Aquamoleculomics: a thermodynamic cornerstone of systems biology

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Abstract: Systems biology has been established for more than a decade in the post-genomic era. With the help of the computational and mathematical tools, systems biology reconstitutes the entire scenario of the cell, tissue and even organism from the pieces data generated in the past decades. However, the modern biology is mainly focusing on the structure and function of the biomolecule, cell, tissue or organ, which are far from the essence of the life because of missing thermodynamic information. It is doubtable that the current systems biology-based omics is no-how to fully understand the dynamic courses of the structure, function and information in life. For this reason, we promote a novel concept of aquamoleculomics, in which the biological structure and function as well as thermodynamic characteristics and bioinformation of the aquamolecule complexes are included in this theoretical model of systems biology. Water is mother of life, matter and matrix of organism. Indeed, the fundamental roles of H_2O molecules in biological processes might be dramatically underestimated. Extremely speaking, H_2O networks in the living system might be engaged in all the biological processes including building all the biological structures, the residential places of the motherhood molecules as the honeycombs of honeybees.

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Induction

During the decades of the molecular biology and cell biology, the mechanisms of the interactions between molecules and signalosome complexes have been well anatomized experimentally and theoretically. In the post-genomic era, the modeling of complex biological systems creates a new biological branch called systems biology through the computational and mathematical analysis (1-5). In systems biology, the complex biological systems are known as various disciplines with the names ending in the suffix -omics, such as phenomics, interferomics, phosphoproteomics, glycoproteomics, glycomics, lipidomics, interactomics, fluxomics, biomics, ionomics, enviromics, regulomics, secretomics, transcriptomics, toponomics, pharmacogenomics, phytochemomics, ionomics, enviromics, which of them collect the bioinformation of the accumulated biomolecules and signalosome based on the structure and function sequentially assembling to the cells, tissues or organs and even organisms (6-11).

However, the current theory of bioinformatics-based omics is not originated from the living organisms, more likely just to meet the requirements of biologist's research activities. Indeed, it might be oversimplified to assemble into the cells, tissues or organs and even organisms just by consequentially accumulating the structures and functions of the biological molecules. In fact, it is well known that the common pitfall of the modern biology is that the importance of H_2O networks in the biological processes might be inadvertently underestimated (12-15). Another critical pitfall is the failure to understand the mental and psychiatric machinery in the modern molecular biology and the omics biology. H_2O molecules occupy above 70% of the body weight in the cells and/or the organisms and engage in the most steps of the biological processes. At the molecular omics (moleculomics), the most biomolecules are resolved and hydrated in H_2O networks as the aqua molecule complexes (16-18). The aqua molecule omics might be the most essential system in the structure, function and even information of the cells and/or the organisms. Therefore, it is impossible to fully describe the mystery of the cells or organisms and understand how the biological pieces interacting one another without engaging in H_2O networks. In other words, the current systems biology perhaps nowhere to completely unveil the mystery of the essence of life through taking the pieces apart and then putting the pieces back as Russian Blocks Game.

To be mentioned, life is a semi-open aqueous solution of thermodynamic system with nonlinear and far from equilibrium. Thus, the laws of thermodynamic mechanism are only powers to fully discover the mysteries of the structure, function and information in all the cells and organisms. To achieve the goal for better understanding biology, we promoted the model of aquamoleculomics, in which the biomolecules or signalosomes and H_2O networks combined to accomplish all the biological processes by following the law of thermodynamic mechanisms.

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H_2O networks is the cradle of life

No water, no life. To be the mother of life, there are many unique physical and chemical properties in H_2O molecular networks, such as proton donor and acceptor, perfect solvent, excellent thermal conductivity and information processing ability. As Albert Szent-Gyorgyi, Nobel Prize winning physiologist said: “Water is life's matter and matrix, mother and medium. There is no life without water”.

1. H_2O molecules function as proton donors and acceptors

H_2O is an amphoteric molecule which can function as a proton donor in an acid environment and acceptor under a base condition. The self-ionization of H_2O molecule can play a dual role in many acid-base reactions (Fig. 1A). The process of diffusion of protons (H^+ ions) in aqueous solution can create a phenomenon of proton hopping or jumping called as Grotthuss mechanism (Fig. 1B) (19-21). Proton jumping is always coupled with electron transfer which might be fundamental mechanism in biochemical reactions include oxidation in photosynthesis and oxygen reduction reaction of energy metabolism.

