The H-bond breakdown switch allows DNA and protein transitions in the brain to control the dynamics of hormonal communication and learning vocalization

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Abstract

The choroid plexus epithelium (CPE) generates cerebrospinal fluid (CSF) in a mutual exclusive vectorial kinetic according to a potential of hydrophilic-plasma 0mV -60mV to hydrophobic-CSF +4mV. Astrocytes are cells with actin filaments for pulsatile propulsion in the cell's skeleton, bi-directional transport of ions gradient Na^+, which impulses the CSF flux into the lumen along a glial network. Luminal K^+ is required for sustained CSF secretion. At ventricular side, the Na^+/K^+-ATPase releases the Na^+. Quantum mechanics microtubules nano scale (10^{-9}m) flow a parallel transportation from the exterior to the nuclei of glucose, nascent Mg^{2+}, O_2, etc., and antiparallel of dimers. The microtubule diameter allows a very small number of molecules in a minimal volume to reach a saturation state for enzyme activity. An increasing in the number of random collisions allows to concatenate Na^+/K^+ translocation into nano space at minimal capacitance to operate at maximal voltage. Myelination discontinuity at the Ranvier nodes allows open systems exchanges with CSF to re-supply the optimal ion concentration to maintain rapid transmission of the propagation of the action potential. The Doppler shift could tune in with the spin-flip of electrons of a 21 cm line of hydrogen, operating as an antenna for the neuronal membrane action potential state of firing for vectorial networking. Thus, synchronizing the electric potential by a sequence of interneuronal crosstalk could avoid electromagnetic neuronal noises. At the nerve terminal, neurotransmitters are present within 35-50 nm synaptic vesicles that release neurotransmitters that dock and fuse at the base of specialized 10–15 nm cup-shaped lipoproteins. These porosomes range from 15 nm in neurons, astrocytes to 100–180 nm in endocrine and exocrine cells. In striatal neurons adenylyl cyclase (AC) coupled via 7TM receptors via stimulatory or inhibitory receptors (Rs and

Ri) on G protein phosphorylation. A dopamine-(DA)-dependent cAMP/PKA interactions with acetylcholine and adenosine signals for DA transients to carry reward-related signals in learning reinforcement. The enthalpies of AC-H-bonds breakdown of intermediates coordinated by Mg^{2+} and bending and sliding when calmodulin release of Ca^{2+} to coordinative into hydrophobic box, and release of dimers in the up-hill thermodynamics cycling AMP into cAMP, creating molecular transitions capable to participate in meaningful encoding signals coordinative stages. The Mg-cAMP response element binding (CREB) protein by insertion for DNA H-bond breakdown unzipping into three strands and transcription cycle turnover by coupling to H-bond donor water cluster.

The membrane potential between the external hydrophilic face vs internal hydrophobic environment

The continuous flow of dimers ($H_2O\sim OH_2$) captures heat by increasing the oscillatory kinetic state of the pairing effect. The vapor by reaching the surface of a mirror spontaneously returns to the liquid state, usually used to detect life. State of water $(H_2O)_{n=3.4}$ allows maintaining polarity and surrounds metallic ions in soluble state vs with hidden polarity, which results $(H_2O)_{n=3.4}$ in could not transit across the double layered membrane to the hydrophobic environment and crossing through specific gates.

Thus, water will require specific channels with modulatory control for opening and closing states by the membrane structure functional to support ion translocation.

Cerebrospinal fluid (CSF) (containing entangled pairs) on the astrocytes, during circulation as a liquid transitional state from liquid to vapor could be characterized by supporting an excess of the kinetic energy (vibrational, rotational and translational), but also the pairs allows to maintain the liquid state (increased solubility of ions in CSF into hydrophobic regions like the microtubules, containing a volume preventing acquisition of the volatile state).

The hidden polarity confers the possibility to a pairing state $H_2O\sim OH_2$ to modify the K^+, Na^+ and Mg^{2+} and hydrated structures of ions. The differential flow senses between both ions: Na^+ vs K^+, on the membrane, allow oscillatory potentials.

The density change of entangled water modifies the solvation state of hydrophilic molecules like metal ions (Mg^{2+}, Na^+, K^+). Thus, during transport across the membrane could maintain the turnover of membrane potentials.

In this scheme the hydrophilic outside of membrane vs the hydrophobic inside could configure a vectorial sense to water, as a carrier of entropy that is released out.
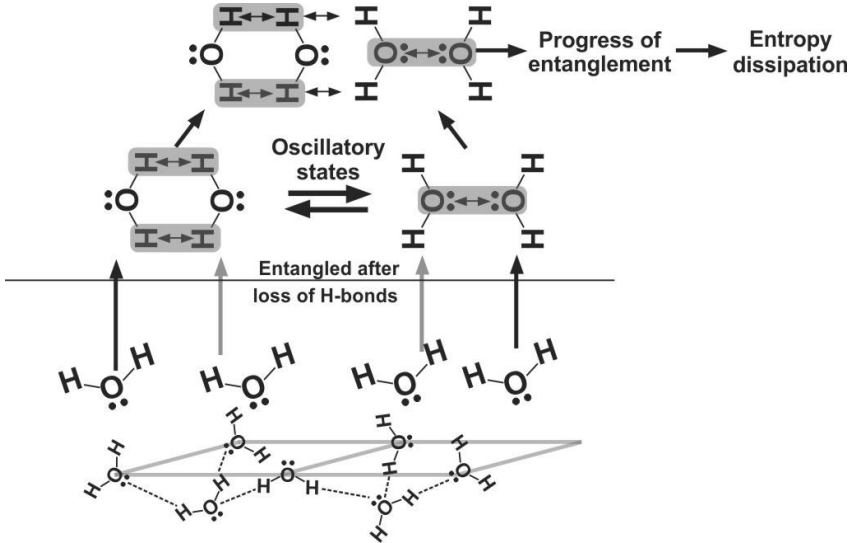

Figure 1: Molecules coherence in resonance *capable by entanglement to contain an excess of energy in water dimers that external pressure maintains in CSF in liquid state. Circulate in astrocyte system to reach quantum decoherence as vapor at 36.6°C, when reaching the oral cavity. Directional entanglement could be calculated to progress at about a rate of molecules per millisecond, for the dissipative function of 500 ml CSF per day.*

The CSF flow progress of H-bond depleted of entangled H_2O molecules involves a large number of molecules, but far from reaching the number that can be expressed by a molarity parameter. A quantum scale referrers to scales where quantum mechanical effects become important, allowing numbers well below the number involves in chemistry using Avogadro numbers involved at the nano-molar concentration.

Single water molecules could not have a liquid state at $(H_2O)_{n=0}$ because lacks H-bonds [1], suggesting the emergence of other structures in

3

the interior of the cell.
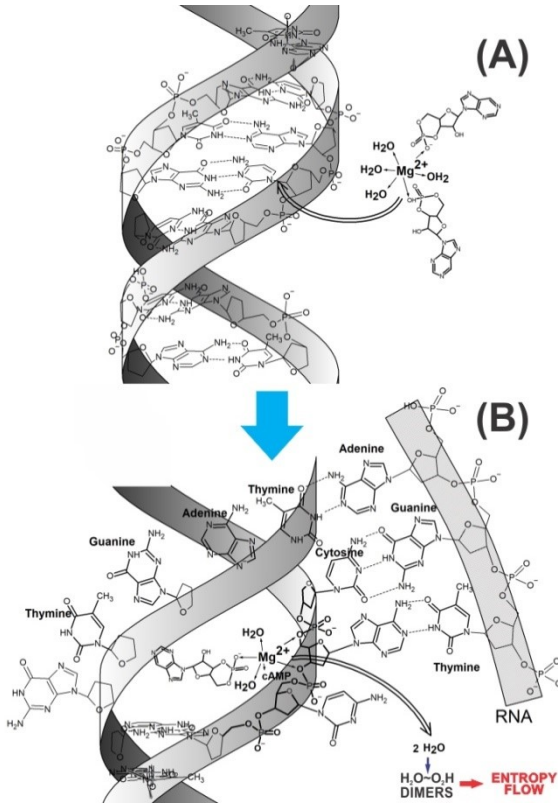
H-bonding between water molecules and DNA base pairs

Figure 2: **(A) *DNA-Mg-cAMP-RNA transcription.*** *It is proposed a function of zipper to cyclic adenosine monophosphate (cAMP). cAMP by binding to Mg^{2+} ion interacts with the negatively charged phosphate groups of a segment of duplex DNA, wherein the base sequence of the two strands acquires a rotational symmetry* [2].*An inducible gene is a gene whose expression is either responsive to environmental change or dependent on the position in the cell cycle. Accordingly could be present in the mechanism of transcriptional activation function called CREB (cAMP response element-binding)* [3] [4]. **(B)** *It is proposed a function to Mg-cAMP a role of energy activation contribution by the H-bonds breakdown coupled to an enthalpy contribution to the switch-on-off of the system and coupled to the release of water dimers at dissipative entropy into microtubules. Neuroexcitation involves isosmolar K^+ release by neurons and uptake of K^+ and facilitates the extracellular space (ECS) volume drives astrocyte*

K+ uptake.

