Can water possibly have a memory? A sceptical view

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Homeopathic medicines are currently used in medical practice, despite controversy about their effectiveness. The preparation method is based on extremely high dilutions of many substances in water, far beyond any detectable level. For this reason, it has been suggested that water could retain a 'memory' of substances that have been dissolved in it before the successive dilutions. The paper stresses the fact that this idea is not compatible with our knowledge of pure water. If an explanation on physical grounds is to be found, research must focus in other aspects of the preparation, such as the presence of other molecules and dissolved gases. *Homeopathy* (2007) **96,** 158–162.

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Introduction

Homeopathy and homeopathic medicines are widespread and well accepted by many doctors, pharmacists and patients. It is officially recognised by health authorities and agencies authorities and at a political level in many parts of the world. However, they are also criticized and attacked by others. It is not my purpose to participate actively in a complex debate that includes not only scientific aspects but also sociological and economic components. My contribution will address only the arguments relying on the properties of water and only from the physical view. Consequently, at best, it is a physicist's view of the role played by water in homeopathic solutions.

To clarify this statement, I think that it is useful to remember that medicine is not only a science but also an art. A good doctor takes into account not only the sickness itself but also the patient, his environment and his psychological aspects. As a consequence, the prescription of a medicine fortunately includes a large part of empiricism. The goal is to restore a 'normal' state. One must admit that the complete knowledge of all the parameters intervening in a real situation is totally illusory and that this situation is unlikely to change in

the foreseeable future. Anyway, even when the active principles and biological receptors are well known and identified, the reactions of different patients are not the same. To circumvent these inherent difficulties the performance of drugs is established via statistical analysis of large numbers of cases with a randomised double-blind methodology which implicitly recognizes the hidden role of components which escape to the normal scientific analysis of 'exact sciences'.

Modern pharmacological research is based on a detailed knowledge of physical and chemical interactions between drugs and living cells. At the confluence of Biophysics and Chemistry, a more detailed and precise picture of those interactions is steadily emerging. Still, many traditional medications and frequently-prescribed drugs are currently used without such detailed knowledge of their action. For them, it is either difficult or useless to define the exact 'paths' from medicine to biology, then to chemistry and physics.

Pure water and homeopathic drugs

Many traditional drugs, as for example those extracted from plants, are extensively used in medicine. In some cases one or more active principles have been identified but even in such cases the exact action is usually not well understood at the level of chemical reactions or physical interactions taking place within living organisms. This situation is very common but has never been a limitation

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to prescribing drugs that have shown their effectiveness through many years of practical use. Certainly, in other cases, the interactions are known in great detail leading to the synthesis of well-defined drugs with specific and well controlled applications. But we remain far from a comprehensive and detailed knowledge of the action of drugs on living organisms.

Homeopathic drugs fall, at least partially, into the first category. Their use has been validated by real or supposed successes, the frontier of the two being probably irrelevant from the point of view of the patient. But there is an essential difference between traditional or 'natural' medicine and homeopathy. The latter is much more recent and based in a quasi philosophical concept (*similia similibus curentur*) stated by Hahnemann, perhaps by analogy with the contemporary first studies of immunization. With modern science, it should, in due course, be possible to understand the mechanisms of action of natural substances and of homeopathic drugs. For natural substances the search for the active principles has been successful in some cases; in others, it has been simply assumed that they are present but the level of interest of the drug or available resources has not justified further studies.

With homeopathic drugs the situation is very different. Their method of preparation is based essentially on two steps: sequential dilution with 'succussion' or 'dynamisation' (vigorous turbulent shaking). A molecular view of the matter and a trivial calculation demonstrates that, often it is extremely improbable that even one molecule of the compound present in the original solution persists in a vial of the final medicine. The role of succussion is not obvious, even less the diverse standards of methods of preparation.

Under the pressure of criticism, the natural evolution of researchers interested in finding acceptable scientific justifications of homeopathy has been to go from purely medical concepts of effective therapy to chemistry and finally to fundamental physics. Ultimately, schematically, the answer: if there is 'only' water in homeopathic medicines, then the explanation of the therapeutic action must be in pure water, itself!

