MOLECULAR PRESENTATIONS

Cubic Hydration - Spatial Order in the Living Cell

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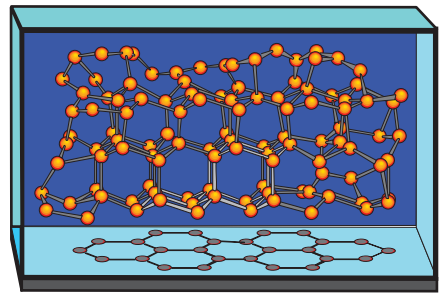
Dedicated to the late Professors Carl Djerassi and William S. Johnson of Stanford University.

Although water on surfaces of proteins and nucleic acids displays the spectral properties of ice[1] and hydration shells have been reported to extend at least three layers out from surfaces of proteins,[2] there are still no accepted concepts with regard to the role of water in providing spatial freedom and order in living cells.

In the liquid state, bonding between water molecules is between opposite points of charge on their surfaces.[3] The bonds are relatively strong but water molecules have such high energy that attachments last only about 10^{-11} seconds.[4] Since liquid water exhibits a number of temperature-related transitions in physical properties, it was thought that those transitions might be responsible for its life-giving properties.[5] However, in 1944, Nobel-Prize-winner, Erwin Schrödinger, in his little book, *What is Life*?, proposed that there must be some sort of order in liquid water to have moved molecules in evolution from randomness toward order and that there might be a law, in addition to thermodynamics, regulating space within the living cell.[6] He referred to the law or principle as *Negentropy*.

As a medicinal chemist in the 1960s, I began constructing permanent molecular models of neurotransmitters and hormones and noted that their dimensions seemed to correspond to ice-like linear elements of hydration. When the studies were extended to water-soluble enzymes, it appeared that their anhydrous cores correspond to spatial units in cubic ice. Since cubic ice is the first form of ice produced as water freezes and is composed entirely of of linear elements,[7] it appeared that ice-like elements of this sort must be forming on non-water-bonding lipid surfaces, and then, as they disassemble and leave, they must withdraw energy from adjacent polypeptides, convert them into lower-energy beta-sheets and coils and bind them together with other lipid surfaces to form the anhydrous cores of proteins.

In fact, in 1984 a molecular orbital study suggested that, indeed, water forms unstable linear elements of 5 or 6 molecules adjacent to lipid surfaces.[8] Thus, as polypeptides are released from ribosomes and small peptides like gycine and serine absorb energy from adjacent water molecules to produce turns and loops, while unstable water in linear elements on lipid surfaces leaves, absorbs energy and extends anhydrous assemblies.

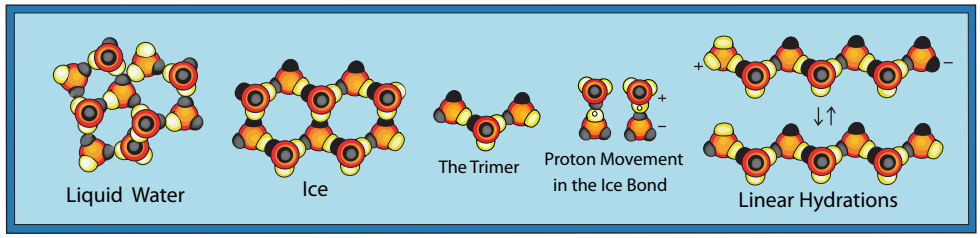


In 1970, in a detailed thermodynamic study, Lumry and Rajender proposed that, as small molecules approach the surface of a protein, there is a rapid exchange in water-to-water bonding between enthalpy and entropy - between liquid and ice bonding.[9] They indicated that water in both bonding states are intimately involved in controlling motions and interactions in living cells. Since the basic problem with water in the cell is the same as electrons in molecules (neither can be defined precisly in space) but both define space around them, I decided to publish my first book, *The Matrix of Life,*[10] in which the proposal was presented that it is Transient Linear Elements of Hydration in Cubic Ice Conformations which regulate space and provide order in living cells, even though I knew that there would be strong resistance to the proposal.

In fact, Schrödinger's Negentropy concept may be answered: water may, indeed, form short-lived linear elements of hydration in cubic conformations on lipid surfaces of vital moleules, and then, by moving into the higher-energy liquid states, move adjacent molecules into lower-energy, more ordered forms.[10]At the same time, regions in cells which periodically contain free sodium and calcium ions, may shift to spherical hydration.

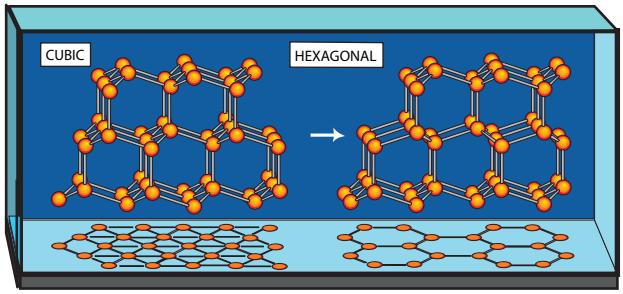
Although the presentation of those concepts in 1991 generated vitriolic negative comments from a number of experts in the fields of water and protein assembly, it was not the first time ice-like units had been suspected in liquid water. In 1972, reflection of X-rays from the surface of water at 25°C produced a major peak at 2.9 Angstroms for the mean distance between liquid water molecules and two minor peaks at 4.5 and 6.8Å for a trimer and tetramer with a bond-length of 2.76Å,[11] the same as in ice.[4] Although ice-like units had not been seen within liquid water before, molecular orbital calculations in 1969 had indicated that the trimer, with the same bond-length, might be the most stable structural unit in liquid water[12] and, again in 1984, that ice-like linear elements of hydration might form on lipid surfaces which do not hydrogen-bond with water.[8] However, it was not until 2005 that hydrophobic surfaces were considered involved in regulating interactions,[2] 2006 that neutron irradiation of liquid water revealed the presence of the trimer[13] and 2009 that linear elements in cubic ice conformations were observed on the super-cooled hydrophobic surface of graphite.[14] Finally, in 2011, professor Sow-Hsin Chen and coworkers, using high-resolution NMR on the lysozome protein, found, (as expected in the Hydration Hypothesis),[10] that its polypeptide was entirely coated with water as released from the ribosome, and then lost a portion of that water as assembly proceeded to produce the functional protein.[15]