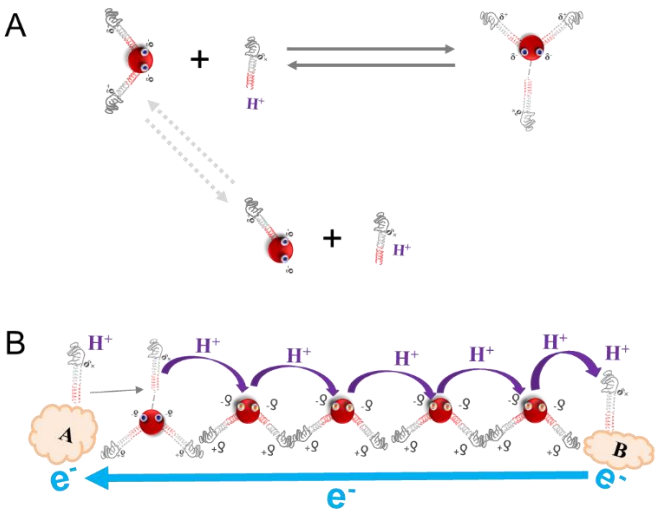

Fig. 1: The schematic depiction for the proton reservoir and proton coupled electron transfer in aqueous solution. A. Proton donor and acceptor of H_2O molecules. B. Proton coupled electron transfer in Grotthuss mechanism.

The proton reservoir and proton flow in aqueous solution play key roles in the life cradle of H_2O networks. The quantum properties of proton jumping coupled with electron transition provide H_2O networks the ability to keep the individual molecule alive in the aqueous solution under the proper temperature. Proton jumping and electron transition are not merely random as thought (22). The information from the proton jumping in

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Grotthuss mechanism and the quantum entanglement between the proton and coupled electron is resultantly from the quantum computation of the thermodynamic equilibrium. From this point of view, quantum mechanics is an essential to the mechanism of life. It is sayable that there is no life without quantum mechanics.

2. The aqua ion complexes and the aqua molecule complexes

The quantum property of proton flow provides H_2O networks a possibility to extend the thermodynamic power in aqueous solution, which naturally create a unique physical and chemical environment as the biophysical and biochemical cradle of the aqua molecule complexes. For example, the ion Na^+ gains its mobility which could respond to the thermodynamics after dissolved as aqua ion complex from the salt crystals, which is typically solvated by two or so layers of hydration H_2O networks (23). The ability of the aqua Na^+ complex is from the hydrate shell of H_2O networks around the ion (Fig. 2). In amphiphiles which containing a nonpolar hydrophobic region and a polar hydrophilic region, the hydrated shells are either the specific orders or the hydrogen bonds along the regions of the molecules to self-assemble distinct structures such as micelles and even protocells, the initiating stages of primitive organisms (Fig. 2).

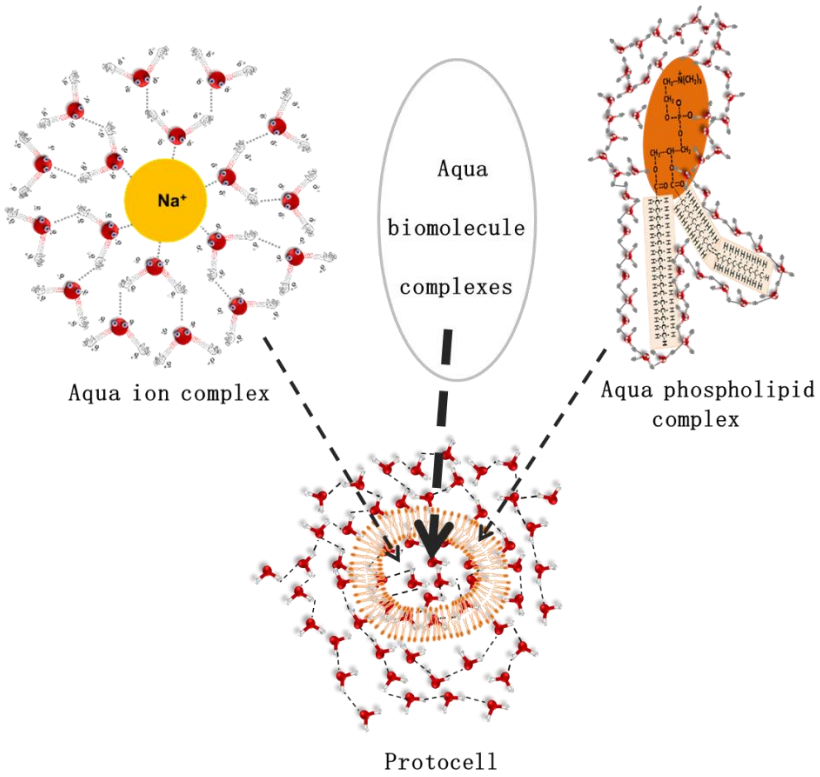

Fig. 2: The schematic depiction for the for the representation of the hydrated Na^+ and phospholipid molecule in H_2O networks, as well as the protocell formed with the aqua molecule complexes.

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3. H_2O molecule life cycles in the synthesis and the lysis of the biomolecules

H_2O molecules are not only perfect media, matrices and solvents of biomolecules, but also integral parts of biomolecular structural organizations, which are directly involved in the biosynthesis and the hydrolysis of the large biomolecules such as DNAs, RNAs, proteins and lipids (sFig. 1A-C). In the metabolism of carbohydrate [$C_m(H_2O)_n$], H_2O molecules are essential for the energy production from the beginning to the end in respiration chain, in which H_2O molecules are generated in the biosynthesis, and broken down in the biomolecule hydrolysis (Fig. 3).

