A protein hydrophilic active site could by mutual exclusion became hydrophobic, allowing this vectorial transition to bypass the microscopic reversibility principle

Dr. Alfred Bennun
Full Professor Emeritus of Biochemistry
Rutgers University

Abstract

Prigogine proposed a coupling between larger sources of enthalpy to allow an open system to operate life. The sun flow of energy is coupled to water cluster thermogenic breakdown of H-bonds to vapor. The position of proline in a polypeptide chain allows sliding between segments, in the tertiary folding structure response to electrostatic attractions, could differentiate positive vs negative domains. Thus, bypass the microscopic reversibility principle, illustrated as a single door, vectorial kinetic only made possible by the jokingly Maxwell proposed operator demons. The physiological function of Hb oxygenation by pO_2 shows a microscopic thermogenesis biological vector, functioning by the enthalpy potential of the large mass action of surrounding air and releasing entropy. The mechanism shows the H-bonds breakdown required for changes in the structure-function levels by the proline mediated folding. The tense (T) to relax (R) forms shows vectorial microscopic dynamics, during Hb oxygenation. Thus involves a sliding by H-bonds breakdown, distancing between subunits β_2 and α_1. Thus, open a larger entrance to a fully hydrated Mg^{2+} to coordinate amphoteric and negative R groups characterizable to a hydrophilic site. The transition of R to T allows positive R groups to bind 2,3-DPG^{5-} to form deoxyHb. Thus, a microscopic smaller entrance by decreasing its opening size does not allow entrance of the fully hydrated Mg^{2+}, but allow the exit of nitric oxide (NO) and a poorly hydrated Mg^{2+}, denominated *nascent*. This one acts for competitive hydration sieving on the shells of Na^+, which in terms take water from the K^+ shell, potentiating a K^+/Na^+-translocation operating the electrogenic transmembrane potential. The deoxygenation in the reverse transition of R to T binds NO, protecting against a premature decrease of the chromosome's telomeres size by stressing factors such as depression, anxiety and physic traumatisms, over endothelial cells delaying premature senescence. The arginine metabolism produces NO, dilating blood vessels, improving the circulatory systems and the muscular recovery-development. A diet rich in arginine by producing a high sustainable level of NO may prevent the resistance to treatment by the consolidation of large vascular masses. The H-bonds donor potential by their breakdown leads to randomness (or entropy) decreasing the kinetic energy of solvation, scaling down the polarity on the thermogenic dissipation of oxy vs deoxyHb and choroid plexus epithelium on plasma generation of cerebrospinal fluid (CSF). The enthalpy of photosynthesis-metabolism releases CO_2, whereas the water cluster mediated thermostatic function releases vapor. In both systems, the entropy release maintains a high potential of enthalpy. Hence, overcomes the thermic and electric noises by an irreversible dissipative kinetics, facilitating a clear development of a meditative level of reasoning and learning. Thus, the brain acquires an autonomous function, beyond behavioral genetic conditioning.

Introduction

At the Weizmann Institute of Science (1964-65) was shows the absence of photophosphorylation reversibility, in the absence of uncoupled reactants. The uncoupling conditions lead to the emergence of a light-dependent and a light-triggered ATPases.

At the time the microscopic reversibility principle dominated the scientific paradigm and therefore encouraged the search for vectorial reactions.

The first resolution by the extraction from the chloroplast membrane of the latter denominated ATP-synthase-ATPase enzyme CF_1 allowed the reconstitution of similar percentage of photo-phosphorylation and the two ATPase activities.

The study of the affinities of substrate ADP/GDP and ATP/GTP for the three enzymatic activities showed similar changes, indicating that a single active site was functional to several differentiable dynamics for the conformational states of a single protein [1] [2].

The ATP synthase was dependent of a tight fit within the membrane, containing the electron carrier, allowing the coupling of oxidation-reduction to proton translocation [3]. The latter, mediated by

changes in the pKa of a proton acceptor R groups in CF_1 or F_1, allowing the enzyme to undergo topological changes at its active site, magnifying vectorial transitions.

Thus, electron displacements induce ADP^{3-} to accept a phosphate to form ATP^{4-}. Hence, the mass action of protons favors the endergonic transition from a lower to a higher pH, shown by the Jagendorf's Jump [4].

