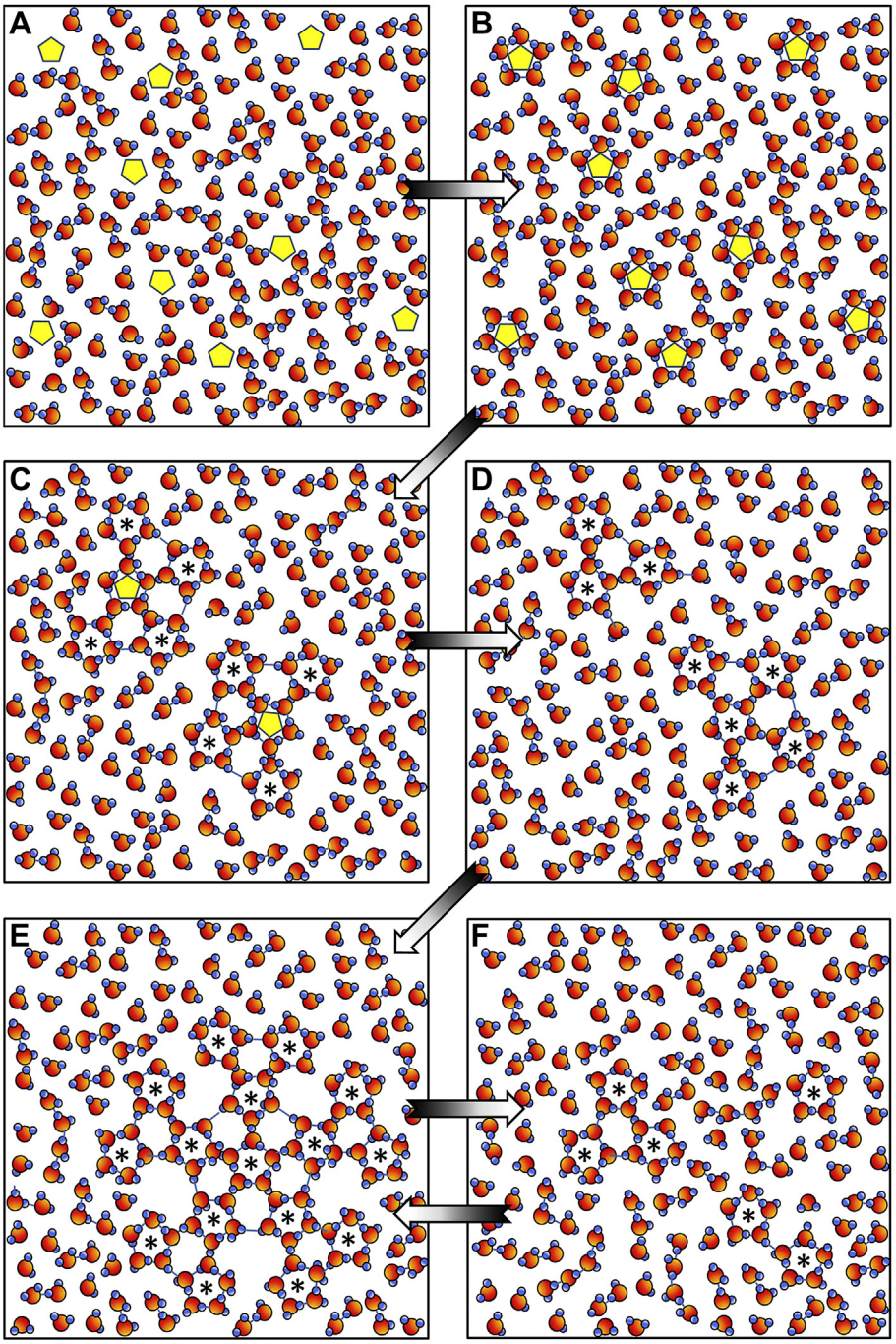

Figure 4 Hypothetical scheme of formation of water clusters with different degrees of complexity. Oxygen atoms are red, hydrogen atoms are blue, drug active molecules with pentagonal shape are yellow. (A) Addition of a certain drug component to bulk water; (B) dissolution of original molecules in water, with redistribution of surrounding molecules (vicinal water); (C) low dilution with formation of pentagonal empty nanoclusters linked by hydrogen bonds (asterisks); (D) HD where the original substance is no longer present; (E) HD with formation of branched (fractal-like) clusters; (F) further dilution with loss of fractal structure leaving residual fragments of original clusters, which may function as 'seeds' for new increase of cluster dimensions.