A companion study published the same year, found that the degree of tetrahedral order in water around protein coils increased with coil length[16] and was followed in 2017 by a study of hydrophobicity which confirmed that water on lipid surfaces demonstrates increased ridgidity and tetrahedral "iceberg" bonding order.[17] Since the primary structural unit which forms most rapidly on lipid and poly-ionic surfaces is cubic, the hypotheses advanced in 1991 appeared to be validated. In fact, if we examine hydration-bonding in more detail, we will have a better idea of what, most likely, is happening as water contacts the lipid surfaces of polypeptides.



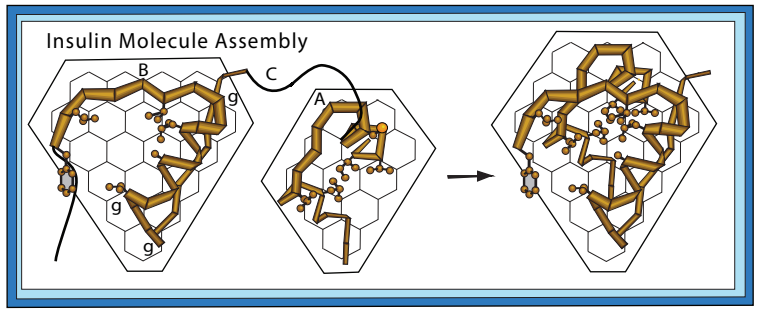
As illustrated above, bonding in the high-density (HD) liquid state is extremely dynamic,[18] with water molecules so close together that they cannot spontaneously form ice at 0°C. Only if water is on an hexagoally-patterned surface will ice form at 0°. On the other hand, bonding between water molecules in the trimer and in ice involves an overlap of electron orbitals in a covalent bond[19] with the proton of the hydrogen atom so close to the neighbor's orbital, that, by moving only a fraction of an Angstrom, the proton can positively-charge the adjacent water molecule. If that happens in liquid water, hydroxide and hydronium ions are produced, but, if produced in ice-ordered linear elements of hydration on the inner surfaces of axons in nerve cells, it can tunnel positive charges from node to node at extremely high speeds.[20]

Actually, if water is cooled to 4°C, the density increases, but, if the water is in a clean glass container, cooling can be continued on down to -30°C without crystallizing. As it cools, the density decreases and viscosity increases,[21] (probably as the proportion of linear elements increase), until, at -40°C, the density is almost that of ice and it freezes.[22] But the ice produced is not hexagonal, it is cubic[7] - only by warming does it isomerize to the normal hexagonal form.



Thus, it is not surprising that, as water molecules approach a surface with atoms or ions in hexagonal positions, like lipid surfaces of proteins or ionic of nucleic acids, they form transient linear elements of hydration. As noted above, water follows closely surfaces of polypeptides as they form, but then leaves as specific surfaces dehydrate to form coils[15] and fold together to form more ordered units.[16] Since it is sequences of aminoacids in polypeptides which define whether water will either bind or form unstable linear elements on surfaces,[17] it should be possible to interpret folding and structure.

For example, the insulin molecule is released as a linear polypeptide chain of 20 different amino--acids.[23]

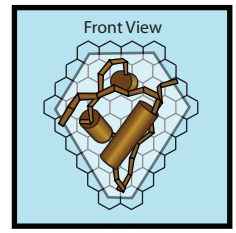


Some regions of the chain are composed of small amino-acids, like glycine, which continually hydrogen bond directly with surface water to maintain chain mobility. Other regions, composed of amino-acids like alanine and leucine, with hydrocarbon side-chains or glutamic acid, with ionic atoms on the ends and methylene-groups in their side chains, shield segments of the chain from hydrogen-bonding with surface water. They force water to form unstable ice-like bonds and, as that water leaves, move those regions into lower-energy more ordered forms. In the middle of the B unit, as shown above, there are so many hydration-ordering peptides on both sides of the chain that it rapidly wraps into a lower-energy coil.[24] Two glycines on the lower end permit turns into a linear segment with ordering peptides on one side which bind into the hydration-ordering back side of the coil with the loss of unstable linear elements of hydration of the same quantized length from both surfaces. The other end of B linearizes and bends over to bring the ring of phenylalanine next to the methyls of the valine on the coil.