The chloroplast's studies showing vectorial activities of the ATP synthase-ATPase, single protein, was in apparent contradiction with the principle of microscopic reversibility. The impossibility to differentiate between hot- and cold-molecules allowed a humorous description by Maxwell that such operators should be called *demons*. Figuratively, the principle describes that a single microscopic door allows transit in both senses. However, to evade that incompatibility [5], were two doors (or more) the complementary of the vectorial senses and the two doors, could be by exclusion close or open but not both in simultaneous state.

Hence, the active site function should be equivalent to a mutual exclusion by the H-bonds breakdown, required for the structural states (or change) related to the coupling to the electron transport system [6] [7] [8].

An endergonic state of the enzyme will depend on the number and strength of R groups on the enzyme, within the membrane in transition from hydrophilic to hydrophobic state. The hydration changes depend of the tendency of the bipolar water molecules to organize H-bonds in a cluster $(H_2O)_{n\approx3.4}$. Thus, allows energy conservation at the enzyme at the structure of the protein chain sliding of the pKa of the amphoteric R group of histidine and the pKa of differentiated R groups in the active site organized from hydrobilic to attract ADP and Pi in a mutual exclusion transition to a into hydrophobic domanin enclosing the substats to optimize the environment for the synthesis of the products: ATP, plus the released H_2O.

The finding that CF_1-ATPase requires Mg^{2+} for binding to the membrane and reconstitution of allotopic properties implicates that vectorial response may depend from both conformational change at the active site coupled to a conformational change displacing the topology of R groups in the membrane from a hydrophilic to hydrophobic conformational domain.

The chloroplast's studies showing the vector kinetic of the ATP synthase-ATPase was in apparent contradiction with the principle of microscopic reversibility. The impossibility to differentiate between hot- and cold-molecules allowed a humorous description by Maxwell that the operators of a single door, capable of doing so, should be called *demons*.

Figuratively, the principle describes that a single microscopic door allows transit in both senses, allowing only a closed thermodynamic system, which only allows changes by mass-action equilibrium. However, an irreversible open system do have vectorial kinetic as long that enthalpy input is continuous as light trapping by the chloroplast and entropy generated is continuously dissipated..

Hence, to evade that incompatibility [9], it is possible to assume two inversely linked doors, mutually exclusive, one to be open when the other is closed. The conformational changes described are operating when one domain is hydrophilic and the other turns to become hydrophobic.

Vectorial kinetics is conferred by the folding dynamics-dependent of a proline within the polypeptide. The H-bonds could be regarded as doors, when open attracts water cluster to the segment containing negative R groups capable to coordinate Mg^{2+} (first door).

This hydrophilic configuration has to be mutually exclusive by H-bonds breakdown (second door) to reconfigure a hydrophobic structure of positive R groups to attract negatively charged molecules like ADP^{3-} and AMP^{-}. However, the endergonic product: cAMP, which could not be liberated from a hydrophobic close environment, which allows water exclusion for vectorial decrease in energy of cyclization. However, Mg-cAMP is released by the large mass action of water clusters and the increase in free Mg^{2+}. Turnover requires the mass-action of water cluster for additional H-bond breakdown, reconfiguring the obligatory Mg site characterizing the hydrophilic state.

These are transitions thermodynamically coupled between an exergonic reaction couples to drive the endergonic, sliding event by the H-bonds breaking of the binding folding dissipative heat release.

The directionality would be given by mutual exclusion and this complementarity would be the

conformational change of the protein, dependent on a breakdown of a small ratio of H-bonds of the total potential of the water cluster. A subsequent event depends on the exergonic uphill event of H-bond breakdown to recreate the hydrophilic domain (3th door). However, this step has the large contribution to the enthalpy of the system by a natural coupling to the high H-bond mass action of water clusters at molar level. The system operates with the remaining H-bonds within the water cluster. This is rather not detectable since at the test tube reactants and products are at μmolar level. However, the water cluster involves the solvation energy of encompassing saturation surroundings [10] [11] [12] [13].

Experimentally the solvation tendency was measured on the activity shown by the CF_1 heat activated-ATPase, determined from its maximal value assayed as basal with glycerol addition at 0% only in the presence of water clusters. The curve obtained by decreasing enzyme activity to zero, reached by adding glycerol up to 8% concentration into the mixture.