This intellectual evolution is a paradox. While for many drugs, the action is known at a biological, sometimes at a chemical, but almost never at a physical level (that of the structure and energies defined with atomic resolution); for homeopathy, the discussion jumped directly into this microscopic sub-molecular physics world. The mixture of the precise methodology characterizing research in physics and procedures deriving from pharmacology in research in homeopathy is striking. For example, several measurements of physical properties of diluted solutions have been done double-blinded. An extreme and provocative hypothesis is that water can retain a 'memory' of substances previously dissolved in it.[1]

A critical analysis of several publications shows that several issues remain open to question. Schematically, one can distinguish the following:

(1) How different from pure water are highly diluted solutions? In other words, is the simple calculation of the number of molecules of the 'active principle' per unit volume of the solution sufficient to account for the composition of homeopathic medicines?

(2) If succussion is an essential step in the preparation of homeopathic medicines, what is exactly its role? How does it influence the dilution procedure?

(3) What is the behaviour of complex molecules (eg biopolymers, organic compounds, surfactants, etc.) during the dilution process?

A clear answer to these (and perhaps other) questions is a necessary and essential precondition to any study of 'pure' water. Indeed, the conditions of preparation and conservation of homeopathic medicines are far from respecting the simplest procedures required in physical studies of pure water.

Some issues should be controlled more systematically:

(1) Pure water is a very powerful solvent of many substances. For example, it dissolves and forms specific bonds with silica. In contact with the surface of quartz, water forms stable silanol groups (Si–O–H). With time, silica molecules and silicon atoms are solubilised and hydrated. The number of these 'impurities' is huge as compared with the calculated amount of molecules of the starting substance in most homeopathic medicines.

It may be useful to recall that the interaction of water with solid surfaces is so strong that studies of nucleation must be done with minute amounts of water kept in levitation, without any contact with solid surfaces. The interaction with solid surfaces is so important that if a supercooled liquid freezes, it must be heated up to temperatures higher than the melting point in order to be supercooled again. Less important for water than for other liquids (eg gallium), this effect is due to more favourable nucleation of the solid form at the solid surface.

Another point deserving investigation is the storage of homeopathic solutions over long periods of time. This procedure is totally incompatible with a chemical purity of water, even at a modest level.

(2) The main consequence of succussion is the insertion of substantial amounts of air from the environment where the procedure takes place. In a laboratory that is not a cleanroom (such as those used for example in electronics), the procedure brings into the solution not only the gases present in the atmosphere (oxygen, nitrogen, argon,...) but also dust particles, microdroplets of water, etc. Recent studies[2] show that the properties of solutions are drastically modified when succussion is done under different atmospheres or at different pressures, a fact which should encourage further studies in this direction.

(3) Many substances, which contain pharmacologically active principles, are not soluble in water. Some are

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previously diluted in alcohol suggesting the presence of surfactant molecules that go spontaneously to interfaces such as the free surface, the interface between the solution and micro-droplets of gases and the interface with the vial. Again, several very promising and striking studies performed by the analysis of the thermoluminescence of frozen solutions open new and exciting perspectives.[3]

To summarize, it is striking that in publications concerning highly diluted solutions, chemical 'purity' is assumed, solely on the basis of a calculation based on the dilution procedure itself. In fact most of the samples studied are far from being 'pure water'. It would be interesting to perform to a real analysis of the composition of the solutions with physical methods such as mass spectroscopy.

Properties of liquid water

As stated above, many experiments with homeopathic medicines assume the purity of the highly diluted solutions and attribute its therapeutic action to modifications of the structure and dynamics of the pure liquid itself due to the past presence of a solute.[1] Such a strong hypothesis would imply not only general or random changes but also a large variety of changes, specific to each solute. The main purpose of this paper is to recall that this hypothesis is totally incompatible with our present knowledge of liquid water.