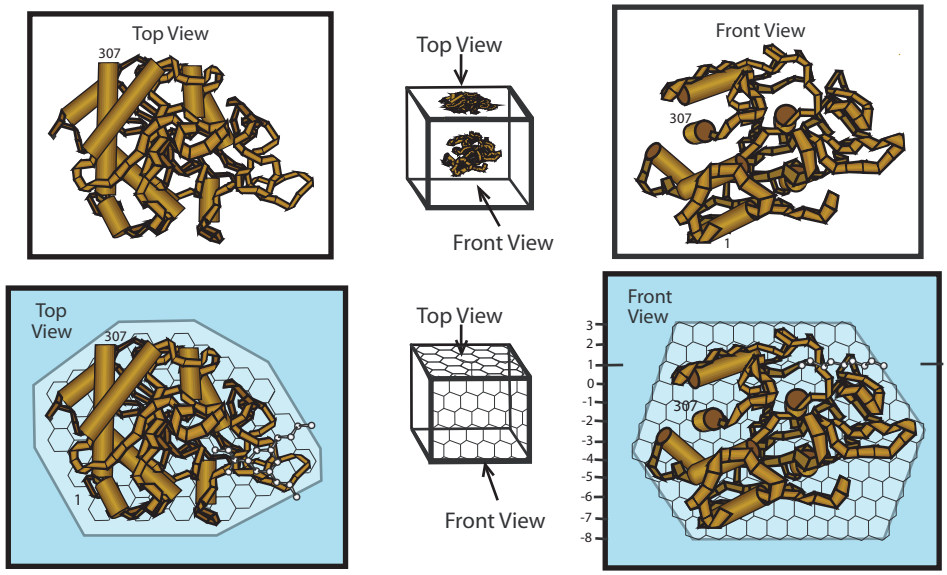
The A-unit forms two short coils with a short linear segment between them and a linear element of hydration on the front side (the same length as those in a groove behind B). Segment C, which contains multiple mobile glycines, carries A into the ordering back side of B with the loss of all water to form the anhydrous main core of the molecule.

Based on the above analysis, surface water either forms hydrogen-bonds directly with small peptides to maintain chain mobility or it forms unstable ice-like linear elements of hydration on chain-shielding peptides. Cores of proteins are formed as linear water leaves.[25]

Although exterior surfaces of most water-soluble proteins do not display cubic patterning, insulin is a hormone which displaces cubically-ordered water from binding sites in receptor proteins. In fact, when insulin crystallizes, it carries water in cubic form into channels between the molecules[26] and recent studies disclose that it is the lipid linear lower right-hand coil-face of the molecule, as shown on the right, which binds most tightly to a receptor site.[27] As you can see, the insulin molecule is an excellent example of how surface water, not only is involved in regulating its assembly, but its function as well.[10]

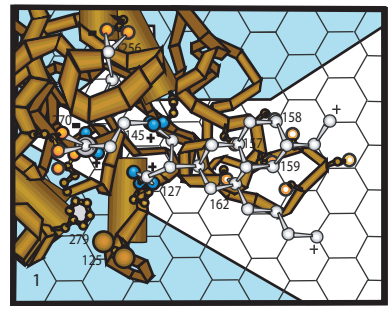


Recently, the Deep Mind organization,[28] as well as David Baker,[29] have reported the development of programs which, by storing information on structures of thousands of proteins, have been able to derive spatial structures for new proteins based solely on their aminoacid sequences. They are, indeed, breakthroughs which should make it possible to advance medical science. However, they do not address the role of water in the assembly process. To do that, X-ray crystallographic structures of proteins must be oriented in space in such way that they can be viewed in-line with major coils or beta-sheets which direct hydration in assembly.[10] For example, in the analysis of the crystallographic structure of the carboxypeptidase A enzyme,[30] the molecule was oriented so it could be viewed parallel to the terminal coil ending in peptide 307.



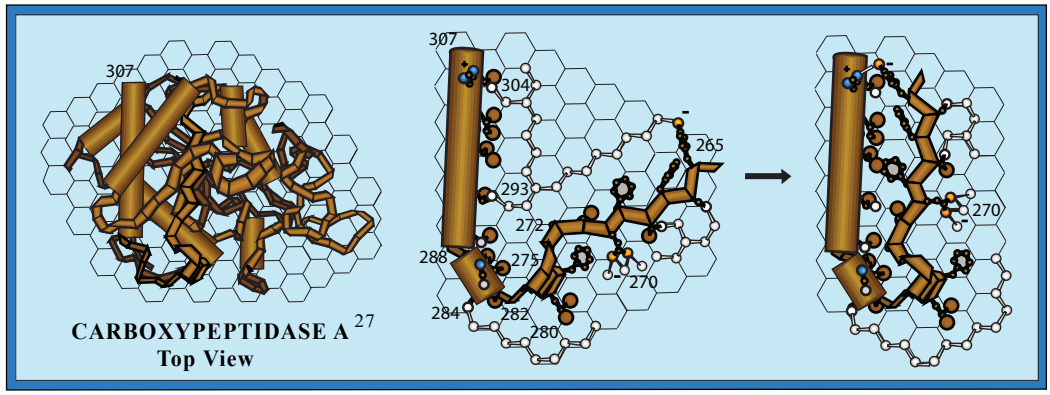
On the left, the upper surface of the molecule in the crystalline lattice is viewed over a regular hexagonal pattern of water molecules (2.25Å apart in the plane). In the Front View, with the cubic lattice shown behind it as a layered form, the coils and linear segments present an entirely different appearance - it is as if they are floating on planes of ice-like water molecules which are numbered to define positions. However, it must be remembered: even though the cubic lattice is illustrated as a complete unit, only short linear elements are present at any instant as the polypeptide folds and they last only about 10^{-11} seconds. The lattice, as presented above, is a cumulative view of the ordering units of surface hydration which propagate one unit of order to the next across lipid surfaces to guide assembly. In like manner, elements of hydration which propagate between ions to neutralize charges, most likely guide assembly of nucleic acids and interactions between molecules in living cells.[10]

If we look at an enlarged view of the enzymatic binding site with the zinc ion at the base, we can see that the hydroxyl groups of the serine peptides at positions 157, 158, 159 and 162 are in spatial locations to hydrogen-bond with transient linear elements of hydration which tunnel positive charge out from the reaction site to direct the negatively-charged ends of polypeptide chains into the reaction site for cleavage of terminal aromatic peptides.[31]



Of extreme importance, is the realization, based on Transient Linear analyses of multiple proteins: *once cubic hydration patterning is established around a primary structural unit in a polypeptide, it is maintained as a quantized unit, not only to direct assembly, but enzymatic activity and lipid interactions with other proteins.*

Another important feature involved in the formation of the anhydrous cores of proteins is that lipid regions which fold together usually hold the same lengths quantized linear elements of hydration so that, in folding together, all water is lost between them to produce a stable anhydrous union.