A Lineweaver plot allowed the determination of a cooperativity number of 16 that divided by two, a value for the microscopic properties internal to the association of water and the protein molecules, expressed as energy of solvation. The presence of two active domains (or sites) in the same CF_1 heat activated-ATPase protein, revealed that each one was structured, by the coupling of their re-configurations to result in the binding of water at 8 solvation sites per domain. These, differential domains appear to be integrated by a transition sequence with a time dynamics, accorded for mutual exclusion, preventing reversal and resulting into a single microscopic acting domain. This complexing integrated mechanism is required to couple the first state as an exergonic reaction of the hydrophilic domain, required for CF_1 to uptake the substrate ADP^{3-} and Pi, and in a second phase configuring a second active site for the CF_1 protein, configuring an hydrophobic cavity, acting for the endergonic formation of the synthetizing site of the product ATP^{4-} and exclusion of water. Thus, jointly consuming the enthalpy energy of water cluster to integrate into microscopic space the two domains, joined for the completion of the dynamics of the total reaction cathalytic environment. Consequently, the enzyme glycerol-depending inhibition mechanism was acting as a competitive antagonist of the H-bond breakdown, involved in each transition state. Accordingly, appears to show that the whole process takes place in a space-time quasi-quantic. Hence, the microscopic mutual exclusion process is equivalent to coherence and decoherence forces, integrating random (R groups sensitive to temperature and pressure) microscopic motion events by a vectorial cyclic mechanism, conforming open microscopic system thermodynamics for the entrance of substrate and exit of product. Therefore, evades the microscopic reversibility principle.

The number of 2-, 3- and 5-coordinated water molecules produced from broken tetrahedral structures increase upon heating [14]. Temperature and shearing can break down a large number of H-bonds within a network. At low temperatures 50% of water molecules are included within clusters.

With increasing cluster size the oxygen to oxygen distance is found to decrease, which is attributed to so-called cooperative many-body interactions: due to a change in charge distribution. The H-acceptor molecule becomes a better H-donor molecule with each expansion of the water assembly. Many isomeric forms seem to exist for the hexamer $(H_2O)_6$ from ring, book, bag, cage, to prism shape with nearly identical energy. Two cage-like isomers exist for heptamers $(H_2O)_7$ and octamers $(H_2O)_8$.

The imidazole ring of proline role in polypeptide dynamics

Primary structure is the amino acids sequence with determines dimensional structure.

Secondary structure of polypeptide chain can fold α helix coiled structure stabilized by intra chain H-bonds.

The polypeptide can change direction by making reverse turns and loops.

Tertiary structure for water soluble proteins folds into compact structures with tendency to form non-polar hydrophobic cores.

The H-bond dynamics on folding allows the peptide bond a resonance stabilized polar and planar structures. Two parallel β-pleated sheets with an intervening strand of α helix domains bends on the surface of globular proteins. This structure offers little steric hindrance to a modification in the

direction of the polypeptide chain.

The imidazole ring, a five-membered ring of proline, allows a second residue to manifest a reverse turn.

Constructing mutual exclusion domains through H-bonds turnover allows the interaction between distant regions of a polypeptide chain. The hydrophobic effect drives protein folding in about 10^{-1} to $10^{-13}s$ to rotate around the $C-C_{\alpha}$ and $N-C_{\alpha}$ bonds of the polypeptide backbone to consolidate a hydrophobic core, which will tend to displace water out.

Required to bend, twists and folds the polypeptide sequence at the secondary in transition to tertiary structure level, by producing differential configurations by hydrophilic associations of cations $(Mg^{2+},\ Ca^{2+},\ \text{etc.})$ and also hydrophobic for Ca^{2+} and anions $(2,3-DPG^{5-},\ ATP^{4-},\ ADP^{3-},\ AMP^{2-},\ cAMP^{-}, \text{etc.})$.