dynamic and complex system. As such, it is highly unstable and 'chaotic'. Therefore, a small change in initial conditions produces enormous changes in the global behaviour of the system on longer or shorter periods of time. A practical consequence of this feature is that the any (unavoidable) small uncertainty of the description of the initial state, or of the technical conditions of preparation, may cause great changes in the physicochemical structure of the liquid and of final biological effects. This aspect may set theoretical and not only practical limits to the concept of reproducibility when applied to HDs studies. Another interesting aspect of this perspective is that chaotic systems are endowed with self-similarity at different scales, a feature which gives rise to fractal structures and dynamics. It has been suggested that fractal behaviours in water may explain some aspects of dilution/dynamization processes.[136,137]

The term '*fractal*' was coined in 1975 by Mandelbrot and gained extensive notoriety in scientific circles in the early

Table 3 Physicochemical aspects of HDs as applied to homeopathy

Mechanism	*Meaning*	*Implications*	*Notes*
'Vicinal' water	Well-ordered water molecules organized by solutes, macromolecules and surfaces	Partial explanation of ultra-low dose effects (information transmission at molecular distances)	Experimentally proven in non-homeopathic models
Increase of electrical conductance	Structuration of water, increasing with time	Hypothetical explanation of structural 'memory' of water solutions; information transmission through water	Experimentally proven in HDs, waiting independent confirmation
Changes in NMR parameters (T1/T2 relaxation time)	Presence of nanosized structures	Explanation of structural 'memory' of diluted water solutions	Not confirmed by all laboratories
Thermoluminescence peaks in HDs	Presence of supramolecular structures in HDs	Explanation of structural 'memory' of diluted water solutions	Confirmed by independent laboratories
Spectroscopic studies (UV, IR)	Proof of changes in hydrogen bonding	Explanation of structural 'memory' of diluted water solutions	Quantitatively small effects
Magnetic field effects on water	Suggests 'non-molecular' information transfer in water solutions	Possible effects of 'dynamization' by physical means. Problems of storage due to inactivation by magnetic fields	Little experimental evidence
Water 'clathrates'	Presence of nanocavities in water	Hypothetical explanation of structural 'memory' of water solutions	Theoretical hypotheses. Never isolated from homeopathic HDs
Water clusters	Demonstration of nanoheterogeneity of water solutions; possibly due to self-organization of clusters	Hypothetical explanation of structural 'memory' of water solutions	Major evidence from theory, little experimental proof of cluster stability. Never isolated from homeopathic HDs
CDs	Two phases of condensed matter	Explanation of dynamic (frequency-based) 'memory' of condensed matter	Strong support from QED theory, little or no direct experimental proof
Nanoparticles	Aggregates of water molecules with gas, salts and minerals (silica)	Hypothetical explanation of structural 'memory' of water solutions. Possible role of container material	Strong experimental evidence of nanoparticles in various science fields, little application to homeopathic HDs
Nanoparticles in the presence of lactose	Remaining material in subsequent dilutions	Explanation of HDs effects by permanence of original substance. Proof of trituration effects	Little experimental proof, unusual technique of dilution (sampling from top layers of liquid)
Quantum entanglement	Non-local connections between remedy, patient and doctor	Highly hypothetical explanation of clinical homeopathic effects	Need of a hypothetical 'weak' quantum theory, highly speculative
Fractal-like clusters	Nanoparticulate clusters in fractal shapes of variable dimensions during subsequent dilution/succussions	Hypothetical explanation of increase of activity on dilution/ dynamization and alternating active/inactive dilution in laboratory models	Highly speculative, waiting experimental proof