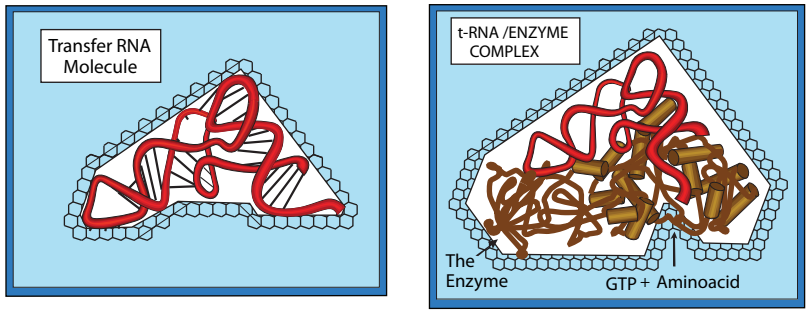


For example, as the polypeptide of the carboxypeptidase enzyme is released from the ribosome, most of the 27 aminoacids on both sides of the chain at the 307 end have hydrocarbon side chains which shield oxygen and nitrogen atoms in the chain from hydrogen-bonding with surface water. As ice-like bonding on those surfaces break and energy is transferred, the chain straightens and then rapidly forms the long coil.[24] A proline at position 288 produces a turn in the coil, and another at 282, produces another turn. Oxygens at threonines 304 and 293 are in precisely the proper positions to induce ice-like bonding of water next to the coil. From 280 to 275, the chain wraps back and forth in hydrated beta-turns so that the 272-265 segment can be at the level of the coil, rotate, bind and release equal lengths of unstable water from both surfaces.

Glutamic acid, at position 270, by clustering water around it to delocalize its charge, breaks hydration order in the next hydration layer. At the same time, lipid surfaces above and below the acid continue to be covered by ordered water which, by being displaced by lipids, continue the formation of the anhydrous core. Polar and ionic side-chains of small peptides, which are left on the surface, bond with surface water and other molecules at a variety of angles. Based on Transient Linear Hydration analyses, it appears that: *it is analogies in spatial-bonding properties between hydrated forms of natural molecules and the order/disorder bonding properties of ordered forms of the ionic aqueous environment which permit the molecules to function in such a coordinated and spon*taneous *manner in living cells.*

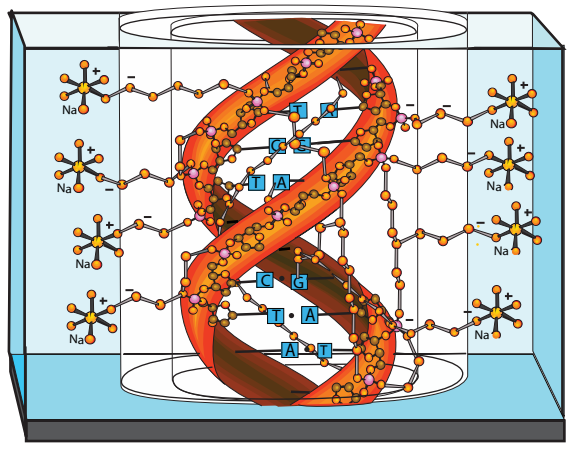
Recently, Irena Roterman, Barbara Kalinowska and co-workers have begun publishing on the importance of water as an active participant in protein folding and the role of the protein core in providing functional properties.[32] Hopefully, their studies will yield the same conclusions as my studies: as vital molecules approach each other, it is regions of dynamic linear and random hydrogen-bonding on their surfacs which direct them into such unique spatial relationships that, when water leaves, they form firm anhydrous associations.

Just as the insulin molecule mimicks a cubically-ordered spatial unit of water molecules, small ribonucleic acids called transfer-RNAs, which bind to multiple sites in ribosomes to produce polypeptides, also mimic spatially-ordered units in cubic ice.[33] Details of the binding and polypeptide-formation are included in www.linearhydration.com but it is important to realize that there are at least twenty of these cubically-ordered t-RNAs in every living cell and the same number of enzymes, with structures as shown below.[34] The enzymes bind a specific three-letter genetic code on the left end of the t-RNA molecule to a specific sequence of peptides in the enzyme and attach a specific amino-acid to the open, right-hand end.