The flow from the brain into a pattern of aquaporin (AQP4) expression into and out of the brain at the borders facilitates the repositioning of new H-bonds by a 55M of water cluster mass action, restoring the DNA to a close steady state. Therefore switch on/off is inactive to active state vectorial transition turnover. The process is vectorial because the genes manifest mutual exclusion preventing equilibrium.

A turnover requires coupling with the H-bond donor function of a water cluster because reversibility is prevented by the generation of water dimers (a dissipative state of entropy) because microtubules allow dimers to enter into the glial system connected to the oral cavity.

Water dimers entanglement has resonance effects that participate in a structure function system for thermic maintenance from muscles (temblor affecting hypothermia), brain pulsations, etc. In perspective the rapid loss of the corporal temperature during death lead to speculations about the meaning of the effect, that at the time of death, there is an instant decrease in body weight of 26g.

Entangled by the complementary pairing between the hydrogen atoms of each water-water pair of molecules as shown: ($H_2O \sim OH_2$), results in repulsion between the atoms of oxygen. Similarly, in the complementary oscillatory state of the pair, entanglement is shown between both oxygen atoms: $H_2O \sim OH_2$, and distancing between the H atoms.

The molecular entanglement surges from the tendency to relate both vibrational configurations by not breaking the water identity. Hence, it is sustained in the first configuration by each H atom participating in a vibrational state with the other opposite electron orbital to reach an oscillatory state. Thus, generates a complementary tendency to have a tendency to configure some but insufficient stability at the two electrons, resembling the orbital connections of molecular hydrogen.

The participation of only two electrons out of the six in each oxygen share entanglement by its partial orbital attraction for pairing to only approach a stable state. Thus, lacking a complementary mutual sharing of orbitals it could stabilize a valence chemical bond. In this case both oxygen atoms could acquire a molecular electrostatic attraction due to

each atom attraction could surge from unstable tendency to relate the orbitals into a larger space.

These allows for electrostatic interactions of variable conformation $H_2O \sim OH_2$ between two oxygens atoms in resonance and alternative states increasing harmonic interaction between H atoms in a mutual exclusion effect.

The oscillatory attraction state by the loss of oxygen entanglement present in the hybrid transition vs the gain of entanglement for the H attraction. Hence, provide transition states between two atoms symmetries, allowing the alternative disruption of the strength tendency of mutual attraction because are in an oscillatory state, coupled to molecular resonance.

These instable configurations of two singles molecules of water could be entangled when interact, or share spatial proximity in a way such that the quantum state of each molecule of the group cannot be described independently of the state of the others. Entanglement has been shown between the rotational states of a 40CaH+ molecular ion and the internal states of a 40CaH+ atomic ion. We extend methods used in quantum logic spectroscopy for pure-state initialization, laser manipulation and state readout of the molecular ion [5].

Substantial interdisciplinary attention due to an intimate entanglement of spin and orbital degrees of freedom which may give rise to a novel spin-orbital insulating behavior and exotic quantum spin liquid phases [6].

Water in molecular pair entanglement allows the hidden of the polarity affinity for ions, etc., which characterizes water cluster configurations for hydration shells of ions. Hence, could allow differential properties in between the hydrophilic phase and the hydrophobic one. This is so because the hidden polarity entanglement allows unidirectional way to cross from the outside of the membrane to its inside.

Decomposition of the pairing yields a non-accumulative state (or dissipative function) allowing non-reversibility to the system thermodynamics, because the dissipative effect by the system mechanism of loss of mass action. This one involves H-bond breakdown at the DNA and protein structures turnover from their activated state to the restoring of the initial condition by the H-bond donor role of 55.5M of water cluster.

The overwhelming mass action of the water clusters pool lead to rather insignificant, decreases in the original mass action potential, established at the coupling state role of biochemical pathways, needed to establish irreversibility.

The role of nano scale on microtubules

The function of coordinative for neuronal contacts configuring a network, a random emission at the microtubule level of the antenna for propagation of the off vs on emergence wavelength signal 21cm line of H.

Thus, allows configuring an algorithm sequencing the time for specific membrane potential activation at the state of the firing propagation connecting neuronal network.

The propagation of a redshift signal allows retraction of dendrites to non-firing positions between the neurons component of the network. The propagation of a blueshift signal allows inter-neuronal firing over distant brain areas. Hence, configures a sequence of events between activated enzyme molecules able to propagate the action potential.
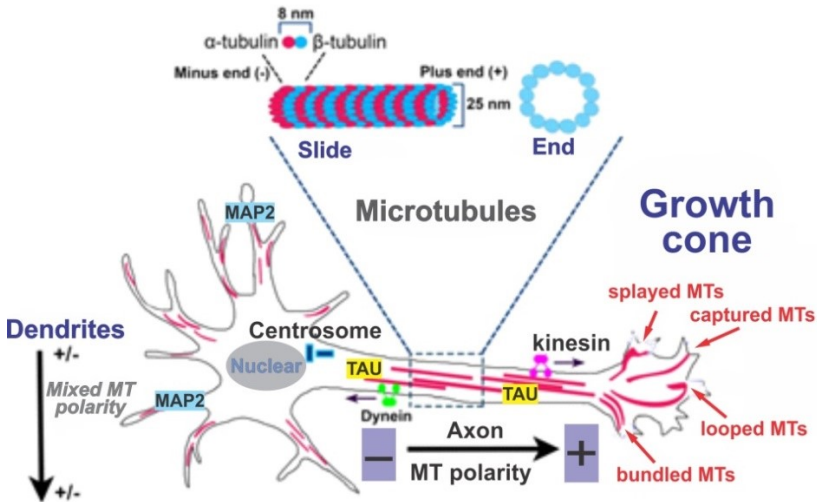

Figure 3: microtubule (MT) neuronal compartments form stable, polarized bundles with uniform polarity orientation. *These ones manifest from a plus to a minus end polarity by emerging away from the cell body. In dendrites, MTs are organized in antiparallel bundles oriented with their plus ends pointing away or toward the soma. The growth cone distributions: splayed, captured at the cortical matrix, looped, and bundled.*

The microtubules are constructed by tubulin molecules magnetized for tunneling function of preserving the dimers structure, by the *quantum* interaction of the electrons at the up and down-spin torque function as magnetic oscillators. The quantum function as emission antenna of radio microwaves could be to synchronize the electric potential. Hence, a fraction of the total photon emitted into the brain is transfer through axon/microtubule. Thus, λ-wavelength patterns allow photon entanglement of quantum nano-time (10^{-9}s) at axon/microtubule, operating in neuronal circuits coordinating transmembrane signal responses, integrating their firing time to organize crosstalk, avoiding electromagnetic neuronal noises.

Synchronization

The formulation for conversion of a random space-time distribution to reach specific neurons has been solved by algorithm implementing artificial intelligence. The capability to function at millions times the searching event is an iterative saturation function, linking to eventually produce the coincidence of causal-effect by synchronization with molecular and ions transport at the microtubules.

Interneuronal firing became a certainty as a function of a repetitive number that eventually convert a random or improbable event, iteratively in a possible event. The indeterminism of quantum mechanics applied by the physics of biology produce a deterministic physiology. Thus, allowing its connection to molecular biology and the organic chemistry of life.

Differentiable affinities between the bipolar state of water with the hydrophilic side of membranes and that of entangled pairs with the hydrophobic side regions allows coupling at the junction between neurons releasing the cerebrospinal fluid (CSF) containing pairs. Hence, the greater diffusion capability into the hydrophobic of the pair for the astrocytes environment, allows rapid circulation.