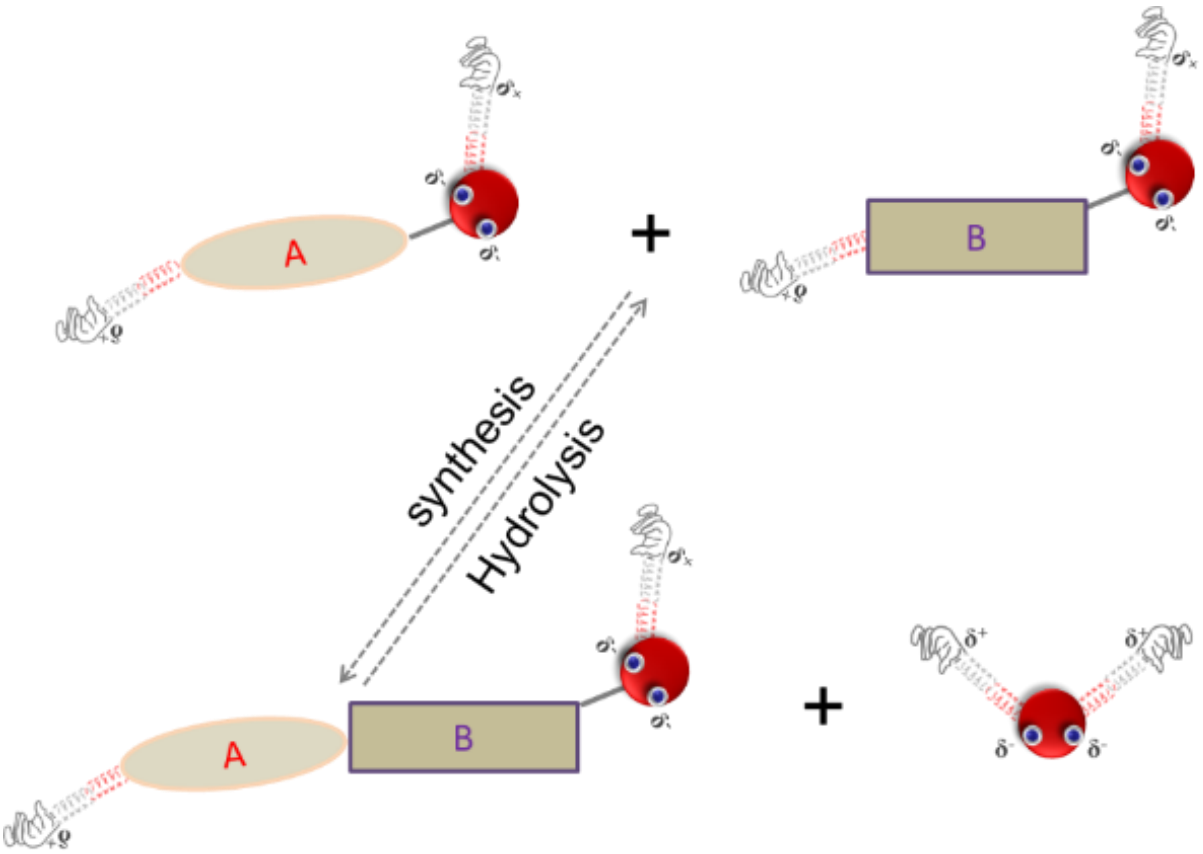

Fig. 3: The schematic depiction for the life cycle of H_2O molecules generated in the biosynthesis and broken down in the biomolecule hydrolysis.

Thus, H_2O molecules directly are the structural parts of organisms residing in the large biomolecules. In other words, the life and death of H_2O molecular cycles are synchronized with the synthesis and lysis of the biomolecules. Except involving in the synthesis and lysis of the biomolecules, H_2O molecules also play the central roles to the two fundamental metabolic reactions in organisms: photosynthesis and cellular respiration. In

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energy metabolism, one glucose molecule together with six oxygen molecules are spliced into six carbon dioxide and six H_2O molecules (sFig. 2)

Conversion of the energy and information in the aqua biomolecule complexes

No H_2O networks, no bioinformation. The thermodynamic bioinformation should be derived from the statistic calculations of the biomolecular properties including the numbers and disorders, symmetry and asymmetry or supersymmetry, especially hydrogen numbers which represent the thermodynamic characteristics of the ions and biomolecules. The dynamics of hydrogen bonds in H_2O networks corresponds to the fluctuations of free energy in the solution around the ions and biomolecules. The most biomolecules are embraced by H_2O networks varied with the hydrophilic and/or hydrophobic characteristics in the water solution.

1. **thermal radiation, conduction and convection**

The mechanism of the heat transfer in living system is the basis of the thermal radiation, conduction and convection. The allosteric conformational shifts of biomolecules are accompanied by the absorption and emission spectra of electromagnetic rays which could radiate other biomolecules including surrounding H_2O networks. Further, the radiation could continuously be transferred through the conduction of the O-H vibrations. However, the convection of heat energy in living system only occurs when existing a high energy resource such as ATP hydrolysis and heart beating in advance organisms.