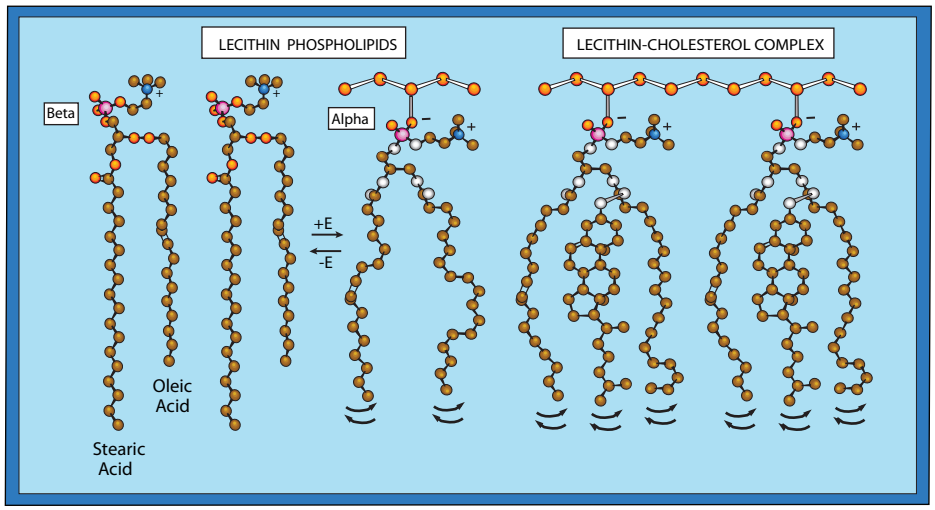
As you can see, the enzymes which bind these t-RNAs have complex structures composed of both coils and linear segments, but they all fit together to form a structurally-stable anhydrous core which, not only fits into the surrounding cubic hydration order, but fits a specific t-RNA molecule into linear grooves in the enzyme with the aminoacid-binding end of the t-RNA molecule drawn down into the catalytic reaction site.

On the other hand, double-helix DNA, which also has a halo of ice around it,[1] appears to induce several different orientations of linear and cubic hydration order.



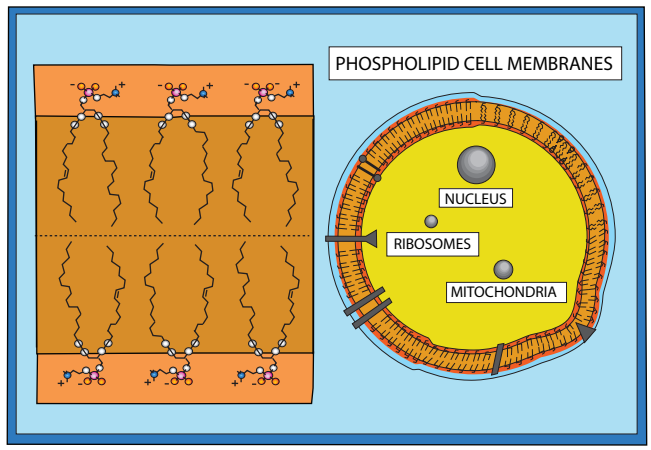
First; as illustrated in the structure of DNA above, there is a linear element of hydration which forms within the small groove of the double helix.[35] Second: hydration-bridging forms between specific base-pairs[36] and last, but not least, water between adjacent phosphates and out to spherically hydrated sodium ions around the helix water forms linear elements to delocalize the charge.[37] None of the linear elements last long, but all contribute to the ice-like shield around DNA.

Now we will turn to the major structural and functional parts of the living cell, the biomembranes - which differ substantially from the other components in that they are composed of molecules which are not held together by chemical bonds but by their lipid and ionic character.[38] Like the hydrocarbon chains of the molecules in oil, when they contact water, they aline next to each other in layers based on lengths.[39] The most common molecule is a phospholipid named "lecithin" with fatty-acid chains of 18 carbons, particularly stearic acid with a saturate chain, and oleic acid, with one double-bond.



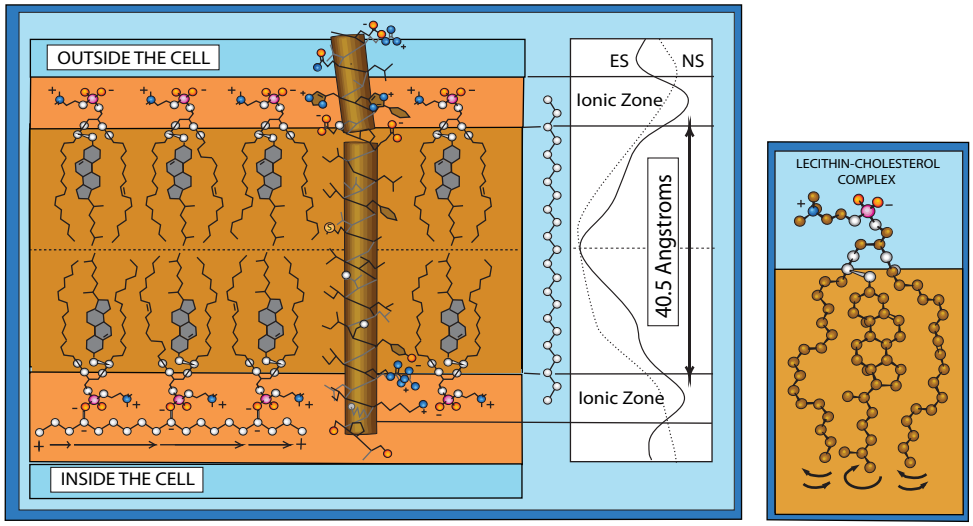
At low temperatures, the chains lay side-by-side as shown above, but at normal temperatures, they have too much energy to remain straight - they twist and spin and occupy more space.[40] As shown above, the mean distance between phosphates in phospholipid/ cholesterol complexes, which compose the axonal myelin membranes of large nerve cells, is about six ice-like bonded water molecules.[41]

As shown on the right, phospholipids form a double-layer with their dynamic tails in contact in the middle. Although they have a variety of head-groups, the major one in nerve and muscle cells has a trimethylamino group on the phosphate.[42] Proteins, which have lipid regions of proper length on their sides, regulate shape, provide pores for ions, molecules and trans-membrane signals.



Once phospholipid membranes developed in evolution, critical components, like nuclei, ribosomes and mitochondria, no longer had to be held in gelatinous masses. Initially, bacteria, molds and virus most likely were the major forms of life. By combining in numerous coordinated ways, they produced the cells which compose you and me.