1980s.[138] Fractal figures appear to have the following characteristics: (a) an enormous variety of details of different shapes, (b) the presence of subtle ramifications that can be pursued in the finest detail, (c) self-similarity, such that magnifying part of the structure reveals details which continue thus to repeat themselves on different scales of magnification. Within some of these particular images one can—surprisingly—find 'mini-sets' very similar to original macroscopic set from which they originated. In the close-up detail, we rediscover an image that appeared to have been lost in the variety of details and ramifications. By increasing the number of iterations, a better definition of the fractal image is obtained. Fractal patterns are easily found in chaotic systems, where they represent an element of regularity. In several chaotic functions, on continuing the iterations and further increasing the coefficient value, after periods of chaos periods of order may reappear, followed by new zones of chaos and then order. There is thus a 'recurrent regularity' in successive generations of transitions from chaos to order, with the reappearance of single solutions or regular oscillations which undergo cascade duplication on increasing the coefficient value.

Examples of natural fractals are easily observable in trees, certain flowers, snowflakes, as well as in noncrystalline molecular aggregates, viscous ramifications in immiscible fluids, corals, electrical discharges such as lightning, the ramifications of the airways and blood vessels, the dendrites of the neurons, the Purkinje system conducting electrical

signals in the heart, and the folds of the intestinal mucosa. It has also been demonstrated that, in many different physical situations, particles floating on the surface of an irregularly moving fluid display a fractal arrangement.[139]

Various experiments have suggested that the biological activity of HDs does not diminish or increase linearly with increasing dilutions, but instead follows a 'pseudosinusoidal' trend, with peaks of activity and troughs of inactivity. The most evident example is in the famous experiment performed by Benveniste's research team,[140] but similar trends have also been reported by others[141–143] and by our group.[106,144] The recurrence pattern of the peaks is not regular, but rather chaotic and unpredictable, yet it must nevertheless be admitted that this recurrence exists, i.e. that the effective information represents itself after a number of dilutions. From the perspective of current chemical logic, such a trend must appear thoroughly and unquestionably absurd, however the new discoveries concerning chaotic phenomena and the nonlinearity of many biological mechanisms may perhaps cast new light on the problem and point to some kind of underlying logic.

Experimental evidence of the recursive appearance and disappearance of biological effects in specific assay settings indicates that the information of the dissolved compound is not completely 'dissipated' in the course of successive dilutions, even when the dilutions are inactive. Evidently, there must exist some mechanism for transmitting and storing the information over the course of successive dilutions, such that the dilution that follows an active sample gives rise to a form (or vibrational frequency) that differs from the preceding one and may have a lower or null biological activity; yet the solution is capable, after a few further diversification steps, of causing the original (active) information to 'reappear'. Thus, dilutions would not produce a loss of information (increased entropy), but only a change and variety of forms, from which in turn the starting form may be eventually regenerated. Such behaviour is reminiscent of what we observe in the mathematical iterations that generate fractals, and hence this phenomenon is analogous to recurrent self-similarity, a typical feature of chaotic systems. Similar concepts have been applied in relation to the pattern maintenance or gradual evolution of silica nanoparticles at higher potencies. According to the 'silica hypothesis',[104] structured water-silicate 'seeds' could direct the formation of replica structures and increasingly evolve right through subsequent cycles of dilution–succussion. Computer simulations of water cluster structures with different number of molecules and types of connections give rise to final fractal structures with nonlinear morphologies.[145]