2. **Bioinformation central dogma in the aqua biomolecule complexes**

In the universe, all systems encompass matter, energy and information three elements. Basically, energy drive matter to interact with matter under the guidance of information. In the living organism, free energy drives one biomolecule to interact with other molecules under the guidance of the bioinformation. In the hydrated biomolecules, the structural features, the thermodynamic characteristics, and the entropic variables of the H_2O molecule surrounded biomolecules (named as “aquamoleculosomes") could be identified by the conversion of the energy and information. Aquaphotomics studies show that the internal free energy of molecule and the information flow in the H_2O capsid may represent Onsager reciprocal-like relation (24-27). In aquamoleculomics, the concepts of aquaphotomics are extended. The hydrated molecules are considered as the intact units essentially representing the thermodynamic characteristics of the molecules in a living system. Since “aquamoleculosomes" hypothetically were designed as fundamental interaction units in living organism, it must contain certain levels of internal energy and quantitative amount of information which could determine them where to go and how to interact with each other. Here, we could design an ideal “aquamoleculosome", in which the hydrated molecule thermodynamically near equilibrium between the molecule and H_2O clusters, and the thermodynamic energy and information (Fig. 4).

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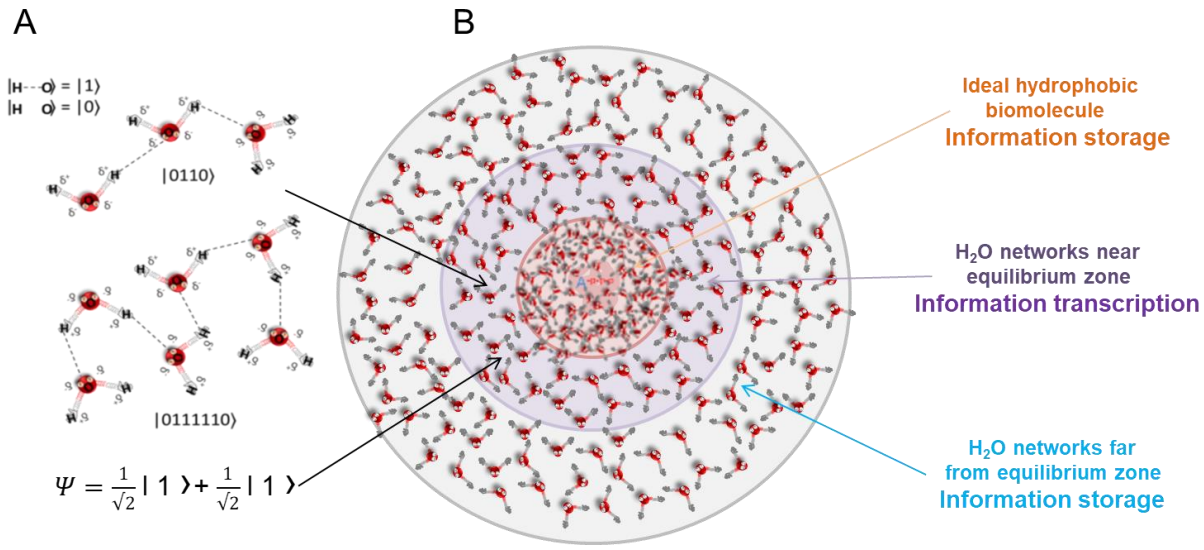

Fig. 4: The schematic depiction for the structure, energy and information of the hypothesized ideal “aquamoleculosome". The quantitation of information in the ideal “aquamoleculosome" is attached at the left side and information transfer so called bioinformatic center dogma is attached at the right side.

The information in H_2O networks could be quantitated with the basic unit of bit and quantum unit or qubit (Fig. 4) (28). For example, if the bit was defined as $|0\rangle$ representing the broken hydrogen bond and $|1\rangle$ representing the intact hydrogen bond. In the equilibrium zone of the given isolated “aquamoleculosome", the thermodynamic characteristics and free energy of the molecule is mimetically transferred into the around H_2O network via radiation and vibration. The energy changing in H_2O network is shown by the molecule symmetry, hydrogen bond formation and H_2O cluster mobility, eventually entropy in “aquamoleculosome". H_2O networks could possess different levels of energy and information, such as low free energy and order in ice, median free energy and disorder in liquid and high free energy and disorder in gas (sFig. 3). H_2O molecule has two O-H bonds with horizontal and vertical symmetric mirrors. When biomolecules, especially DNA/RNA, protein and their complexes, absorb or release free energy, the symmetries of H_2O molecules and disorder of H_2O networks in the surrounding zones will be consequentially changed with the conformation dynamics of “aquamoleculosomes". Through this mechanism, free energy changing in “aquamoleculosome" could be realtimely converted to information at the levels of both thermodynamics and quantum mechanics. Thus, when the structure and conformation of biomolecules change from primary to secondary, tertiary and quaternary, free energy and information of the molecules could thermodynamically be transferred into the surrounding H_2O networks. This information transfer process in the equilibrium zone is equally to RNA transcription using DNA as a template. The information conversion will be continuously transmitted

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from the equilibrium zone to the far from equilibrium zone, which is functionally equally to the translation process from RNA to protein in the biological center dogma. The conversion of the energy and information in “aquamoleculosome" could be called as bioinformatic central dogma or as the second central dogma of biology in living organism. In this bioinformatic central dogma, H_2O networks functionally monitor and calculate the conversion of the energy and the information in a manner of the quantum computation.