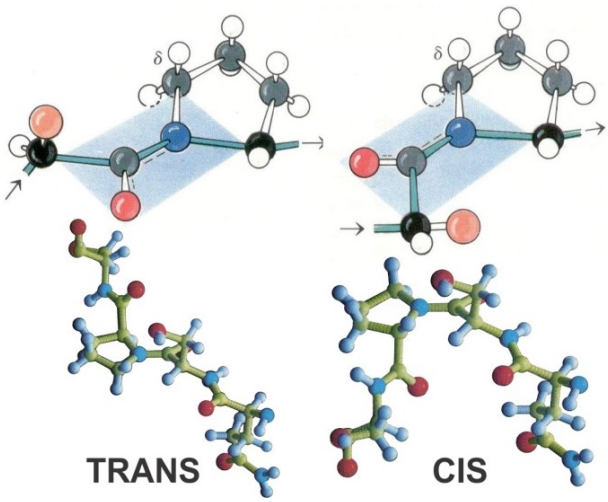
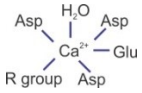


Figure 1: Dynamics of isomer cis of proline in configuration allowing sliding between two domains helix-turn-helix changing the correspondence between a hydrophobic vs hydrophilic site.

All biological membranes are asymmetric. P type ATPases couple phosphorylation and conformational changes to pump Ca^{2+} across membrane. Ca^{2+} at cell interior level: 10nM and 100nM extracellular fluid, binds strongly to proteins, producing large structural re-arrangements. Bonding to the negatively charged



site chains glutamate and aspartate: Frequently coordinated to six oxygen atoms of a protein and water on top.

The flow of ions as the channel transits between open and close states 143mM Na^{+} outside could not freely enter because the charged ion cannot cross into the hydrophobic membrane interior. However, during the nerve impulse Na^{+} enters through the opening specific gate by the facilitated movement by the ion gradient created of 14mM in the inside, because the use the energy by the breakdown of ATP called active transport.

Hemoglobin and O_2/Mg^{2+} control of a membrane action potential

The crystallography x-ray analysis by Max Perutz [15] was able to determine the quaternary structure of oxyHb, without characterization of the Mg^{2+} role for a hydrophilic site.

The oxyHb has a topology of two hydrophilic interphase $\beta_2\alpha_1$ and $\alpha_2\beta_1$ that coordinate one Mg^{2+} each. In deoxyHb the topology is restructured by the tetramer subunits, lining positivity-charged R groups of amino acids and His β_2 143 that turns around into the central pocket to bind $2,3–DPG^{5-}$. A decrease in pH favors the protonated forms for formation of deoxyHb. Hence, the oxyHb contains two interphases to coordinate $2Mg^{2+}$ into hydrophilic domains, which are mutually exclusive with a single $2,3–DPG$-dependent domain, included in the tetramer structure of deoxyHb [16] [17] [18] [19] [20] [21].

The conformational irreversible change involved two Mg^{2+} chelating dynamics interfaces in the Hb tetramer, with a His R groups at the interface of $\beta_1\alpha_2$ chains of Hb, an a second symmetric chelating site at the $\beta_2\alpha_1$ interface for each Mg^{2+}. The conformational change by the release of $4O_2$ and $2Mg^{2+}$ at tissue level became irreversible because the amphoteric R group His 143 move from coordinating Mg^{2+} at oxyHb to integrate the deoxyHb. Thus, conforms to positive R groups form a single binding center for $2,3–DPG^{5-}$, leading to the deoxyHb by a mutual exclusion process, which requires that the oxyHb structure disappears to be replaced, by the 2,3-DPG dependent deoxyHb structure, an enthalpy producing entropy process, reversing only by a vectorial cycling that results in an thermodynamics open system. Thus, is incompatible with the

principle of microscopic reversibility.

At the deoxyHb a vectorial by kinetic by the sieving effect at the α_1 subunit by the R group of Pro 44 sliding between β_2 His 97 and α_1 Thr 41 to block now the entrance of the larger fully hydrated Mg^{2+} into the interface of β_2 and α_1 chains, which now only allows the exit of the smaller incompletely hydrated: nascent Mg^{2+}. The neutral soluble in fat and water NO enters attracted by the positive R groups, holding $2,3{-}DPG^{5-}$.

The absence of guanylate cyclase activity at the human red cells shows its capability to be a carrier of cGMP by its uptake from extracellular fluids.

The erythrocyte uptake of cAMP and cGMP allow their signaling to participate in the regulation of intracellular process, without *in situ* formation because could be delivered by blood [22].