If we look more closely at biomembranes, we find that they are so loosely tied together that they cannot be isolated - they have to be constructed primaily based on spectroscopic data. In fact, it was in 1972 that Singer and Nicolson proposed the "Fluid Moseic Model" with the bilayer structure shown on the previous page[43] and 1971 that Caspar and Kirschner published the electron-scattering (ES) and neutron-scattering (NS) curves for rabbit nerve cell lecithin/cholesterol membrane.[44]

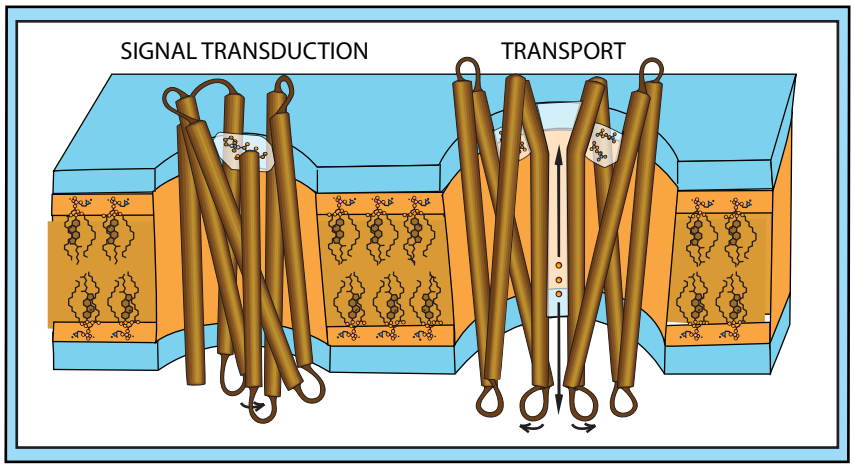


With the amino-phosphates of the phospholipids positioned at the peaks of the electron scattering curves on both sides of the membrane, (in the same locations as the ionic and polar groups on the protein coil which was isolated from a red-blood cell),[45] the lipid zone correlates to a distance of 40.5 Angstroms - 18 ice-like-bonded water molecules (2.25Å per water molecule), lecithin/cholesterol molecules which meet in the middle and 27 peptides in the coil (1.5Å between them). Once again, linear elements of hydration appear to have defined, both the width of the membrane as well as mean distances between phospholipids on the surface.

Furthermore, this idealized model provides an answer to a question that has plagued physiologists for years.[46] In small nerves, when neurotransmitters like acetyl choline, open pores in nerve endings to permit sodium ions into negatively-charged nerves, positively-charged potassium ions in the nerve carry the charge end to end. However, in large axon nerves, it is too far from end to end for potassium ions to carry the charge. In fact, the charge passes through axonal nerves at a much higher speed than small nerves. The difference is that the inner walls of axons are composed, almost entirely of lecithin/cholesterol complexes.[41] Positive charges generated in the nerve ending aline the ionic heads of the lecithin molecules and, as illustrated in the figure above, positively-charged protons in adjacent ice-like-bonded linear elements of hydration carry the charge at almost superconductive speeds from anionic phosphate to phosphate and amplifying node-to-node to the end.[47] For many years, molecular biologists have searched for a mechanism by which the positive pulse could be carried with very little loss of energy.[46] Based on the Transient Linear Hydration Hypothesis,[9] the answer is through linear elements of hydration which last for only about 10^{-11} seconds.

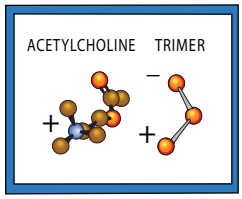
Currently, there is a search for materials which can carry the negative charges of electrons at superconductive speeds. The problem is that electrons must be cooled to extremely low temperatures or in complex media to hold them in conductive orientations. That's not a problem for protons in transient linear elements of hydration. It fact, it appears that nature may have been the first to discover and utilize superconductivity.

Now let us look at the functional proteins in membrane. On the right below is an illustration of the type of protein that is involved in producing the positive charge in afferent nerve ends. It is composed of a pair of coiled proteins with lipid peptides on their outer surfaces in contact with the phospholipids and polar and ionic ones on the inside forming an ion-conductive pore.[48]

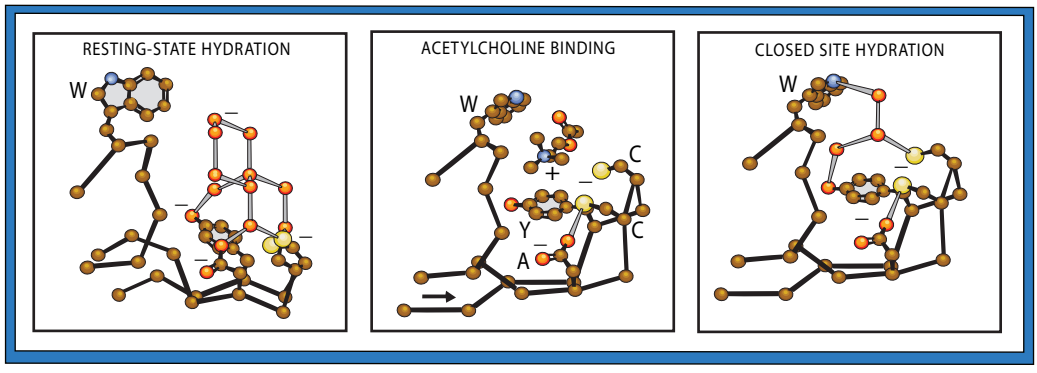


When a neurotransmitter, like acetylcholine shown below, binds to sites near the outer surface, the inner coils turn, open the pore and permit sodium ions in to trigger the discharge.