In the living organisms, the free energy and information of the equilibrium zones in the “aquamoleculosomes" will dramatically vary with the concentration of ATP molecules which could release heat energy into the H_2O networks when hydrolyzed. Usually, one ATP molecule could release about 75 KJ per mol of heat energy which could potentially break the hydrogen bonds of the surrounding H_2O molecules (sFig. 4). Since both proton flow and hydrogen bond dynamics possess the excellent quantum properties, it means that if there will be no quantum mechanics, there will be no bioinformation in life.

Aquamoleculomics in self-organization of the living organisms

No H_2O networks, no self-organizations in the living organisms. As mentioned above, all molecules in the aqueous solutions are hydrated through the mechanisms of hydrophobic and hydrophilic interaction. In the prototype theoretical model of the sand piling, the self-organization in the living organisms could supposedly be a process of the chemical bond formation triggered by the biological self-organized criticality (SOC) and 1/f noise, a biological self-organization triggering factor (SOTF) (29). The “aquamoleculosomes" function as the cornerstones in the self-organization of the living organisms. When the hieratical SOC receiving a corresponsive self-organization initiator SOTF, the local group of “aquamoleculosomes" could form the ordered structures via variety of chemical bonds. The self-organization in the living system are totally thermodynamic processes strictly controlled by the law of the entropic system. The self-organization should be the processes of the thermodynamic equilibrium of biological structure, energy and information from uncertain to relative certain the equation of the entropic system (Fig. 5) (30).

$$\underbrace{\left(\frac{\Delta X}{ln\,\Omega}\right)}_{\text{Structure}}\underbrace{\left(\frac{F_{\Delta X}}{Q}\right)}_{\text{Energy}} = \underbrace{\left(\frac{E_C}{S}\right)}_{\text{Information}} \frac{\text{Relative certain}}{\text{Uncertain}}$$

Fig. 5: The schematic depiction for the entropic system of a given “aquamoleculosome" in which contains the structure, energy and information.

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The self-organizations are the key phenomena in the living organisms, through which the organisms can make the progressions in replication, growth, differentiation, and especially in revolution from protocell to organism. The self-organizations in the organisms are equal to the original residents of H_2O networks to build its “houses", “cities" and “nations" with the later joiners of biomolecules, just like honeybees to build its honeycombs. The self-organization of the “aquamoleculosomes" often occur in the chemical oscillation and thermal convection which are mimicable to Belousov-Zhabotinsky (B-Z) chemical oscillation and/or Rayleigh-Bénard (RB) convection (31-34).

1. Aquamoleculomics in the origin and evolution of life

Protocell is believed the stepping-stone toward the origin of the living organisms, which is phospholipid bilayer membranes with the endogenous ordered “aquamoleculosomes". The late phases of protocells exhibit some life-related biological activities such as simple metabolisms and excitability pathways probably obtaining through the self-organizations of “aquamoleculosomes". It is well known that phospholipids could spontaneously form liposomes and microspheres in H_2O solutions through an entropic force mediated mechanism (Fig. 2). The mechanism why the H_2O networks can be the mother of life might be due to its physical and chemical properties of the H_2O molecules, specifically the approximate linear relationships between the free energy and structure of H_2O networks (e.g., the numbers of the hydrogen bonds) (sFig. 5). H_2O networks properties of the thermodynamic characteristics are well expressed in the phase of liquid water, in which there are dramatically correlated between the microstate and macrostates (such as the temperature, pressure etc.), free energy and entropic force, probably entropy and constant of the entropic systems (Fig. 5). Protocells are composed of various “aquamoleculosomes" which could be self-organized to large biomolecules such as DNAs/RNAs and proteins. Therefore, it is “aquamoleculosomes" which are the initial units of matter, energy and information, but not cell in the origin and evolution of the living organisms.