At tissue level the erythrocyte, at low O_2 the Hb protein release of $4O_2$ jointly with the breakdown of 2 coordinated Mg^{2+} (Mn^{2+} or Zn^{2+}) atoms, involved the existent of vectorial kinetic by the movement of the pyrrole R group of Pro α 44, allowing the tertiary structure for sliding of the α_1 vs β_2 positions in amino acids polypeptide subunits.

Thus opening in the T-->R transition for uptake and coordination of Mg^{2+} and closing in the R-->T transition for releasing and preventing the coming back of Mg^{2+} the system shows vectorial kinetic. Thus, evading the principle of microscopic reversibility since the event could be characterized by over two linked conformational changes, acting synchronized in inverse relationship, one open and the other closed hereby described as mutual domain exclusion.

Peptide bonds are rigid and fixed in a plane in where two α-carbons, 3.6 Å apart, rotate by angles ϕ (fi) and ψ (psi). The tertiary structure in the 2α and 2β polypeptide chains of Hb bends, twists and folds over and back upon imidazole R-groups. With pKa of 6.5 that at about pH 6 shows two NH bonds that share in a resonance a positive charge. Hence, the hydrophobic state form of the protein by an O_2 induce conformational changes $\alpha_1\beta_1$ dimer to rotate 15° around of other dimer $\alpha_2\beta_2$.

The O_2 pressure between lung and tissue level becomes the physiological/biological driving for an open system function of pH decreasing at the extremities. Cooperativity is functional to release O_2, but since the turnover itself comprises conformation changes, is also coupled to the H-bond breaking out, releasing energy and the large mass action of water cluster $(H_2O)_n$ to reconstruct the solvation state. The H-bonds decreases "n" and the single molecule of water formed without H-bond as vapor. Thus, both sources of energy are dissipative functions with irreversible kinetic in the absence of solar energy.

The two His β_1 and β_2 143 during oxygenation are changed in relative position by the quaternary restructuring topology and move to the interphase $\beta_2\alpha_1$ and $\alpha_2\beta_1$ to participate in the disruption of the 2,3-DPG binding site. Hence, the oxyHb contains two ions at the interphases: Mg^{2+}-dependent hydrophilic domain, which is mutually exclusive by rotating His β_2 143 into binding with 2,3-DPG. This R group, the amphoteric or zwitterionic form (can react both as an acid and as a base) changes hydrophilic state to be included in the positive R group domain of $2,3{-}DPG^{5-}$, within the tetramer structure of positive deoxyHb.

The two dimer interfaces: $\alpha_2\beta_1$ and $\beta_2\alpha_1$ link by two $Mg^{2+}.(H_2O)_n$ the dynamics of conformational change to an hydrophilic state of the protein, by chelating [23] the R groups His β_2 92, Cys β_2 93 and Asp β_2 94, could attract sequentially the iron in the 4 hemes by His β_2 92, moving to coordinate Mg^{2+} and coordinate to His α_1 87. The 4 irons within the 4 Hemes could move to the outside surface to interact with the distal His β 63, increasing Hb affinity for the ligands by forming an H-bond with O_2.

The publications at Rutgers [24] showed conformational allosteric changes, were kinetically depend of hydrophilic configuration to form a coordinative center for Mg^{2+} (or Zn^{2+}), operating the dynamics of R groups response to oxygenation.

The His α_1 87 moves by Mg^{2+} coordination to interact with the oxy Heme α_1. Deoxygenation by 2,3-DPG dependent allows His β_2 143 to be released from Mg^{2+} to participate in the stability of the $2,3{-}DPG$ binding site.

Thus, shows that the mutual exclusion between binding O_2 or $2,3{-}DPG$ has synchronized the motion of R groups responding to oxygenation function.