The CSF expended H-bond water is in liquid state at 36.6°C, allowing a transition state in which the internal (intrinsic) structure of the water molecule itself, forming pairs, allow absorption of kinetic energy: rotation, vibration and translation.

This allows an aggregate state, until the space allows the translational energy that characterizes the vapor state. In physics the phenomenon is

described as a transition state of second order that became independent of the microscopic structure. In a laboratory is well known that the distilled and condensed water is highly active (energy excess on the individual molecules) and has to be stationed for 24hs, before the fitting between water molecules allows to reach normalized state as: $(H_2O)_{n=3.4}$.

Approaching a mirror to the mouth, a condensation test for vital signs, allows detection of a 5% vapor present in breath, to become evident. The thermodynamics turnover for an out of the system release of waste water, maintains a dissipative state characteristic of open systems. Thus, prevents a reversal of the metabolic flow and therefore conserve the energy capable to support the hydration shell turnover of ions and proteins, which maintains the cell membrane action potential.

Daily turnover of cerebrospinal fluid (CSF)

The system endergonic consumption to produce the exergonic reaction of vapor has an equivalent of ATP-enthalpy consumption in the decomposition of the state of water: $ATP+(H_2O)_{n=3.4} \rightarrow AMP+PPi+3.4$ $(H_2O)_{n=0}$ isolated molecules of vapor, $\Delta G=-45.6$ kJ/mol (-10.9 kcal/mol), equivalent to 28 mol of substrate MgATP.

Thermodynamically a donor solvation media, like cerebrospinal fluid (CSF) could be calculated on the bases of a turnover value of 500ml CSF, which could be expressed as 27.77 H_2O mol, considering an average value of 3.4 mol H-bonds and -5kcal per H-bond mol breakdown (O-H--:O).

$$\text{Energy}=27.77 mol\ H_2O \frac{3.4 mol\ H-bond}{1 mol\ H_2O} \frac{-5kcal}{mol\ H-bond} = -472 kcal$$

Flow of entangled water molecules per millisecond calculated from all daily the entanglement processes carried by 500ml CSF.

$$\frac{27.77 mol\ H_2O}{day} = \frac{27.77 \times 6.02 \times 10^{23}\ H_2O}{24hs} = 3.2 \times 10^{26} \frac{H_2O\ pairs}{millisecond}$$

Outside the body exhausted H-bond water regenerates by cooling into cluster water because is a favorable thermodynamic process.

Brain thermogenesis

The turnover per day of 500ml cerebrospinal fluid (CSF) from liquid at 36.6℃ to vapor could have involve an increase of 60℃, if were not prevented by entanglement.

The temperature increases 1℃ by 1kcal/ml are calculated to 3000kcal to show that it is outside the physiological parameter. This value divided by the standard assigned to ATP breakdown: 7.5kcal. The brain in glucose terms consumes about 25% of total body energy.

Thermogenesis by H-bonds loss is equivalent to 63 mol of ATP. Therefore, the release as vapor does not occur at 100℃, but at body temperature, therefore, has not implicated jump of temperature.

The lab experience with water distillation and vapor cooling shows a liquid state, which requires to be stationed for 24hs to release the excess kinetic energy. Therefore, decoherence is a very slow process. In nature decoherence process couples with the day to night cycle, which release of vapor to air, coupled for decoherence changes by temperature and pressure to produce rain.

The epithelial membranes with an outside and inside confers the properties of open systems, because the depleted H-bonds from water in CSF does not have the tendency to aggregate, but by entering in the spongy tissue of the palate it rapidly became separated in individual molecules and evaporate.

Thus, exhaled air in adults of about 6 liters per minute has a 5% vapor contribution from the VNO [7] [8] conductance process of depleted H-bonds from water in CSF. This process operates for entropy dissipation.

The thermodynamics coupling of the water-protein structure modulated by the turnover of H-bond breakdown

In linear systems entropy production is the possibility of cosmic evolution to support self-organization in other regimes of local dynamics [9] [10] [11] [12].

Microscopic reversibility of dynamics implies that the matrix for events is symmetric [13] and generates a single Ea peak for either the forward or reverse sense of the reactions.

Prigogine's premise: "Dynamics and thermodynamics limit each other" [14] indicates that these processes could be differentiated. The forms of the enzyme within membrane allow transition complexes which would be maintained, under asymmetric phase angles, between conformational structure dynamics for coupling and thermodynamic equilibrium and kinetics [15].

The organization of molecules within defined membrane structures imposes physicochemical constraints, which are not especially subject to a random distribution of Ea. By the contrary in a lipidenzyme membrane [16] the inter- and intra-molecular kinetic energy could be represented by coupling between several peaks driving specific transitions states, along the vectorial progress of an energy transduction process [17].

Intra-molecular asymmetry could be confers by water dynamics capacity to differentiate a hydrophilic space, or region from a hydrophobic one. This allows that the hydration shell of proteins and ions could confer turnover to water architectures when couple with the dissipative potentials of water cluster $(H_2O)n$. Hence, the H-bonds formed by a $-\Delta G$ of restructuring hydration shells enhances the energy requirements to reach transition state.

MUTUAL EXCLUSION

Deoxygenation
O_2 and Mg^{2+} +60H_2O
lower pH

Oxygenation
pO_2 in Lungs
hydration by 60H_2O

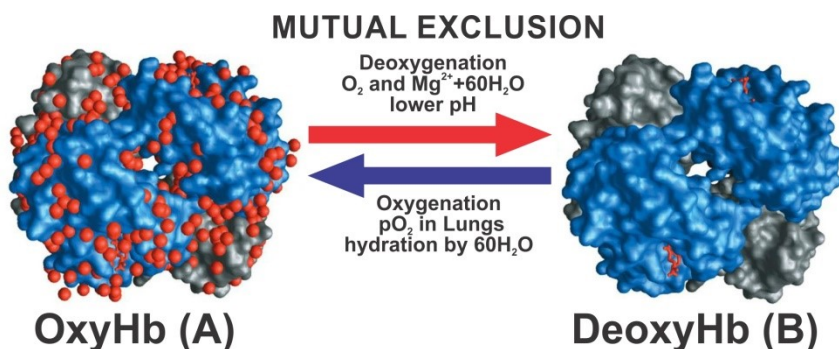**OxyHb (A)**   **DeoxyHb (B)**

Figure 4: Mutual exclusion prevents the two forms of Hb to coexist at the same time for that the loss of 60 molecules of water is a vectorial transition from oxyHb to deoxyHb in the circulatory system that adds an energy barrier the location requirement. R-residues of Hb participate to form by mutual exclusion a two chelating sites for $2Mg^{2+}$ in oxyHb. Transition from oxyHb associated to 60 molecules of waters (A) to a dehydrated loss of water molecules in deoxyHb (B) associated to binding site in deoxyHb for 2,3-DPG, increasing and decreasing affinity for O_2, respectively [18].

The four Heme groups of Hb show a 2-fold symmetric axis [19] [20] [21] leading to the idea that any one Heme site, would interact equally over the 24Å inter Heme to Heme distances for cooperative O_2-ligation [22].

A homotropic system (crystals) was used by Perutz to show that the breaking of salt-links could trigger a one-way T to R change of Hb. The implicated on the alkaline Bohr's effect were the β_1 and β_2 His 146 becoming protonated to salt-link β_1 and β_2 Asp 94.

The binding of O_2 (as well as allosteric effectors, such as protons and organic phosphates) altered the relative stabilities of the T (low O_2 affinity) and R (high O_2 affinity). The hindrance by the salt-bridges in the T form lead proximal histidine to restrain the movement of the iron atom within the porphyrin plane required for oxygen binding to Hemes. At the beta-Hemes, the distal valine and histidine block the oxygen-combining site in the T-structure. Oxygenations rupture of salt-bridges in T allowing a pKa decrease in oxyHb [23].

The amphoteric response of histidine in deoxy to oxy allows the imidazole side chains to acquire a negative charge N and by $C\alpha$ -rotation to attract divalent metals to form chelating site at the $\beta_2\alpha_1$ and the $\beta_1\alpha_2$ interface [24]. Pulling out both β His 143 from conforming the central cavity releases 2,3-DPG. Thus, allowing to postulate that Mg^{2+} and Zn^{2+} compete with 2,3-DPG in a mutually exclusive manner [25].