2. Hierarchical emergent properties in the self-organization processes

The key processes in the life evolution from protocell to cell are the emergences of the biological properties such as metabolism and reproduction. The emergent properties in the self-organization of the “aquamoleculosomes" are the serial consequences of the phenotypes (macrostates) transitions through the SOC formations (such as signal pathways, enzymes and receptors etc.) and the SOTF productions (such as activated enzymes, hormones/cytokines, ATP hydrolyses, biomolecule modifications and signalosome formations etc.). Based on the equation of the entropic system, the macrostates (the emergent phenotypes) are determined by the rest variables as following:

$$\Delta X = \left(\frac{E_C}{S}\right)\left(\frac{Q}{F\Delta x}\right) ln\Omega \qquad (1)$$

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For example, the aquanucleotides aquaadenine (A), aquathymine (T) and aquaguanine (G) are free “aquamoleculosomes" with their own entropic variables in the cytoplasm of the cells. Once they are conjugated by DNA polymerase as ATG in the synthesis of DNA molecules, AquaATG could function as an emergent biological property of the triplet start code of a gene and code for the amino acid methionine. And so forth, the various recombination of three aquanucleotides in A, T, C and G resulting in the variety of the potential genetic codes to code the different amino acids of protein molecules, which create the function domains including the biological active centers and interaction motifs. Besides the vertical hierarchies of the emergent phenotypes, there are also the horizontal hierarchies of the emergent phenotypes in the “aquamoleculosomes" formed through secondary bond coupling between aquaDNAs/RNAs and aquaproteins. The homo- and/or heterodimerizations of the biomolecules are absolutely required for some stages of emergent phenotypes such double stand DNA and homodimers of enzymes, and so on as complexes, subcellular organs, cells, organs or tissues, systems and entire organism body. It is the vertical and horizontal hierarchies of the emergent phenotypes or macrostates which constitute the biological structures of the phenotypic networks temporally and spatially carrying out the biological activities in the DNA-RNA-protein central dogma chain.

Except directly involving in the syntheses of DNA replication, RNA transcription and protein translation, H_2O networks might surveil all the stage transitions of hierarchical complexity in the DNA-RNA-protein axis of the biological central dogma. In the model of entropic systems biology, a cell might be composed of various hierarchical complexities of entropic systems including vertical chain of large molecules with the concatenated residues and horizontal coupling of different large molecules such as DNA-protein complexes, RNA-protein complexes and protein-protein complexes. In each level of entropic system, there are specific constitutional microstate (Ω) and macrostate (ΔX), free energy (Q), entropic force ($F_{\Delta X}$), entropy (S) and entropic system constant (E_C), which are surveilled, calculated and transmitted by the surrounding H_2O networks. The transitions between DNA replication and RNA transcription, RNA transcription and protein translation are respectively coordinated by the specific SOCs and SOTFs sequentially. In the life evolution, protocells could be maturated into cells or organs through the emergent hierarchical properties.

3. Entropic systems biology of aquamoleculomics in cell proliferation, differentiation, survival and death

Cell is an essential unit of the biological structure and function in advanced organisms, which is also a semi-open thermodynamic system or semi-open entropic system composed of variety of hierarchical “aquamoleculosomes". Therefore, the approach to study cell biology is not only putting the pieces of information about biomolecules, biomolecule complexes, signalosomes etc. together to build their interaction networks,

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but also digging out the systemic information and forces to fully understand the deep mechanism of the cell proliferation, differentiation, survival and death. It is well known that the cells from the same tissue of the body almost share the same DNA sequences and quantitative numbers of biomolecules. The question is why they not always share the same fate of the proliferation, differentiation, survival and death. To answer the question, the key step is to consider the cells in the tissue as the thermodynamic systems with the different entropic variables.

The cell proliferation, differentiation, survival and death might be considered as the phenotype transitions occurred in the processes of the self-organizations. Every cell in tissues bearing the systemic SOCs of the proliferation, differentiation, survival and death. When the cells met the specific SOTFs, the transitions could be triggered through the activations of the downstream signaling pathways of the specific SOC-SOTF systems. For example, while oocyte could correspond to sperm, resting tissue cells could correspond to the hormones and cytokines. After stimulated by the SOTFs, cells could replicate when the variables doubly increased, and differentiate when *S* decreased but ΔX and/or $F_{\Delta x}$ increased. All the cell behaviors including proliferation, differentiation, reprogramming, and migration are determined by the equation of the entropic system:

$$\left(\frac{\Delta X}{In\Omega}\right)\left(\frac{F_{\Delta x}}{Q}\right)\left(\frac{S}{E_C}\right)=1 \text{ (cell)} \qquad (2)$$

Thus, the cell fates of the proliferation, differentiation, survival and death might be the thermodynamic equilibrium processes of the entropic system variables. Inside the cells, the microstates (Ω) of statistical mechanics in the isolated “aquamoleculosome" are from both ions or biomolecules and H_2O molecules, which generally rely on the temperature and free energy,

$$\Omega = e^{\frac{Q}{kT}} \qquad (3)$$

The macrostates inside the cells include all the biological properties emerged in the self-organization processes of the aquamolecules and/or “aquamoleculosomes". The macrostate transitions are driven by the entropic forces ($F_{\Delta x}$) which come from the thermodynamic equilibrium processes of the variables such as (ΔX), entropy (*S*) and Temperature (*T*) or free energy (*Q*):

$$F_{\Delta x} = E_c \frac{ST}{\Delta X} == E_c \frac{Q}{\Delta X} \qquad (4)$$

the entropic forces ($F_{\Delta x}$) are the phenotypic forces deriving from the free energy and acting on the emergent phenomena (macrostates) resulting from the entire living organisms. Theoretically, all the biological interactions between the phenotype-phenotype are mediated by the entropic forces. Nonetheless, it is undoubted that all the

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phenotype transitions and the entropic variable equilibria could be accomplished without the environment of H_2O networks. Definitely, the properties of H_2O networks and aquamolecules or “aquamoleculosomes" are the prerequisite for the entropic variable thermodynamic equilibrium and the phenotype transition in the cell proliferation, differentiation, survival and death.