Water, in all its forms (crystal, liquid, gas and amorphous forms) is certainly the most studied of all substances. All its properties have been measured with extremely high accuracy in very different conditions, including metastable states and 'extreme' conditions. This is due to the central role of water in many scientific domains in physics, chemistry, geophysics and, of course, biophysics. Essentially all known experimental techniques and computer simulations have been used to precise details of the behaviour of water at scales extending from hydrodynamics to the nuclear and electronic levels. In other words, water is not an unknown substance!

However, do we know 'everything' about water? Certainly not: several puzzling questions are open to discussion. In brief, the main open question about pure water concerns the supercooled (metastable) state (ie liquid water at temperatures below its freezing point) and its relation with different amorphous (glassy) states. The structure of liquid water, at atmospheric pressure, is not known in a large temperature range extending from the vicinity of the temperature of homogeneous nucleation of ice ($-42\,°C$) down to the temperature of the glass transition ($-140\,°C$). This problem is the object of debate and speculation mostly based in extrapolations of simulations of molecular dynamics performed by computer.[4,5]

Another important domain of research is 'confined water', ie water occupying extremely small volumes, for example, in porous materials, in thin layers or in small pools formed at hydrophobic sites of bio-molecules. In this case, there is a large variety of situations that depend essentially on the nature of the substrate and on the relative importance of the number of molecules at the surface and in the bulk of the small volume. However, pure water at ambient conditions is well understood. Let us review some of its main properties that may be related to the subject of this paper.

Water is a simple molecule containing three atoms: one of oxygen and two of hydrogen strongly bound by covalent bonds. Because of the hybridisation of the molecular orbitals, the shape of the molecule is a V with the oxygen occupying the vertex of an angle of $104°$; the O–H distance is almost exactly 0.1 nm. When two water molecules are sufficiently close, they orient one against the other to establish a chemical bond, called hydrogen bond. In this bond, one hydrogen atom is shared by two neighbouring molecules (Figure 1). The bonding energy is about 10 times larger than the kinetic energy but the bond is 'fragile' due the vibratory motions of the hydrogen atom particularly in the direction perpendicular to the line O–H⋯O. It is possible to measure accurately the typical time for which the three atoms are aligned (the lifetime of hydrogen bonds): it is of the order of 0.9 ps (9×10^{-13} s) at room temperature.

Because of its geometry, a water molecule can easily form four hydrogen bonds with four neighbouring molecules. This corresponds to the structural arrangement in common ice (I_h or hexagonal form). The angle of $104°$ is sufficiently close to the tetrahedral angle ($109°$) to impose this very open structure where each molecule is surrounded by four others at the apex of a tetrahedron (Figure 2). In liquid water this local geometry exists partly: on average a water molecule has 4.5 neighbours but this number decreases with decreasing temperature because the average number of 'intact' bonds increases. Incidentally, it is this decrease of the number of first neighbours that explains why the density of water decreases at low temperatures. At $4\,°C$, which is the temperature of maximum density, this effect compensates that of thermal expansion.
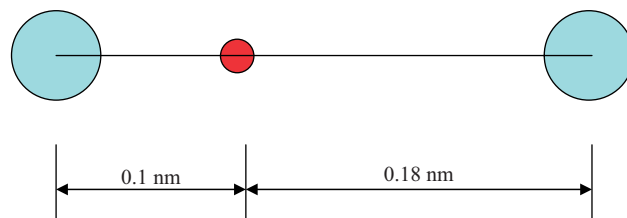

0.1 nm   0.18 nm

Figure 1 Schematic representation of a hydrogen bond in water. The large circles represent two oxygen atoms of neighbouring molecules; the small circle is the hydrogen atom attached to the oxygen on the left hand side by a covalent bond. The length of the hydrogen bond is 0.18 nm. The hydrogen atom vibrates in all directions. Vibrations perpendicular to the bond are most likely to break the bond.
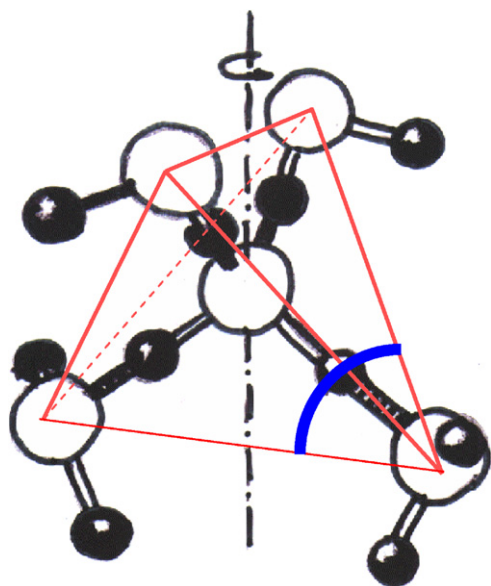
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Figure 2 Tetrahedral arrangement of five water molecules. The vibrational motion of a hydrogen atom is represented by an arc on the right-hand side of the figure (adapted from G Walrafen).