Hb structure shows hydrophobic regions at $\beta_1\alpha_1$ and $\beta_2\alpha_2$ intradimer interfaces and hydrophilic polar R-groups at the $\beta_2\alpha_1$ and $\beta_1\alpha_2$ interfaces [26].

During oxygenation the hydrophilic asymmetry of Hb allows a fully hydrated Mg^{2+}/Zn^{2+} ($[Mg(H_2O)_6](H_2O)_{12}$) to enter first into the $\beta2\alpha1$ interface for specific sequential chelation of R-groups. The process leads the hydrated metal to an exergonic binding with Hb compensated by the endergonic loss of most of the divalent metal hydration shell [27].

The level of glucose at the red cell could act as an integrated sensor of the brain needs, because in the Rapapport-Luebering scheme the 2,3-DPG phosphormutase, which is inhibited by low pH, becomes maximally activated at pH=7.4. Since cerebrospinal fluid (CSF) is slightly alkaline could signal the red cell to increase the erythrocyte level of 2,3-DPG [28] to form 2,3-DPG-deoxyHb-$(H_2O)_T$ and release of O_2 to match glucose uptake and maintain aerobic glycolysis in brain generating the ATP required to operate Na^+-pump [29]. OxyHb in transition to deoxy releases

a $[Mg(H_2O)inc]^{2+}$ in CSF, which by binding proteins to the membrane could protect the tendency of ATP^{4-} to subtract Mg^{2+} from the protein lipid structure of neuron.

CSF is produced in clusters at the thin walled capillaries called chorideplexes that line the walls of the ventricles. Its high water turnover maintains allostasis of cerebral water with cluster sizes of about 12 molecules [30].

Temperature is a colligative measurement and the endergonic process of H-bond breaking in $(H_2O)n$ is incomplete in the $(H_2O)n*$ state. The reduction in the contained number of water in the cluster by decreasing its size may ease cell hydration. The increase in the internal vibrational state of molecules in an incomplete H-bonded network, could contribute within CSF, to maintain its homeostatic temperature.

The turnover process breaks the electrical bonding of H_2O molecules in $(H_2O)n$ from n=12-14 to about n=5-6 [31]. Thus, $(H2O)n*$ by decreasing the number of H-bonds within the cluster traps a heat-attenuated carrier of the increment in entropy, to be released-out of the reaction boundary. However, outside the body in contact with lower temperature, the dipole tendency of H_2O [32] slowly but spontaneously will allows reconstitution of $(H_2O)n$ state.

The steady state of available cluster rich water demands a 3.7 times of the 160ml volume of CSF/24hs about 600ml of CSF, matching the brain requirement of 20% of total body metabolic activity.

Sliding of the dimer $\beta_1\alpha_1$ versus $\beta_2\alpha_2$ displaces α Pro 44 α_1 increases the size of the central cavity allowing binding of 2,3-DPG, a characteristic of the T form.

Proline is prevented from turning around its Cα because the single N in the cyclic structure, is bound to two alkyl groups in $-60°$ dihedral angle φ (phi, involving the backbone atoms C'-N-Cα-C'), which unstrained allows conformational rigidity [33].

Helping to dissolve and eliminate waste and toxins. Integrated within an open system, water enters with a larger cluster size than the one eliminated.

The intradimer interfaces at $\alpha_1\beta_1$ and $\alpha_2\beta_2$ are hydrophobic. Hydrophilic interface $\beta_2\alpha_1$ do not show its symmetric interface $\beta_1\alpha_2$. Both contain Polar Regions and water with tendency to partially dissociate but initially $\beta_2\alpha_1$ is the more water reactive [34].

The α-chain down-sliding vs the β-chain. The $β_2$ His 97 tends to became adjacent in the position between Thr 38 and Thr 41 of $α_1$ chain, but $α_1$ Pro 44 shift out of contact with β chain. The fully hydrated $[Mg(H_2O)_6](H_2O)_{12}$ can move inside the hydrophilic region [35].

In deoxyHb the imidazole ring of histidines could bear two NH bonds equal distributed by resonance structures in between both N. Hence, at the central cavity the negative charged 2,3-DPG binds by interaction with positive charged $β_2$ and $β_1$ His 143.

OxyHb pKa=6 releases H^+ from histidines and breaks the salt-link between $β_2$ His 146 with $β_2$ Asp 94. The negative charged residues of $β_2$ Cys 93 and $β_2$ Asp 94 are attractants to the fully hydrated $[Mg(H_2O)_6](H_2O)_{12}$.

An initial Mg^{2+} bidentate by coordination with $β_2$ Cys 93 and $β_2$ Asp 94 could be expanded to tetradentate by Cα-rotation of $β_2$ His 92 shifting away from its hindrance position, to allow O_2 to become a ligand at the $β_2$ Heme. Also $β_2$ His 143 by shifting from its position could initiating shrinkage of the central cavity and release of 2,3-DPG.

The coupling of an H-bond increment at the hydration shell of proteins and ions decreases entropy in the system itself, but increases it at the level of water cluster.

Vascular Doppler ultrasound

The Doppler ultrasound is a non-invasive diagnostic test used to determine the amount of blood flow moving through blood vessels by aiming high-frequency sound waves (ultrasound) at red blood cells and then receiving them back via the traducer/probe to measure for strength and frequency. There is an auditory and visual display to record the sounds and display pictures. Most ultrasound machines today have Doppler capabilities to measure blood flow and to evaluate veins and arteries in the organs that the ultrasound is visualizing. This is called Duplex ultrasound. Color images can be superimposed on the vessels to see which way the blood is flowing.

Vascular Doppler units range from basic units that perform high level vascular assessments to more advanced models that additionally perform diabetic foot assessments, ankle brachial pressure index tests (ABPI), peripheral arterial disease tests (PAD), toe-brachial index tests (TBI),

segmental vascular assessments, stress tests, and more. These tests help identify vascular conditions that can cause heart attacks, strokes, and even death.

The rise in the cortisol levels inhibits the hypothalamus and pituitary, which in turn decrease CRH and ACTH production. ACTH also stimulates the adrenal medulla, to secrete the "flight or fight" hormones, epinephrine and norepinephrine. These lack feedback action because could not transverse the blood-brain barrier.

The cortisol level in the blood changes in circadian fashion higher in the morning and lower in the afternoon/evening. The hypothalamic sensitivity and CNS sensitivity are due to variations in CRH and ACTH output. Under normal conditions, basal morning cortisol concentrations are twice those at night. The cortisol peak decreases to its minimal levels by night.

With normal diurnal rhythm, blood ACTH levels rise between 3 and 6 a.m., causing increases in blood cortisol, this acts to release from corporal muscle during sleep about 1% of free amino acids. These are taken up by the liver and converted to glucose to support brain and heart.

Doppler in cardiovascular system

Glucocorticoids in the cardiovascular system are required for sustaining normal blood pressure by maintaining normal myocardial function and the responsiveness of arterioles to catecholamines and angiotensin II.

The Doppler equation: Calculating blood flow velocity: $\Delta F = v\,cos\theta \times \frac{F_T}{c}$ and $v = \frac{\Delta F}{\cos\theta}\frac{c}{2\,F_T}$

Closed enzyme-systems thermodynamics, at a body constant temperature, allows reactions to function according to Ea, to overcome the barrier of the differences in energy of formation between substrate (S) and product (P), and that of its coupled systems.