Aquamolecuomics of conscious minds

Water is not only the mother of life’s body, but also of the life’s soul. If there is no H_2O networks and thermodynamic mechanism, there would be no conscious minds in the living organisms. H_2O molecules are not just the media, matrices and solvents, but also the key parts of the biological structure and soul of the organisms. The conscious mind is a systemic macrostate phenotype of thermodynamic or entropic system and the emergent properties of an ability to detect and response to the information from both inside and outside of the living system. All thermodynamic systems possess their own “conscious minds" except the absolute temperature of the system is equal to zero.

1. **Thermodynamic mechanism of the conscious mind**

What is the conscious? What is the mind? The questions are not clear as the same as “what is life? ", which have no answers so far. Basically, life is an open system far from thermodynamic equilibrium. So, it is clear the answers for these questions could only be obtained from the thermodynamic mechanism.

The most forlornness in past decades of the genome and post-genome era is failed to deeply understand the essences of life and mechanisms of the conscious mind. The conscious mind might be one of the emergent systemic properties created in the living organisms through the entropic mechanisms (30). Indeed, all the subject movements are controlled by the weak or strong “consciousnesses", even in the stochastic electron transition (22), Brownian motion and Markov chain mechanism when they are processed under the thermodynamic environment (35-36). Because of the essence of mass, energy and information in the thermodynamic universe, a subject moves around within the three-dimensional space defined by the microstate-macrostate, free energy-entropic force and entropic system constant-entropy of an entropic system (Fig. 5). In the biological system, the “conscious minds" of the “aquamoleculosomes", “aquamoleculosome" complexes, subcellular organs, cells, organs and organisms are hierarchically accompanied by H_2O networks.

Water memory: a view from aquamoleculomics

It is believed that the concept of water memory was mis-manipulated experimentally and theoretically for a long time (37-42). It is true that ancient philosophies of animism believed all creatures including objects and places in the universe possess their spiritual minds. It

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might be the “conscious mind" to allow H_2O molecules freely flying in the gas phase, strictly assembling various snowflakes in ice phase and flowing flexibility in liquid phase. However, once become the selfless mother of life, H_2O molecules completely contribute the “conscious minds" to the “adopted children" (biomolecules) in a mirror-inverted manner. In other words, H_2O networks think what the biomolecules thought and remember what the biomolecules remembered. However, it is impossible for H_2O networks to form and keep the conscious minds by themselves alone neither in the oceans nor in our bodies since the lifetime of a hydrogen bond in water is between 10^{-12}-10^{-13} second (39).

From the aspect of aquamoleculomics, it is not so hard to understand the unique roles of H_2O networks in memory. In the entropic system of “aquamoleculosome", the thermodynamic characteristics fully rely on the biomolecule which of the energy and information were merely reflected in surrounding H_2O networks. In the neural networks of brain, the order and symmetry of H_2O molecules, and the numbers of H_2O networks are entirely determined by the conformation and free energy of the phospholipid molecules (Fig. 6). The information transcribed from the molecules and neural networks in H_2O networks could vary with the nervous morphologies and the potential pulses of the dendrite fibers. As in other parts of the human body, water occupies 85% weights in the brain tissues. In other words, all neurons and neural networks are soaked in H_2O networks (Fig. 6).