The average number of 'intact' bonds at a given moment is relatively high, although lower than in alcohols, for example. It is of the order of 60% which justifies seeing liquid water as a 3-dimensional network of hydrogen bonds, like a gel. But a gel with a life time of 1 picosecond (ps)! This means that in an 'instantaneous picture' of water structure (possible to obtain by computer simulations) one can identify local structures such as rings of 5, 6 or 7 molecules, regions with higher density of bonds than others, etc. All these structural properties can be identified by several techniques and correspond to thermodynamic properties. For example, the increase of isothermal compressibility observed at low temperatures is due to the enhancement of density fluctuations. It is very important to note that such fluctuations are not due to aggregation or formation of clusters. Hydrogen bonds form and break very rapidly generating short lived fluctuations of local density. In other words, even if at a given moment one can identify a region of higher density than the average, it will disappear after a very short time and will appear statistically in another place without any form of coherent motion such as would exist if a cluster was diffusing inside the liquid.

Historically, the first models of liquid water (due to WC Roentgen) represented liquid water as a mixture of an ideal liquid and small ice-like clusters. This model has been ruled out by many experiments. Among them, small angle X-ray scattering eliminates unambiguously any possibility of existence of clusters or aggregates in liquid water, even at very low temperatures.[6,7]

Isolated or confined water molecules can have their mobility totally restricted. In such cases, the lifetime of a hydrogen bond can be infinite. This situation is frequent in proteins where hydrogen bonds with water can play a central role in protein structure. But, in

these situations, water molecules don't constitute a liquid. Consequently, it is worth emphasizing that to postulate the existence of stable structures in pure water is totally wrong. This is one of the limits imposed by the knowledge of the structure of water.

Aqueous solutions

In aqueous solutions, the situation is more diverse. Water can dissolve and mix with many substances in different proportions (salts, acids, various alcohols, sugars, and gases, etc). Both local structure and dynamic properties may be drastically modified. Two well known examples give an idea of the diversity of situations. Trehalose is a sugar that promotes the formation of glassy water even when extremely dilute. It is present in animals and plants which, because of this property, can survive very low temperatures. Other examples are aerogels of silica with a huge content of water, which can contain more than 95% water while remaining macroscopically solid.

Generally speaking, the inclusion of molecules or ions destroys local tetrahedral geometry. Depending on the nature of the compound, the molecules of water arrange in a large variety of local structures. For example, when a salt is dissolved in water, it is dissociated into two ions each of which is surrounded by a layer of hydration where the strong electrostatic interactions between the charge of the ion and the dipoles of water generate a mini-cluster (Figure 3). The life time of this cluster is 10 to 100 times longer than the lifetime of hydrogen bonds but is not infinite, because of the exchange between molecules of water in the hydration shell and those of the bulk.

However, it is erroneous to believe that the electrical field generated by the ions extends over large distances. Actually, it is screened by the hydration layer. There is a large literature about the structure in hydration shells. The number of water molecules, distances and angles are known with great accuracy from neutron scattering experiments based on isotopic substitution.[8]

A very different situation concerns the solubility of hydrophobic atoms and molecules, such as methane or noble gases. In this case, water has tendency to form clathrate-like structures around the solute. A clathrate is a polyhedral structure; frequently a dodecahedron with pentagonal faces. This is a very stable structure, because the internal angle of the pentagon (104°) is equal to the internal angle, HOH, of the molecule. It forms a cage and the prisoner is the hydrophobic solute. The short lifetime of hydrogen bonds does not allow the formation of stable or long-lived clusters. Experiments simply detect, at best, a tendency to the formation of short lived planar pentagons.