Figure 4 shows an intuitive sketch of the possible relation between fractal structures and nanoclusters in HDs. Dissolution of a given substance in water (panel A) is rapidly followed by rearrangement of surrounding water molecules, which take a precise shape (in this case, a roughly pentagonal geometry) depending on the substance dissolved (panel B). Assuming that these nanoparticles and nanoclusters were sufficiently stable in time (see above), the first dilution and dynamization step would cause the 'replication' of further clusters based on the first template (panel C). Nanoclusters made of water molecules (without excluding participation of other trace compounds, ions, gas, silica, etc.) would then persist and act as a 'mold' to guide self-organization of further clusters (D), even in the absence of the initial substance. The process of further dilution/dynamization steps would then enhance the fractal dimension of these nanoclusters or nanoparticles, with a gain of precision and of information storage (E). In the circumstance of a further dilution/dynamization, these big nanoclusters could collapse and disintegrate in minor pieces, with increase of entropy and dissipation of the drug power (F). However, residual pieces of the former pentagonal structures could give rise to a new generation of branched fractal structures, associated with renewal or reappearance of biological activity. According to this hypothesis, the serial dilutions and dynamizations performed in the preparation of a homeopathic remedy may introduce an element of information gain as increase of details of nanoparticle geometries (or CD vibration frequencies), as is observed in fractal geometries over successive iterations. Analogously, certain iteration steps of the same procedure of dilution/succussion, where the chaotic regimen (turbulence) prevails, produce structures with poor definition of details and carry rough and imprecise information. After repeated cycles of dilution/succussion the image is again precise and, surprisingly, 'reappears', i.e. it is reproduced in detail in subsets and in subsets of subsets. We can thus hypothesise that the image of a certain structure (in the case of homeopathy, the MT) reappears in a 'similar' form, but with better definition, in successive dilutions.

It is tempting to speculate that such a phenomenon may basically account for why, in classic homeopathy, HDs are regarded as having a more specific and profound therapeutic effect if there is perfect matching of the symptoms of the patient and the remedy, i.e. if the 'details' of the analogy have emerged clearly from the homeopathic history-taking. In practice, the fewer the symptoms shared by the patient and the remedy, the lower will be the dilutions used; the more symptoms they have in common, the higher will be the dilutions prescribed. On the other hand, this theory, based on the dynamics of chaos and fractals, would imply that minimal differences in the condition of the drug manufacturing procedures may affect the final structuration of nanoparticles in a specific dilution.

Conclusions and perspectives

The problem of the nature of an active ingredient in HDs and homeopathic solutions is still far from to be clarified but the present evidence strongly supports the notion that the structuring of water and its solutes play a fundamental role.

Liquid water is clearly a very complex system. Further complexity is added by formation of clusters with other materials, electromagnetic processing and presence of ethanol. The information gathered from experiments, theoretical calculations, and computer simulations has led to the development of several 'models' that attempt to explain the structure and behaviour of water solutions, but water science has

not produced any definitive answer. As a consequence, the present state of knowledge does not allow definite conclusions in favor of against the existence of specific physical states of highly diluted homeopathic remedies, accounting for the permanence of pharmacologic information. Skeptics may remain unconvinced by the available knowledge. On the other hand, people with more open-minded position are reinforced in their belief, since evidence of nanoheterogeneity of water and other puzzling results of biophysical sciences are giving an increased credibility to HDs and their use in homeopathic medicine.

Experience from laboratory research of our and other's laboratories indicates that the phenomena described in many 'HD' experiments do really exist, but they are difficult to be reproduced because the experiments are markedly affected by minimal technical differences and conditions, including the skill of the operator, the type of blood donors, the season and the day of the experiment, perhaps atmospheric pressure, the electromagnetic 'pollution' of the laboratory, the time left between a dilution and the subsequent, and similar factors. In addition to these methodological problems, the 'ingredients' of the homeopathic HDs may vary due to trace compounds present in the triturations and in water solutions used to make the remedies and to different methods of succussion and storage of solutions.

In Table 3 the major hypotheses so far presented and their experimental evidence and/or theoretical background are summarized. Each of the presented models has strengths and weaknesses, and none is fully convincing, because it cannot explain all the experimental observations. Further development of basic research is highly desirable, and one major challenge will be the development of test systems able to yield consistent and reproducible results. A variety of protocols and different experimental conditions in terms of types of dilution/shaking procedures and solvent used should be explored. Research on extremely sensitive systems and very HDs of substances suggests that trace elements, container materials, storage duration and shaking methods may influence the results. Therefore, suitable water controls prepared in an identical manner and subjected to a same storage time must be used. As a function of these considerations and the controversial nature of the investigated subject, independent replications are crucial to establish stable models that might be used by different investigators worldwide. We hope that the work presented here will shed some light on a puzzling subject and will stimulate further theoretical and experimental research on the science of homeopathy.

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