As catalysts enzymes (E) do not participate in the reaction stoichiometry. The protein structure itself is not consumed. However, it could be assumed that hydration shells change first in the direction of $E.(H_2O)n$ binding S to form the $E\text{-}S.(H_2O)n\pm xH_2O$ complex and after the reaction forming $E\text{-}P.(H_2O)n\pm yH_2O$ and when releasing P to complete turnover to free $E.(H_2O)n$. The hydration shell of some enzymes may

determine turn-on versus -off states. The hydration states of the enzyme within the E-S vs E-P complexes requires H-bonds structural turnover in equilibrium with the dynamics of $(H_2O)n$. Hence, enzyme-protein conformational dynamics could uptake H-bonds consuming the dissipative potential between cluster states of surrounding water [36].
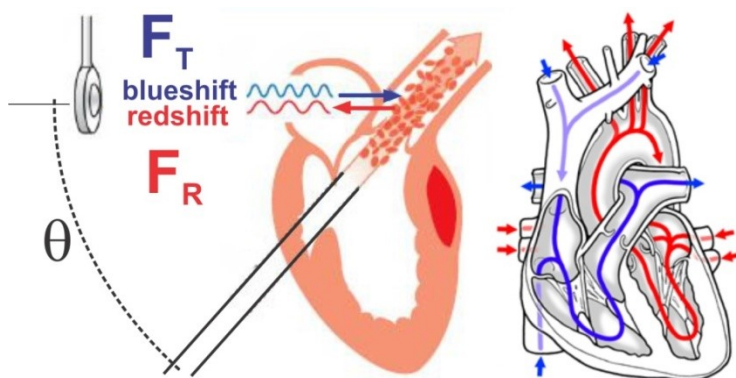

Figure 5: Doppler examinations are based on principles fundamentally different from those underlying two-dimensional imaging. *As is addressed in the sections that follow, these differences necessitate altered approaches and techniques when Doppler examinations are performed. Many times, the required view and imaging frequencies are contrary to those selected for two-dimensional imaging of the same anatomic region. To obtain an optimal assessment of both the form and function of the desired cardiac structure, it is essential to remain cognizant of the underlying physical principles of the two approaches and how they differ.*

ATPase contributes to confer free energy to the overall thermodynamics of energy transduction process. Water dynamics may be complementary involved, since has been shown that ATPase activity is dependent on the hydration state of the protein.

The release of the divalent metal from Hb during deoxygenation is endergonic process requiring the amphoteric response turning the imidazole N atoms of R-His groups from negative into to positive. If these are not involve in forming salt-links the positive charges tend to form H-bonds, with the water taken-out from $(H_2O)n$.

Hence, coupling to water dynamics drives an overall exergonic process for Hb releasing $[Mg(H_2O)inc]^{2+}$ into CSF.

The dynamics of the hydration shells structure of ions and proteins

could be correlated as structures that through dissipative process, generate enthalpy and lead reactions to completion, but turnover of the hydration shell requires water dynamics supported by a decrease in "n" of $(H_2O)n$ [37].
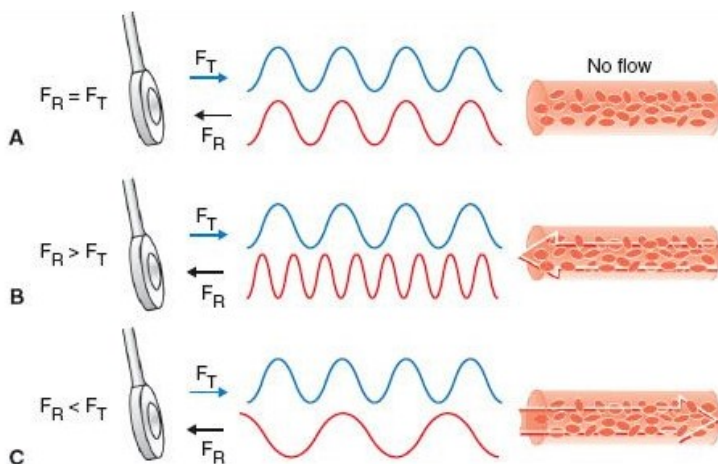

Figure 6: The Doppler equation calculates blood flow velocity based on two variables: The Doppler frequency shift (⏋F) and the cosine of the angle of incidence between the ultrasound beam and the blood flow. The Doppler frequency shift is measured by the echocardiographic system, but cos θ is unknown, and manual entry by the echocardiographer is required for its estimation. v, blood flow velocity; FT, transmitted signal frequency; FR, reflected signal frequency; ⏋F, difference between FR and FT; c, speed of sound in tissue; θ, angle of incidence between the orientation of the ultrasound beam and that of the blood flow [38].

An $[Mg(H_2O)inc]^{2+}$ could initiate H-bond capture from fully hydrated Na^+ leaving an incomplete hydrated shell around Na^+. The chaotropic $[Na(H_2O)inc]^+$ uptakes water from the fully hydrated K^+. The process decreases the effective ion size of Na^+ and K^+ concatenating sieving effects for ion translocation at the Na^+/K^+-pump.

Additionally free Mg^{2+} is required to activate basal AC and for norepinephrine binding to its receptor in AC, to bind to its receptor hormones like oxytocin and for attachment into the neuronal membrane of proteins generated by the cAMP Response Element-Binding (CREB) transcription.

Water mobility of the bulk-$(H_2O)n$ increases by the transfer of H-

bonds decreasing mobility in the hydration shell of Hb. Water dynamic implies acquisition of a latent activator potential, which allows the energy of breaking and reconstitution of H-bonds, to become a source for enthalpy release during formation of the transition states of Hb.

At room temperature thermal processes affect R-groups translational, vibrational, and rotational kinetics at the level of 0.8kcal/mol. The breakdown of H-bonds in $(H_2O)n$ could be evaluated for the bond O-H…:O as 5kcal/mol and for HO-H…:OH^{3+} as 4kcal/mol. The decrease in "n" within $(H_2O)n$ could couple with the increase (exergonic) in the number of H-bonds within a protein or an incomplete hydrated ion. These events increase tendency to drive the progress of transition states with a vector-sense. Therefore, coupling Ea with water dynamics provide an energy level, which can overcome thermic randomness. Moreover, allows the increment in the H-bonds within a molecule to retain a coupling potential for a longer time that allowed by the heat dissipation of Ea.

The need to discern for vectorial systems a mechanism, which could prevents microscopic reversibility from entangling the directionality of processes lead to analyze Hb in function of multiple-equilibrium including $(H_2O)n$. Open systems couple the continuous entrance of S and its P exit, with a dissipative potential $-\Delta G$ to operate at far from the system final thermodynamic equilibrium. A thermodynamic dissipative potential of O_2 and metabolites uptake with CO_2 releases out of the system for entropy exclusion.

After Ea of sliding dissipates the molecule of Hb could no longer acquire the transition states capable to allow microscopic reversibility, because the R-groups which were previously in a reactive proximity shift into a more distant no longer reactive position. The separated of unidirectionality formed 2,3-DPG-deoxyHb-$(H_2O)_T$ to $[(O_2)4Hb(Mg)_2].(H_2O)_R$ complex and vice versa functions in both senses as a exergonic ligand-sequence by coupling to H-bonds dissipative potential of $(H_2O)n$.

Not only the mass-action of ligand at the lungs vs CSF separate oxygenation from deoxygenation but also the dissipative clustering potential of $(H_2O)n$ into $(H_2O)n*$, which allows structural dynamics, with the capability to transfer free energy for the turnover of hydrated molecular architectures, well surpassing a simplistic radiator role.

CSF became replaced at a rate of three and a half times its volume

per 24 hours helping to dissolve and eliminate toxins and $(H_2O)n*$. H_2O enters in CSF with a larger cluster size than the one eliminated, to function as a carrier of entropy [39] to the outside of the open system reactive phase boundaries.

Open thermodynamics allows the dissipative potential of water cluster $(H_2O)n$ to interact with the hydrophilic asymmetries of Hb, to restrict the kinetic sense randomness of a single peak for activation energy (Ea). Instead the conformational dynamics of hydration shells could sequence an enhanced Ea into several peaks, to sequentially activate intermediate transitions states.

Hence, $\Delta\mu$ (dipole states), $\Delta\_sliding$, ΔpKa, Δn-H-bonds, etc., could become concatenated for vectoriality. $(H_2O)n$ by the loss of H-bonds couple with to the hydration turnover of proteins and ions to result in incomplete water cluster $(H_2O)n*$, with a lower "n". $(H_2O)n*$ became a carrier of heat/entropy into the cerebrospinal fluid (CSF) which has to be replaced 3.7 times per day. OxyHb formation involves sliding of $\beta_1\alpha_1$ vs $\beta_2\alpha_2$, to shift α_1 and α_2 Pro 44 into allowing the entrance of a fully hydrated $[Mg.(H_2O)_6](H_2O)_{12\text{-}14}^{2+}$ (or Zn^{2+}) into the hydrophilic $\beta_2\alpha_1$ and $\beta_1\alpha_2$ interfaces.

The dynamics of Mg^{2+} coordination at two sites restricts His β_2 and His 143 of Hb in the hydrophilic oxyHb moving away to allow His β_2 to conform into a single site for the tetramer binding of 2,3-DPG forming deoxyHb. Therefore, the molecule transition from oxy to deoxyHb releases to became a transporter of $4O_2$, $2Mg^{2+}$ allowing the lungs to supply the O_2 supply and nascent Mg^{2+} required to activate the mechanism of Na^+/K^+-translocation maintaining the action potential.