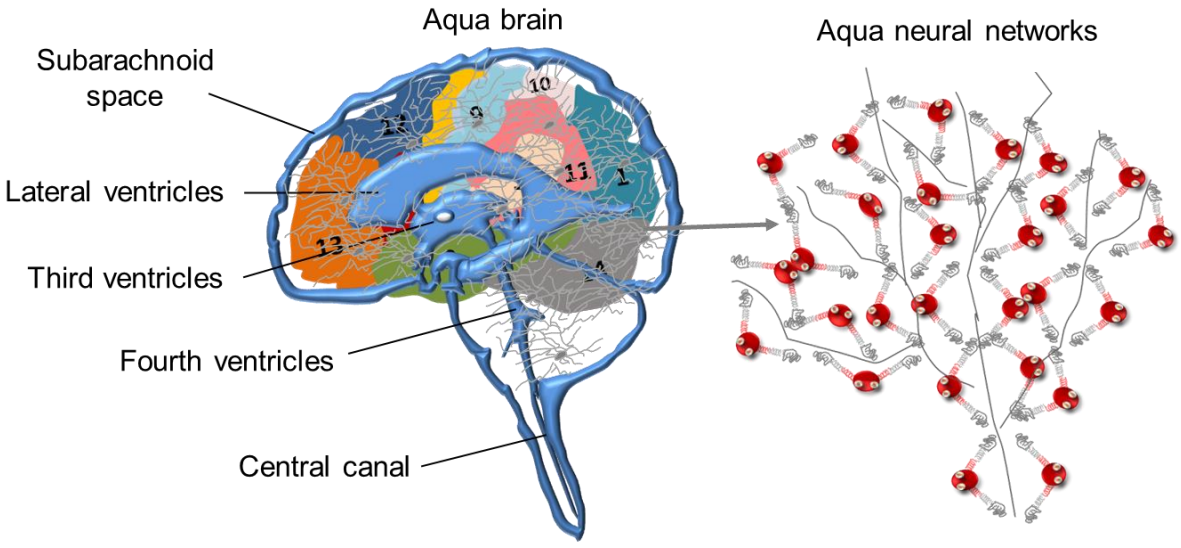

Fig. 6: The schematic depiction for the scenarios of brain and neural networks in H_2O networks.

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In fact, the brain contains much more water than any other organs in adult human body. Beside in the cells and tissues, especially in ventricles there are additional 100 to 150 ml of CSF, 99% of which is water cycling inside the head. The neural networks in brain might vertically and horizontally provide the hierarchical emergent properties to monitor, calculate, store, passage and integrate the most complicated information when thinking.

Discussion

Water molecules make up 70% to 98% components in the various organisms. The properties of H_2O molecules are the keys to be as the mother of life, perhaps the only candidate to be as the motherhood of life in the universe. In the living systems, all biomolecules are surrounded by the H_2O networks varying with their hydrophilic and hydrophobic properties. The properties of the interactions between H_2O molecules and biomolecules in aqueous solutions have been well studied by the approach called aquaphotomics for decades (24-25). There is also commercial bio-companies studying moleculomics (Moleculomics Inc.). In the present article, we promote a novel concept of aquamoleculomics in which aquaphotomics and moleculomics are combined to interpret the biological processes in the systems biology of entropic systems.

If it was true that a unicellular organism might be derived from a protocell, H_2O molecules must be primitive biomolecules in the living organism. During the processes of life revolution, the successors of other biomolecules gradually dominate the emergences of the biological properties which attract innumerable biologists to contribute to the studies of explorations. However, the significances of the primitive biomolecules, H_2O molecules in life are obviously underestimated or even ignored for so long. For example, during the syntheses of large biomolecules such as DNAs, RNAs and proteins, H_2O molecules are also produced at each residual bond formation of the molecular chain extensions (sFig. 1A-C). When the organisms replicate, the most replicated are H_2O molecules which occupy 98% components in jellyfishes. In metabolism, H_2O molecules also play the key roles. More importantly, H_2O networks play the fundamental roles in the conversion of energy and information, and in calculation of the thermodynamic properties. Seriously, it could be arguable that the organisms are dominated by biomolecules such as DNAs, RNAs and proteins etc., or mainly by H_2O networks. Apparently, the frozen organisms are no more animals because H_2O networks lost all functions inside the bodies. Tardigrade (water bear) accounts for more than 80% of water molecules in its body. When Tardigrade shed 90% of its water molecules in a harsh desert environment, it will curl up into a bucket in a pseudo-death state even there are all the biological structural molecules including about 10% of bound H_2O molecules. But once exposed to proper H_2O environments, Tardigrade can restore its normal lifestyle (sFig. 6) (43). From these phenomena, we might promote the following questions: What is the essence of life? Who are the real host molecules, H_2O molecules or other biomolecules? If H_2O molecules were the real host molecules, could it be that the biomolecule complexes, subcellular organs,

cells, organs and the entire body are just the type of the constructions for the residential places of H_2O molecules? Could H_2O networks be able to build the biological structures with the resolved molecules in the solution just like the honeycomb honeybee made?

In summary, it could be concluded that if there were no H_2O molecules and no thermodynamic mechanism, there would be no life and no biology at all. In past decades, modern biology was developed from anatomy, cell biology, molecular biology and systems biology relatively to be independent on thermodynamic mechanism and the properties of aqueous solutions. It is perhaps one of the pitfalls, which leads the weak power for the current biology to unveil the mysteries of the mechanisms in the conscious mind and psychiatry activities. It is about time to realize that it is inevitable to include the thermodynamic mechanism of H_2O networks when the biologists are establishing the consummate systems biology. The ideal systems biology of the living organisms might be better designed as a quantum computer, in which hardware of biomolecules constitutes the basic structures, and software of H_2O networks masters the energy conversions and information processes including the monitors, computations and transfers. To be mentioned, thermodynamic mechanism of the living organisms only could be interpreted by the approach of the entropic system, in which the bioinformation functions as the guider to control the continuous ongoing steps of the body. Meanwhile, the entropic systems biology might also provide us the wider and deeper visions in the developing mechanisms of the diseases including cancer and dementia, even aging.

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