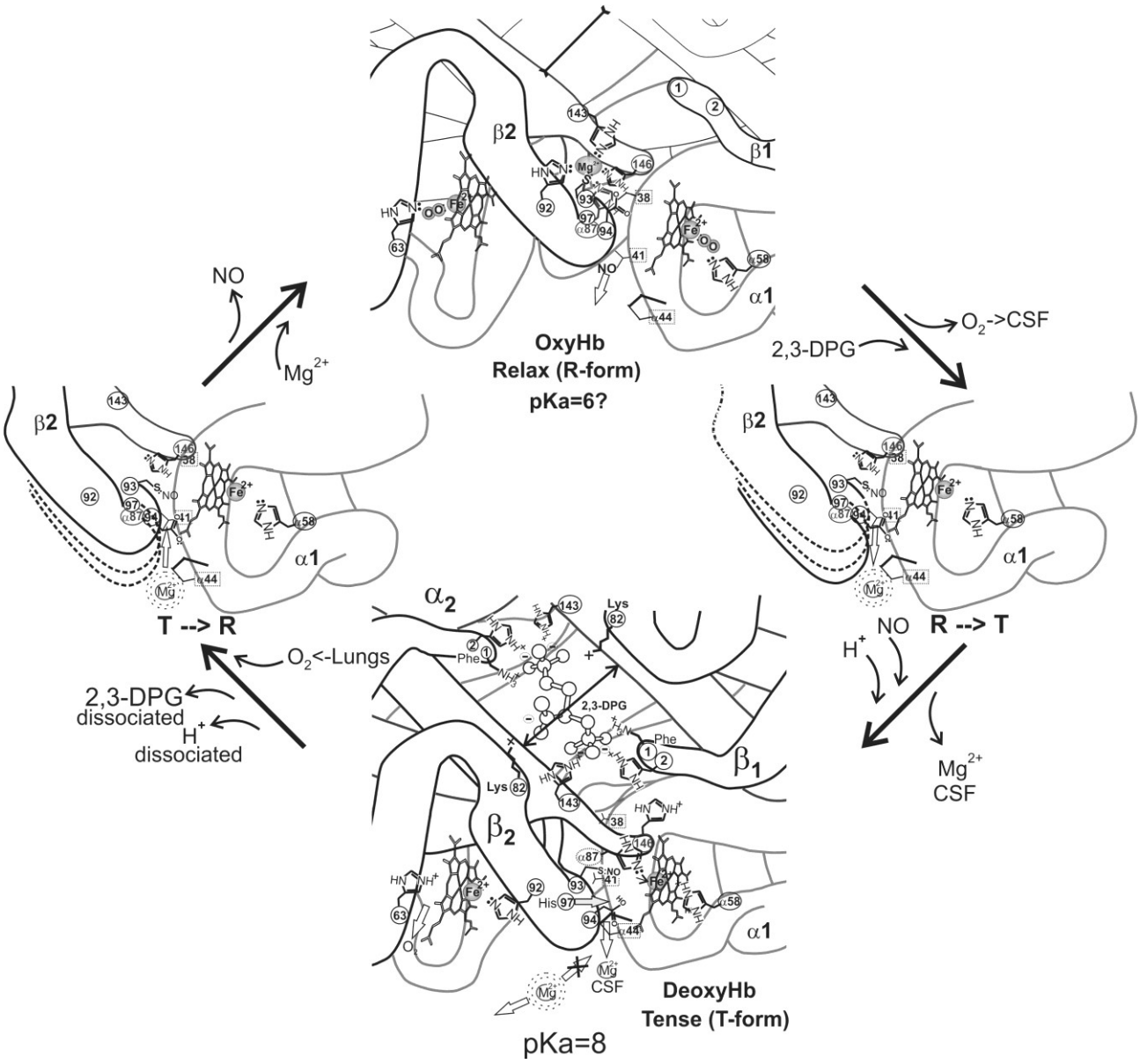


Figure 2: The four Heme oxygenation sites correspond to two dimer interfaces: $\alpha_2\beta_1$ and $\beta_2\alpha_1$. *The negative R groups force the release of NO when $2Mg^{2+}$ by the sliding between the chains. The $4O_2$ occupy the 4 heme to form the hydrophilic oxyHb. A relax (R) form of oxyHb has a pKa=6.2 acting as a carrier for O_2 and Mg^{2+} to be release at tissue level, when binding 2,3-DPG^{5-} to form the hydrophobic tense (T) form of deoxyHb pKa=8.2. The in between H-bond breakdown allows an irreversible kinetic step, between both forms of Hb, because are mutually exclusive.*

The importance of this contribution was to show protein dynamics in reference to pressure of O_2 mass action in the orientation of hydrophilic R groups (His, Cys, Asp).