The oxy to deoxyHb is also coupled to the loss of 60 molecules of water from the hydrated structure of oxyHb that configure a highly exergonic reaction that support irreversibility in the directional sense of oxy to deoxyHb turnover, preventing any reversibility, during physiological function. Thus a vectorial mutual exclusion conformational change supports an enthalpy input into the system.

Choroid plexus epithelium generate CSF

Astrocytes are cells with actin filaments in the cell's skeleton, which impulses the cerebrospinal fluid (CSF) flux along the glial network for

pulsatile propulsion and the support of the metabolic needs of the neurons. Also its handedness transport entropy and potentiate learning. Smaller entropy magnifies the enthalpy potential.
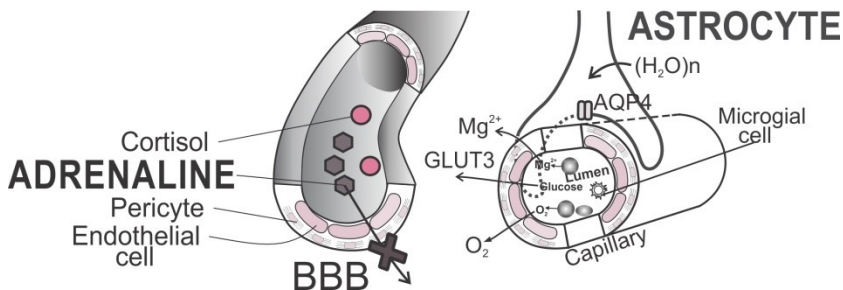

Figure 7: Shows the blood-brain barrier (BBB). *Net ion movement from the blood to the CSF creates a small osmolarity between both compartments, retaining in plasma polypeptides.*

The choroid plexus epithelium (CPE) generates CSF and functions in the mutual exclusive vectorial kinetic according to a potential of hydrophilic-plasma to hydrophobic-CSF flow.

Water is subsequently "dragged" via osmotic forces across the epithelium and traverses the apical membrane of the choroid plexus epithelial cell through AQP1 in both the luminal and basolateral membranes.

Secretion by the aquaporin-1 (AQP1), AE2 and NCBE at a Na^+/Cl⁻ /$HCOO_3^-$ ratio o 18:15:3 transports ions taken up from the basolateral membrane. Na^+ into the CSF enter via NKCCl (Na^+-K^+-2Cl⁻-cotransporter) to keep and mediate the bidirectional transport of ions gradients of blood vs CSF and is regulated by SPAK (Ste20/SPS1-related proline-alanine-rich protein kinase).

The brain of the newborn enjoys a hormonal system development involving about 60% of total calories ingested, which became stabilized at adult age as 25% of total body energy.

At maturity the contributions of the H-bond breakdown energy, by the enzyme state of hydration vs dehydration turnovers, adds to a thermogenic flow of energy, which requires that the brain develops an autonomous cooling system. Thus, at the blood-brain barrier 150ml CSF are maintained permanently, and 0.3-0.4 ml/min CSF are renovated constantly to generate about 500ml/daily output. The equivalence H-bond

contribution is $(H_2O)_{n=3.4}$ for each water cluster kinetic configuration about 3.4×5kcal/mol=17kcal/mol.
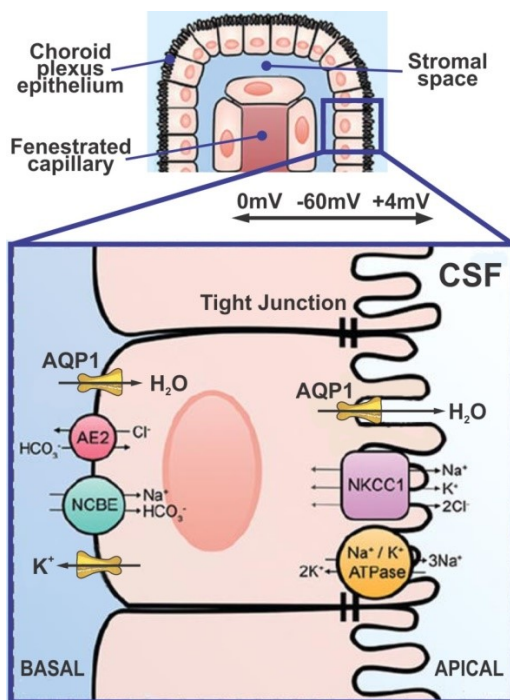

Figure 8: Plasma crossing the choroid plexus generates CSF. *The choroid plexus (CPE) generates CSF functions in the mutual exclusive vectorial kinetic according to a potential of hydrophilic-plasma to hydrophobic-CSF flow. Cl and HCO_3^- influx is recycled across the membrane. At ventricular side, the Na^+/K^+-ATPase releases the Na^+. The K^+-Cl-cotransporter (KCC4) secretes Cl into the lumen containing CSF. Luminal K^+ is required for sustained CSF secretion.*

The thermodynamics relationship between structure and function requires an astrocytes network for circulation after breakdown of H-bonds.

The water clusters exhausted at the H-bond transition of hydrated negative R groups in polypeptide dynamics of folding in oxyHb are in mutual exclusion with the dehydrated positive R groups in deoxyHb. Accordingly, the circulation sense, decreasing oxygenation, continuously depletes H-bonds energy until reaching a choroid plexus epithelium to generate CSF, but its circulation requires a liquid state. Thus, allows a non-

polar kinetic tension between orbitals to conform a resonance state at the water dimer ($H_2O{\sim}OH_2$) integration.

Catecholaminergic synaptic transmission

A proline-dependent bending and sliding of the NA-AC polypeptide potentials neuronal transmission without any reversibility in the direction sense of Mg-ATP as a substrate precede turnover until the highly irreversibility of the kinetic of dead end inhibition involving the effect of substitution of the activatory role of Mg^{2+} to generate AMP and the enzyme form capable to react at the active site with Ca^{2+} to generate cAMP. This one is a highly irreversible structure that requires displacement of Ca^{2+} by a new input of Mg^{2+} to generate again the free form of the enzyme to complete turnover.

Hence, maintaining the directionality of the reactions in a sequence without reversibility for which has to operate Mg^{2+}-dependent sliding first and them produce a Ca^{2+}-dependent sliding. This proline dependent auto segmental sliding's within a single protein operates a bypassing of microscopic reversibility by mass action of H-bond breakdown coupled to consume the H-bonds of water clusters.

The enthalpy flow from water clusters becomes irreversible because a saturation effect of 55.5M of water that turns very unlikely a return to a previous condition of H-bond restored by participating of a system that allows the microscopic principle that operate by equilibrium process. Evidently, since the enzyme is at micro molar level could not interact for capturing from a product the H-bond required to return to an intermediate substrate state.

The associated glial and microtubules transfer a dissipative entropy output at the oral cavity confers a near autonomous open system to brain, whereas cycles deoxy to oxyHb into the lungs.

The partially hydrated nascent Mg^{2+} in membrane activates the Na^+/K^+-ATPase in neuronal axons generate by a size fitting dynamics of the Δ hydration shell of Na^+/K^+-ions their translocation the action potential for the inter-neuronal electric firing the NA vesicles in the synaptic cleft.

Physiological integration between psyche and soma

Serotonin signaling on the hypothalamic dopaminergic wakefulness signaling, the fight-or-flight response leads to an increase on the available glucose to the activated neurons. Also, allows the nucleus accumbens to enhance reward. Summation of controls includes the striatum action of increasing motor activity and peripheral autonomic effects like increased blood pressure and heart rate. The hypothalamus activity relates to increase wakefulness at the sleep/wake center and the body metabolic controls, increasing adrenaline and cortisol. The cortisol feedback is unable to turn-off the metabolic stress, because the system lacks and adrenaline negative feedback.

During nurturing conectomas for sex differentiation had been characterized in men by prefrontal to visual cortex and by transversal connectivity in woman.

Stronger structural connectivity in motor, sensory, and executive functions matched higher spatial and motor skills in men. In the latter there is an increase of neural connectivity within one hemisphere of the brain. Thus, suggesting that men's brains are structured to facilitate connectivity and coordination between perception and action.

In women, there are stronger neural connections between both cerebral hemispheres, which would facilitate communication between the analytical mind and intuition. In women, the subnets associated with social cognition, attention and memory showed greater connectivity, which was consistent with higher cognitive-social and memory skills in women than in men.