Although a number of neurotransmitters open ion pores, acetylcholine is the most important in nerve and muscle cells. Notice that it is one of the smallest in mimicking the trimer of water.[13]

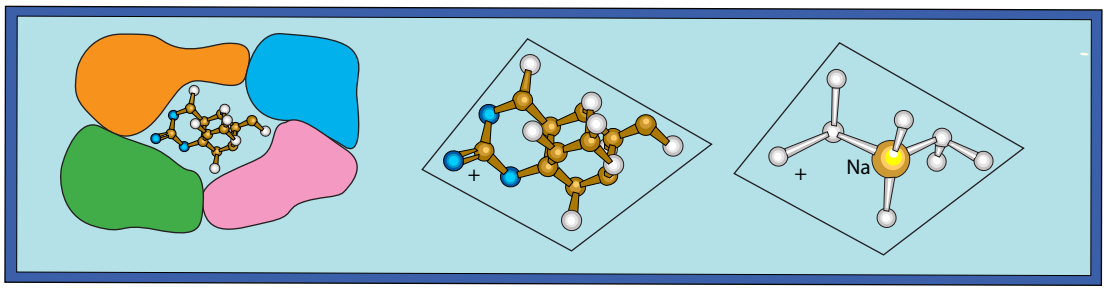


After an intensive study of the receptor protein in the electric eel, Dr. Nigel Unwin, in 1999, published the structure of the receptor protein and how it functions.[49]



Based on the Transient Linear Hydration hypothesis,[10] the receptor site most likely is highly hydrated in the resting state with linear elements of hydration periodically forming in preferred locations. When the acetylcholine molecule enters, water is displaced and two aromatic rings and two yellow sulfur atoms are drawn around it displacing all water from the site. When that happens, a polypeptide chain, which is attached to a central coil, rotates the coil. As water enters to displace acetylcholine from the site, as shown on the right, it fills with water and then opens. Once again, it appears that linearly-ordered water provides quantized spatial order for the spontaneous function of this receptor.

In addition to sodium-ion channels which are activated by acetyl-choline at nerve endings, large axons contain transport proteins in the nodes. When positive pulses reach the nodes, they open and release additional sodium ions into the axon to amplify the charge.[48] In fact, pulse-conduction in the axon is like electrons in a vacuum tube - if the initiating charge is not potent enough, no pulse will be generated. Thus, conduction through the axon is extremely fast but extremely fragile. If positive charge gets through the axon wall, it will not reach the end. If it is interrupted by a connecting nerve which reduces the pulse potential, it will not reach the end. And, if a chemical is present which blocks the entrance of sodium ions into even in one of the nodes, the axon will not function. Thus, tetrodotoxin, a chemical which is produced by a bacteria in the salt-water puffer fish, is one of the most potent toxins known to man.[50] If absorbed into the blood-stream, it produces almost immediate death by binding within the voltage-sensitive sodium ion transport channels of the axon.



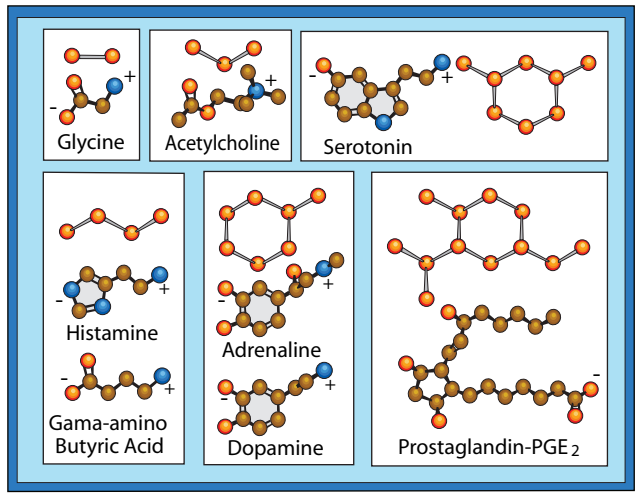
The structure of the tetrodotoxin molecule is absolutely unique.[47] It is as if one set out to produce a molecule which would mimick the structure of a hydrated sodium ion. As illustrated above, it has five alcoholic oxygens, two ether oxygens in a bridge that comes toward you and a guandine group to give the molecule a positive charge. The binding hydrated sodium ion has eight water molecules around it bound in the channel entrance by two glutamic acids, an aspartic acid and a lysine peptide on four coils.

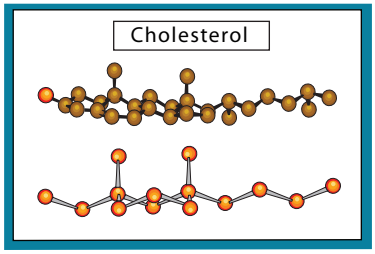
On the left, tetrototoxin is viewed schematically in the wide entrance site for hydrated sodium. Usually water is viewed in its dynamic state in random positions but, in this binding site as well as most other receptor and reaction sites, water appears to be bound in specific low-energy ice-like forms. Since mean bond-length between the sodium ion and water molecules is 2.35 Angstroms, compared to 2.76 Å between water molecules, sodium ions can readily exchange quantized positions with neighboring water molecules as it passes through the channel. In fact, one can imagine sodium ion jumping two water molecule positions to the left to enter the narrowing in the channel which permits only the sodium ion through.

Isn't it amazing to be able to simulate how water and molecules most likely move in such a coordinated and spontaneous manner that they can give us life. The day will come when water molecules, in preferred cubic and spherically-oriented spatial positions around natural molecules and ions, will be used to interpret their motions and interactions in the living cell. It will be at that time when the beauty of life processes will be revealed for all to see. It was not long ago when the uniformity of bonding within molecules was just a dream - now, everyone can "see," in the structure of DNA, the role that molecules play in genetics and health. Unfortunalely, positions of hydration around vital molecules and ions, like electrons around the nuclei of atoms, are in probability positions which can be "seen" only in theory.