Finally, it is interesting to consider situations in which stable aggregates are formed. The most interesting, including many industrial applications, are surfactants, which are molecules with a hydrophilic head (sometimes
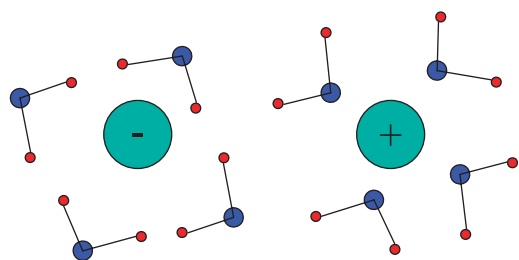
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Figure 3 Schematic representation of the arrangement around an anion (left) and a cation (right). In the first case the dipolar moment of the water molecules is directed towards the ion; in the opposite direction in the case of the anion. The screening of the electrical field of the ions is very efficient and the structure of water beyond the first hydration layer is almost not modified.
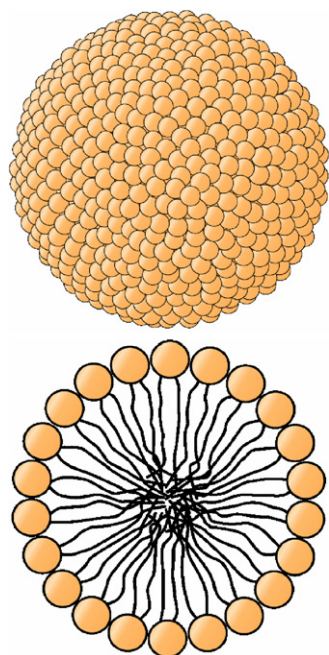

Figure 4 Spherical micellar aggregate showing the hydrophilic heads in contacts with the surrounding water or aqueous solvent. The hydrophobic tails fill the internal part of the spherical droplet.

polar) and one or two hydrophobic tails. When dissolved in water in sufficiently large amount (above a critical micellar concentration, c.m.c.) they form structured clusters called micelles (Figure 4). The heads are at the external surface and the hydrophobic tails minimise the interaction energy with water inside the sphere. These structures are very stable. They persist essentially for ever, even if there are many exchanges of surfactant molecules between micelles, either by diffusion or as a result of collisions. Many structures of this type are known, of different sizes and shapes. Some are very important in biology or in pharmacy. For example, bi-layers of phospholipids mimic quite well some physical properties of biologic membranes, and vesicles are sometimes used as vectors or carriers of drugs.

In small quantities, surfactant molecules migrate to interfaces in geometries that minimise the interaction between the tails and water. Even at very low concentration they can modify substantially the surface tension of water. Whenever surfactant molecules are present in a substance, one must take into account their specific interactions with water.

Conclusion

To summarize this short overview, one can say that water is a 'complex' liquid with many fascinating, sometimes unique aspects. Except for some academic aspects concerning supercooled water, the structure of the liquid is well known. In particular, it is certain that:

(a) There are no water clusters in pure liquid water, but only density fluctuations.
(b) The longest life of any structure observed in liquid water is of the order of 1 ps (10^{-12} s).

This is why any interpretation calling for 'memory' effects in pure water must be totally excluded.

In contrast, there is great variety of behaviour of solutes depending on many parameters. Even in small quantities, some solutes can modify substantially some properties of pure water. Special attention should be given to surfactants, sugars and polymeric substances. Since homeopathic medicines are prepared in 'extremely high dilutions' but following a procedure that does not produce necessarily extremely pure water, experiments should address the problem of the presence of minute amounts of solutes as has recently been done recently, with striking results.[2]

Otherwise, as stressed at the beginning, the advantages of homeopathic treatments should be taken at a medical level, which, after all, is the case for other drugs recognized for their remarkable although not yet explained effectiveness.

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