No differences have been found in the size of the corpus callosum or in the white matter, which allows the two sides of the brain to communicate with each other.

Studies of human patterns resulting from interaction of mother-infant separation, as related with decreased glucocorticoid receptor gene methylation of post-traumatic from early life stress.

In the human newborn the residual structure from evolutional deletion of the olfactory sense allows a memory unable to coordinate muscles most likely, the sympathetic motor pathway has yet to be integrated. This process requires a long period of parental care, before reaching the brain structure of neuronal circuits, capable to support

muscular interaction and the developments of audition, linked to a hormonal operative cognitive visual-hearing language.
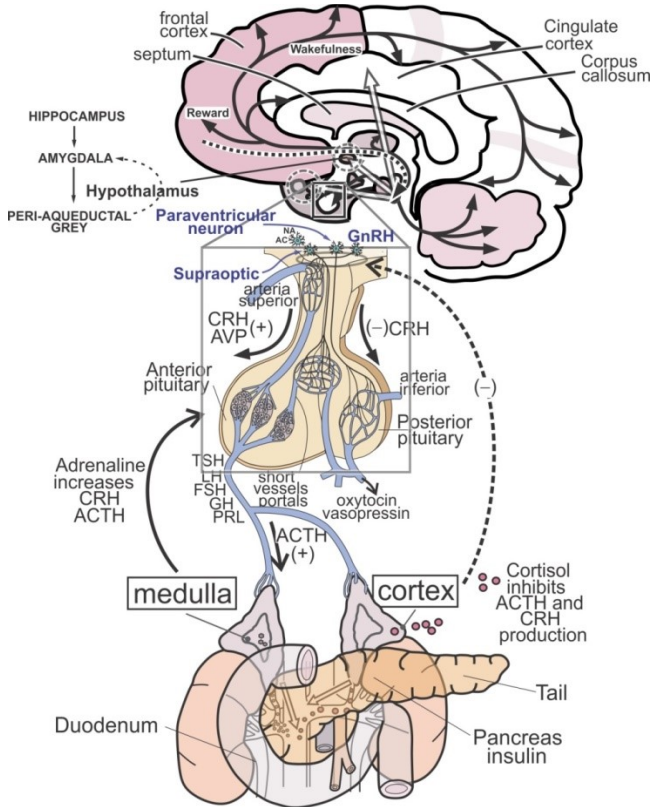

Figure 9: Emotional cognitive connection hypothalamic-NA-AC-brain axis. *The hypothalamus (bidirectional) receives projections from sympathetic motor system (carried by the hypothalamospinal tract and they activate the sympathetic motor pathway), from the medial forebrain bundle carried by the mammillothalamic tract. Thus, notable inputs are from the nucleus of the ventrolateral medulla and locus coeruleus.*

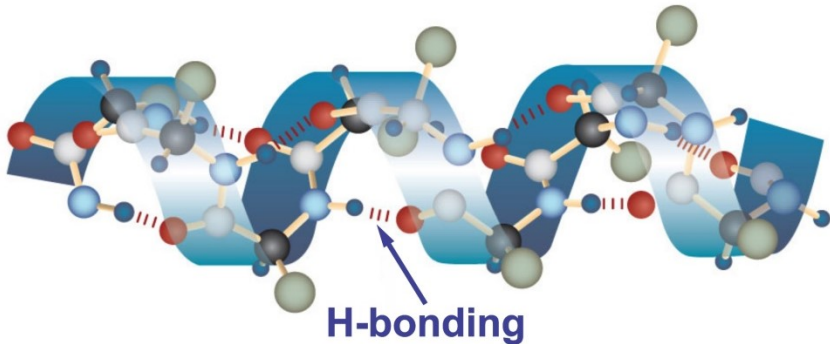## H-bonding between water molecules and proteins

Figure 10: The H-bond breakdown allows enthalpy work to proteins by H-bond breakdown, allowing transitional changes to a protein like (adenylate cyclase) AC. A proline allows bending and sliding with H-bonds breakdown play the role of activation energy with release of dimers. At each transitional state of AC the new configurations respond to a sequence of coordinative state first with Mg^{2+} to create AMP and them replacing Mg^{2+} by Ca^{2+} and a new configuration of coordinative R-groups, allowing cycling to cAMP to AMP and release of water dimers.

The increase of tau within the brain leads to psychological pathologies at the frontal cortex, for impulse control, judgment and the ability to control multitask. The locus coeruleus located in brain stem structure has been associated with depression. In latter stages, tau is located in the amygdala, with a role in impulse control and in the hippocampus, with role in forming and retaining memories.

The locus coeruleus contains about 6×10^4 noradrenaline-adenylate-cyclase (NA-AC) neurons, characterized by their very long axons reaching almost every region. Thus, inputs from saliva at the 7TM receptors of AC, located at the rostral-oral-cavity reach [40] the hypothalamic-pituitary-adrenal (HTPA) axis controls on the psychosomatic metabolic network.

The adrenaline secretion increment [41] [42] shifts metabolism of body in the direction of depleting metabolic reserves, like fats, without entering the cerebrospinal fluid (CSF) [43]. Cortisol releasing amino acids from some proteins overcoming gluconeogenesis feedback control.

This mechanism is based in the absence of negative feedback by adrenaline. The latter could not cross the blood-brain barrier (BBB) and therefore have only an incomplete control over the inhibitory signaling,

allowing to stop adrenal secretion.

A metabolic perspective could explain the function and structure thermodynamics advantage of assigning to the brain, unchallenging nutritional control of body metabolism for maximizing its own development.

A brain pattern of emotional-hormonal control, over metabolic supporting functions, may participate on the psychosomatic bases of the unconscious [44]. Thus, emotional rewards are granted for human competitions adding a selective control response to the primitive animal fight-or-flight conditioning.

Hormonal glands secretion at the arterioles irrigating the oral cavity could represent a near autonomous hormonal signaling control of behavior, through the emotional responses of the oral-cavity-NA-AC-Hypothalamic (OC-NA-AC-HT) axis.

The sensorial 7TM hormonal receptor structure of the NA activated AC at the locus coeruleus from distant regions, could integrate the five senses (sound, smells, touch, visual and gustatory regions) into simultaneous multiple perception associated to emotional events.

The auditory cortex processes signals from the ears. The neuronal network responses for attention, only when the dorsolateral prefrontal cortex and a part of the parietal cortex are simultaneously activated, resulting in acoustic signals is more discernible because of human ability to integrate the visual perception of lips movement.

The stimulation the frontal cortex communication tie with the deep brain at the limbic centers related to emotions, memory and learning of the hyperactive depressed patients were calm down. Thus, shows that reason and emotion are link by a crossing turnover.

The oral-cavity-hypothalamic-brain axis appears to provide a therapeutic alternative to medication to the brain implantation of electrodes. It is suggested a treatment localized at vomeronasal organ (VNO) and/or the surrounding palate areas with stimulatory procedures either: electric discharge or pharmacological access to hormones like oxytocin, dopamine, NA, etc.

The thalamus prevents sensorial signaling to reach the cerebral cortex.

Synaptic strengthening is promoted by oxytocin and dopamine for maternal cognitive memory [45].

Oxytocin release into nucleus accumbens shell is also activated by vaginocervical and lactation stimulation.

The paraventricular hypothalamic area is the source of oxytocin input into nucleus accumbens shell, which is signal by dopamine [46] for reward-seeking behaviors.

Adrenaline, oxytocin and dopamine rewards link the emotional responses, coupling with the cognitive reasoning pathways originated at the amygdala and the hippocampus.

Periodic breaks and breathing times at work do the brain good. An important control center (the prefrontal cortex) sends signals to deeper and older brain regions: the hippocampus and the amygdala, decreasing stress. This interaction favors the transmission of social information, and the development of selective recognition.

Function magnetic resonance image (fMRI) studies, with participants, evaluated for the neuronal activity of the hippocampus. Results showed an inverse relation, differentiating between the tasks measurements for predictability vs memory functionality. Thus, indicating that both processes compete for use of shared, limiting neurological requirements. However, these could be not only structural, but functional like metabolic ones, thermogenic dissipation, etc. Hence, responding to homeostatic controls.

The human brain could be characterized by reflexive behavior of self-language interactions rather than genetically triggered reflexes, which appears to be hormonal configured, at first instance generating an emotional intelligence before an intellectual one.