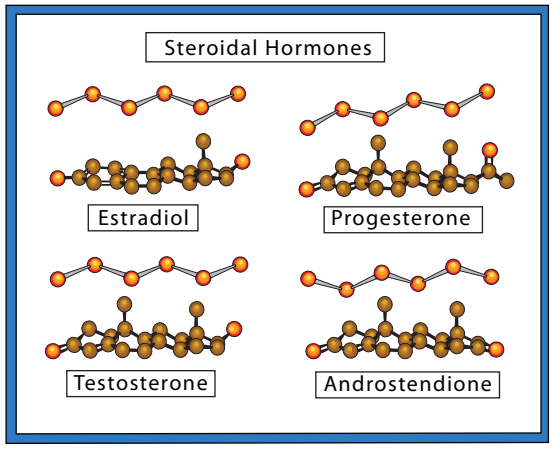
Looking back at the image of the Signal Transduction Protein on page 9, hormone and neurotransmitter molecules, which bind to sites near the outer surfaces of coils in receptor proteins to activate processes within the cell, also appear to mimic units of water. However, ordered-units occupy binding sites for such brief periods of time that, as yet, they have not yet been identified.

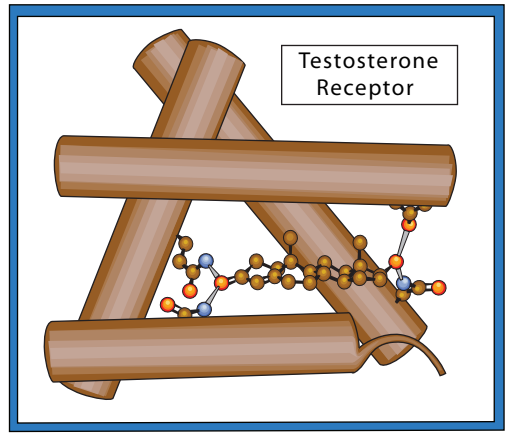
Since, regulator molecules are in their low-energy forms when they occupy the binding sites,[51] it should not be surprising that water, which fills those site as they open to admit regulators, also are in their low-energy forms. Once again, water occupies the sites for no more than about 10^{-10} seconds,[4] not long enough to to be detected, but long enough to open the site and assist regulator molecules in and out.[9]





The cholesterol molecule, which forms a complex with phospholipids to stabilize membranes, not only mimics a unit of linearly-ordered water but, by enzymatically losing its tail, is converted into a number of steroidal hormones which mimick six or seven linearly-ordered water molecules.





In 2006, Breton published the structure of testosterone in the binding site shown on the right.[52] It is not hard to imagine how water, in the linear form shown on the left, may occupy the site, even for a short period of time, as the testosterone molecule enters and leaves. In fact, when sites are not occupied by regulator molecules they may open to admit water in an equilibrium condition. The problem is that water does not occupy the site long enough to be recorded experimentally, and there is so much random water around the site, that the ordered water cannot be "seen." Some day, the importance of transient linear elements of hydration and cubic patterning will be recognized and used to explain how natural molecules and ions function in such a marvelously coordinated manner to give us life.[10]

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Dr. Collins received his degrees in Chemistry from Wayne University and the University of Wisconsin. After employment at General Motors Research, Central Research at E. I. Dupont in Wilmington, Delaware and Sterling Winthrop Research Institute in Rensselaer, NY, he accepted a position as Associate Professor and Chairman of the Chemistry Department at Illinois Wesleyan University. In 1967, he returned to Sterling Winthrop to direct Medicinal Chemistry Research and then handle Technical Affairs for the Corporation until 1987 when he retired to devote full time to his study of the role of water in the living cell.

He has a number of publications and patents to his credit and, while at Illinois Wesleyan, developed a technique for selectively oxidizing primary alcohols to aldehydes which, subsequently, was named *The Collins Reagent*. However, it was during his first employment at Sterling Winthrop that he began constructing permanent models of vital molecules and drugs and noticed that distances between polar atoms on their ends corresponded those of linear elements of water molecules in ice and that the anhydrous spatial polypeptide units in the inner cores of a number of water-soluble enzymes correspond to those in cubic ice. Since ice-like bonding between water molecules would be unstable above 0^{o}C and last only about 10^{-10} seconds it would explain why they have not been isolated or detected in receptor sites or on surfaces of polypeptides, proteins and nucleic acids.

Furthermore, when other classes of vital molecules were examined and dimensions of linear elements of water appeared over and over again, it suggested that low-energy ice-like elements of water, which most likely formed on lipid surfaces and between ions and molecules as they evolved may have influenced their the formation and selection as functional units in the living cell. In fact, it appeared that molecules within the cell function so smoothly and spontaneously becaause they are spatial analogues of order/disorder units of the environment in which they evolved. Based on that view of water in the living cell, he retired in 1987, took courses in computer graphics and, in 1991, published his first book, *The Matrix of Life*,

Since he was interested in getting responses regarding the concept, a number of copies were sent to experts in molecular biology. Most responses were extremely negative and demeaning but one from Linus Pauling, whom I respected more than any of the others, responded: “You are on the right track, but I think your concepts are too simple.” The other positive response was from Dr. Michael New, a lead investigator at NASA, who reviewed a preprint of my third book “Biomolecular Evolution from Water to the Molecules of Life:” “Your concepts of Transient Linear Hyhdration and Cubic Hydration Patterning are valuable contributions to our understanding the unique role of water in origin of life research.”