Water

The Forgotten Biological Molecule

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Dropwise
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Being water

Being stream
Being waterfall
Being wave
Being dew
Being trickle
Being steam
Being ice

The being of water is
A guest homing on water

—Dilip Chitre, *Shesha: Selected Marathi Poems (1954–2008)*

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Another Book on Water?

At the onset of the 21st century, humankind is focusing its attention on a very small molecule made of three atoms, one carbon atom and two oxygen atoms. Controlling CO_2 in the atmosphere is becoming a major goal economically, socially, and politically. Yet, there is another small molecule, also made of three atoms, one oxygen atom and two hydrogen atoms, that is going to play a similarly, if not more, prominent role in the near future. While an excessive concentration of CO_2 might be harmful to life on earth as we know it, H_2O, especially in its liquid form, the "Blue Gold" (hence the color of the book cover), is just indispensable to our lives. Over the past centuries, lack of access to water has triggered death, through drought, famine, and even wars. Most capitals have been established near large rivers. The preservation of the quality and abundance of drinking water will become a major challenge for nations during this century. This is no surprise. Water makes 60% to 70% of the human body weight and is crucial to the working of the biological machinery. So far humankind has more or less imprinted the importance of water for its survival in its collective unconsciousness, and it is noticeable that water has a central position in many religions on earth and is sometimes even considered as a sacred element.

Although the concept that water is the molecule of life is today evident, the exact mechanisms underlying the contribution of water to life remain largely unclear. Worse, the physics of this tiny, extremely common, and abundant molecule is still not fully understood. Water is a very atypical molecule in the first place. Why is it in the liquid state at the earth's temperature and pressure, while other molecules of similar size, again CO_2, are in the gaseous state? Why is ice, the solid state of water, lighter than liquid water, so that it can float, like icebergs? Why is water in the liquid form in clouds, while the temperatures there are well below the freezing level? All these "abnormal" features make water as we know it on earth and give it a form that is compatible with life. Water is abundant in the universe, but we have not yet found another place where similar atmospheric conditions exist. Hence, one should not be surprised that the physics of water is still an object of intense research, with reports appearing in the highest-ranking scientific journals.

The abnormal properties of water are not so easy to explain, but most of them lie in the geometry of its molecule, especially the angle between the hydrogen and oxygen atoms, which is about 105°. Yes, life on earth has been made possible because of this peculiar angle. Had this angle been a little larger (109°), water molecules would have condensed themselves as crystals, like carbon atoms in diamonds, and we would not be here. Beside the physics of single water molecules resides the "sociology" of water molecules: how water molecules are organized in space and time as a dynamic network because of their electrical charges and their location around the molecule, thereby allowing “hydrogen bounding,” which is especially important to understand liquid water.

Life has been made possible because the water molecules can accommodate other atoms or molecules, smaller or bigger, within their network in a particular way, whether water “likes” or “dislikes” them. It should be emphasized that water is never an “inert” compound, but a rather reactive molecule, which will interact, negatively or positively, with the other moieties present within its network. Reciprocally, those moieties interact with the water network and might induce changes in the water network structure. Those interactions explain why water is so important in almost all chemical reactions taking place in cells, photosynthesis, enzyme reactions, metabolism, etc., without a need for the cells to provide energy. The shape of those very complex biological molecules, such as enzymes or cell receptors, is crucial for them to interact with their intended targets. Water molecules play a direct role in giving those molecules their shape. Water may also play a more direct role in the reactions, for instance by dissociating molecules in ions. How could such interactions take place in living systems is the object of this book.

Progress has been made in our understanding of protein hydration and protein dynamics, on the interaction of water with hydrophobic or hydrophilic interfaces, such as membranes, but many questions remain largely unanswered and sometimes even subject of big controversies. There is no reason to think that water molecules in cells would be different than water molecules in a glass. But life has capitalized on water. It might well be that cell compounds that are extremely numerous and dense are interacting so strongly with the water network so as to affect the mobility of the water molecules, or perhaps modulate the structure of the entire network. Those effects could be very local, encompassing a layer of one or two water molecules at the contact of the proteins, or propagate themselves to hundred layers through electrostatic interactions within the water network. Some researchers consider that water in cells has the structure of a gel, whereas others do not. Those different views are presented in this book.

It should be pointed out, however, that results of experiments are extremely dependent on the methods used to obtain them. It is not at all the same to “observe” the behavior of single water molecules at a time resolution of picoseconds and to “integrate” the movement of billions of water molecules in a dynamic network over time intervals of milliseconds. Scaling in space and time is clearly an issue that must be kept in mind when comparing results obtained with different techniques, as it could contribute to the discrepancies. What is true at a molecular scale might not hold at a network scale. Interactions between scales are complex and not necessarily linear, especially in the crowed environment present in living cells. Furthermore, it is also quite different to observe the effects of water on complex molecules *in vitro* in a carefully controlled environment, and *in vivo* in intact cell systems. Unfortunately, there is no perfect technique at our disposal.

Researchers have so far used mainly neutron scattering methodology and nuclear magnetic resonance to study the interactions of biological molecules with water. Both approaches have their benefits and limitations, but they do not address at all the same scales in time and space. Hence, caution is required when extrapolating results obtained by one method to the other. Both provide extremely valuable information and should rather be considered as complementary. Another powerful approach that has been introduced more recently with the availability of powerful computing systems is the simulation of molecular dynamics of water molecules. With reasonable hypotheses on the local forces involved in molecular interactions it is possible to simulate the individual movement of a large number of water molecules in the vicinity of complex molecules, such as proteins or receptors, or interfaces, such as membranes. Predictions can then be made on the interactions, which can be tested against experimental evidence.

There is still a higher order of interaction and integration to consider when dealing with cells, tissues, or even organisms as a whole. The implication of water in molecular biology and basic cellular mechanisms, such as those defining the cells' shape or volume or regulating interaction between cells, cannot be ignored. A lot of work remains to be done in order to understand the mechanisms in detail, but recent studies of water mobility, whether diffusion or flow, in biological structures have pointed out its importance to cellular physiology. Different organisms have adopted different strategies in the way they get the most out of water, depending on their environment, and water contributes to the biodiversity. Faulty mechanisms in the use of water by tissues may lead to severe diseases or death.

Clearly, water deserves to be seen as the prime "biological molecule," and its importance should not be forgotten and taken for granted. How such a tiny molecule with its 105° "magic" angle could have been at the origin of life remains clearly an amazing question, which this book modestly attempts to address. This is motivation that led us to cover a large variety of timely issues regarding the importance of water for biological systems, from molecular biology to whole organisms. Life has led to intelligence, and recent studies have suggested that water (9 out of 10 molecules in the brain are water molecules) may also actively contribute to the mechanisms underlying brain function. Could the "molecule of life" also be the "molecule of the mind"?

Advice to readers

The book covers a wide variety of topics. Depending on the advancement of knowledge for each of those topics and the methods used to investigate them, the technical level of the chapters greatly varies. Indeed, the book was rather conceived as a collection of independent chapters dealing with those issues, and not written for a continuous reading. Readers are invited to browse the book freely, as chapters could easily be omitted in a first approach and read in any order, without altering its intended meaning.

Denis Le Bihan
Kyoto, February 2010

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Denis Le Bihan and Hidenao Fukuyama

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