Thus, lead to infer that opens a learning period through emotional communication, which allows humans to develop an emotional brain and emotional intelligence. This event has evolved out of genetic restriction, but responds to a pathway introducing self-rewards feedbacks like achievement. Thus, could emanate from competition that human evolution consolidates as behavioral responses coupled to the reasoning as an expectation response for emotional reward.

Regulation of endocrine secretion on brain function

The steroid hormones actions result from effects on gene expression. Have a slow onset and are long-lived clinically significant adrenocortical

hypo-, hyper-, and dysfunction are known.

Transport of cholesterol from intracellular stores to the inner mitochondrial in which is located cytochrome P450scc.

P450scc catalyzes the first, slowest, and therefore, rate limiting step for hormone synthesis, is also the major site of physiological regulation. In each steroid synthetic tissue, the control hormone for that endocrine gland activates P450scc, this catalyzes the conversion of cholesterol to pregnenolone.

Pregnenolone moves from the mitochondria to the microsomal compartment, where it is converted to the Δ4-3-keto steroid progesterone by the 3β-hydroxysteroid dehydrogenase.

Pregnenolone is converted to the final hormone product by sequential steps along depending on the enzymes that are present in that tissue. Thus, the zone glomerulosa makes aldosterone, because it contains 3b-HSD, P450-21, and P450-18, and lacks P450-17a. Gonadal tissues lack P450-21 and therefore can only make the sex steroids progesterone, testosterone and estradiol.

Because the placenta lacks P450-17a, it cannot produce DHEA or androstenedione by itself; therefore, the placenta can only make estrogens by converting substrates (e.g., DHEA and 16a-hydroxy-DHEA) synthesized elsewhere. Because the fetus makes and secretes large quantities of these steroids, placental estrogen production is quite high.

Hormonal control of brain function
Pathway-signaling between the synapse and the nucleus in neuronal network plasticity

Sensory experience is critical for the proper development and plasticity of the brain throughout life. Successful adaptation to the environment is necessary for the survival of an organism, and this process requires the translation of specific sensory stimuli into changes in the structure and function of relevant neural circuits. Sensory-evoked activity drives synaptic input onto neurons within these behavioral circuits, initiating membrane depolarization and calcium influx into the cytoplasm.

Calcium signaling triggers the molecular mechanisms underlying neuronal adaptation, including the activity-dependent transcriptional programs that drive the synthesis of the effector molecules required for

long-term changes in neuronal function. Insight into the signaling pathways between the synapse and the nucleus that translate specific stimuli into coded neuronal sequences.

The altered connectivity patterns provide circuit clues as to how activity-dependent programs of gene expression are coordinated and synchronized by microtubule cytoskeleton. Movement of neurotransmitters and ions like: Ca^{2+} and Mg^{2+} in the microtubules signaling allow the sequential response involved in molecular activation of enzymatic process, like NA-AC activatory state. Hence, synchronization disruptions of these processes may contribute to disorders of cognitive function, like schizophrenia.

The histaminergic network in the brain: basic organization and role in disease

Histamine pathways in brain initiate in the tuberomammillary nucleus (TMN). Several brain neurotransmitters are regulated by histamine. Its signaling controls feeding behavior. Histamine decreases the drive to consume food. Histamine neurons respond to both mechanical and chemical sensory input from the oral cavity, functioning as a danger detection system.

Aberrant histamine signaling may be a key factor in addictive behaviors, Parkinson's disease and multiple sclerosis.

Histamine acts as a modulatory neurotransmitter in the mammalian brain.

It has an important role in the maintenance of wakefulness, and dysfunction in the histaminergic system has been linked to narcolepsy.

Recent evidence suggests that aberrant histamine signaling in the brain may also be a key factor in Gilles de la Tourette syndrome, Parkinson's disease and addictive behaviors. Furthermore, multiple sclerosis (MS) and experimental autoimmune encephalitis, which is an often-used model for MS, are associated with changes in the histaminergic system.
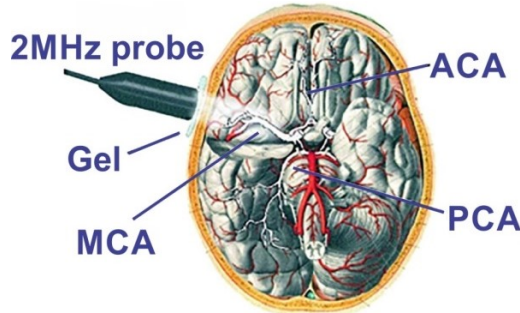
Transcranial Doppler parameters and relevance

Figure 11: Measurement of the cerebral blood flow velocity (CBFV) in the MCA by TCD. *The anterior, middle, and posterior windows make up the transtemporal window. When the intracranial carotid artery (ICA) bifurcation terminates in the anterior, middle, and posterior cerebral arteries (abbreviated as ACA, MCA, and PCA, accordingly), it can be identified at depths of 55–65 mm with the simultaneous flow toward or outward from the probe.*

The Circle of Willis and the MCA can be seen when the 2 MHz probe is positioned transtemporally [47].
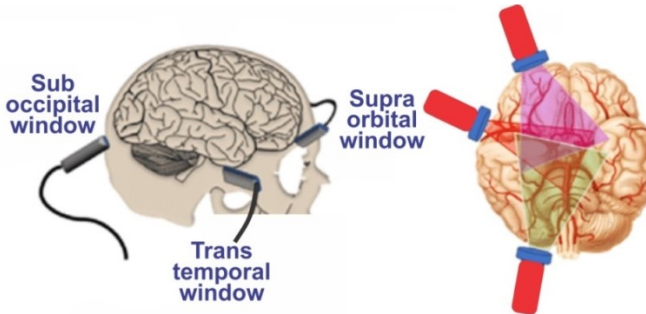

Figure 12: *illustrates the available acoustic windows for insonation and the spread of ultrasound waves across Circle of Willis through the available acoustic windows. Abbreviations: Vmax, maximal cerebral blood flow velocity; Vmin, minimal cerebral blood flow velocity; MBFv, mean blood flow velocity; MBFv (b) , mean blood flow velocity at baseline; MBFv (r) , mean blood flow velocity during/ after hypercapnic stimulus; VMR, vasomotor reactivity; CVC, cerebrovascular conductance index; CVR, cerebrovascular resistance index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PI, pulsatility index; PR, pulsatility ratio; CPP, cerebral pulse pressure* [48].

TCD parameters	Physiological relevance
Cerebral blood flow velocity Vmax Vmin MBFv=(2×Vmax+Vmin)/3	Peak systolic velocity Lowest diastolic velocity Time averaged mean velocity
Cerebrovascular Vasomotor Reactivity: VMR=$\left(\frac{(MBFv_r - MBFv_b)}{MBFv_b}\right) \times 100$	VMR tests the tone of the small resistance vessels

In the CNS, cortisol can alter the excitability of neurons induce neuronal death in the hippocampus. Affect the mood and behavior of individuals. Depression may be a feature of glucocorticoid therapy. Depressed individuals show increased cortisol altering the circadian rhythm.

Conclusions

The H-bond breakdown mechanism for water clusters coupling the flow of enthalpy contribution to the propagation activation energy and operates open nano systems of quantum mechanics, for example: at the myelinated Ranvier nodes.

Generalization the H-bond turnover is not only present in the brain-system but in many other organs. Thus, coupling operates to activate (on) and static (off) state of internal molecular transitions, requiring individual enzymes, like the membrane located adenylate cyclase operating enthalpy in DNA and protein dynamics along sequences to synchronize flow of the action potential. Generalizing, vectorial irreversibility implies a dissipative state of entropy connected to a secretion flow out of the body-system.

In the brain a nanoscale quantum mechanics domain by Doppler shifts emission of 21 cm photon-signaling for synchronization in vectorial movements from nucleus to cytoplasm and vice versa, linking neuronal networks and connectomes. The newborn's immature brain requires about three years of nurturing under hormonal communication before learning relating face expressions to vocalized sounds. Freud's psychoanalysis allows exploring the relation between the unconscious hereby is proposed

as the brain state of only hormonal communication and the conscious the individual state after having learned language. The suppression mechanisms may also participate in the elimination of the individual perception of the electrographic neuronal activity. The Doppler ultrasound devices are now available for psychoanalytic assistance of the location presence of connectomes for hidden memory.

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