The binding of $2{,}3{-}DPG$ to charged positive R groups lead to hydrophobic state of the protein, with the energy potential in the protein structure in the direction of the spontaneous exergonic dissipative state and therefore the system becomes a potential dissipative thermodynamic path, between hydrophilic oxyHb and hydrophobic deoxyHb.

The dissipative potential functions from the greater atmospheric O_2 pressure to the lower one at the tissue level, became self-organized by Mg^{2+} sequential coordinative from negative residues and the amphoteric histidine. Thus, O_2 pressure creates maximizes potential by Mg^{2+} saturation through bi-, tetra-, hexa-dentate stages, and steadily releases along the differential axis of tissue consumption of O_2 delimited by lower and lower pH (the vertical human posture favors oxygenation of its brain, over that its lower extremities, absent at the quadruple posture of other mammalian.

The model explains sigmoidal binding properties (cooperativity) by the progressive binding by $[Mg.(H_2O)_6]^{2+}$ from two to fourth to six

coordinative states with the corresponding number of R groups.

An open system magnifies the function of the mass action of substrate concentration because the product is in a dissipative state and therefore could acquire a lower concentration than predicted from kinetic equilibrium.

This system allows the human brain to be conditioned by achievement related to the euphoric sense of an athletic successful performance, even at the cost of stressful events. The mechanism may involve the conversion of dopamine to noradrenaline (NA) by dopamine β-monooxygenase, which occurs predominantly inside neurotransmitter vesicles.

Most vertebrate species devote between 2% and 8% of basal metabolism to the brain. In primates, however, the percentage is much higher in humans it raises to 20–25%, a person uses about 320 calories only to think. Thus, this exceptional energy expenditure leads to autonomous thermogenesis, involved in the daily turnover consuming 450ml of cerebrospinal fluid (CSF), to be released as a 5% of vapor in exhaled air.

The vomeronasal organ (VNO) [25] [26] in the oral cavity contains the cell bodies of sensory neurons which have receptors that detect specific volatile and non-volatile (liquid) organic compounds or hormones, which are conveyed to them from the saliva, environment, etc.

Hb transport of nitric oxide

The enzyme nitric oxide (NO) synthase catalyzes from arginine the products citrulline and NO. This one is a strongly reactive radical by having an unpaired electron, solubility in water and lipids, which allows crossing biological membranes. Endothelial cells at the blood vessels surround smooth muscles, which do not have sarcomeres (involuntary non-striated muscle). Muscarinic receptors to acetyl choline (ACh) distend muscle. The endothelial release of Ca^{2+} binds to calmodulin activating the enzymes hemoxygenase: HO-1 (spleen and liver) for NO and HO-2 (brain) for CO from Heme group of Hb, and a third system CSE producing H_2S.

Nitric oxide synthases (NOSs) synthesize the metastable free radical NO. Three isoforms are known for the NOS enzyme: endothelial (eNOS), neuronal (nNOS), and inducible (iNOS), each with separate functions.

NO and CO integrate to activate the cellular smooth muscle activating guanylate cyclase (sGC), generating from GTP the product cGMP. The latter by bridging actin and myosin relaxing muscle and H_2S, activating the K^+ discharge through the K^+ channel, and dilatation of blood vessels.

At low concentrations of the 3 gases contribute to control blood pressure, favor the release of other transmitters and hormones, protecting cells from the oxidative stress. At the brain stimulates learning and cognition. NO differentiates from other transmitters usually enclosed in vesicles and liberated at synapsis like acetylcholine, dopamine and glutamate. NO could diffuse to a distance of $300\mu m$, reaching simultaneously 2×10^6 synapses. Thus, activates in a retrogression manner, the presynaptic neuron. Thus, the process could prolong for many hours the liberation of neurotransmitters by the neurons to potentiate a learning state.

The broad spectrum of NO release of other transmitters in the nervous system, dilates blood vessels in the cardiocirculatory system, protects against oxidizing agents in somatic cells, participates in learning and memory processes in the brain, in the lungs relaxes the respiratory muscles and relaxes the digestive tract and produces erections.

The NO protector effect is expressed along the body and it is considered aggressive at large concentration, it has an odd electron that makes it very reactive and volatile.

The macrophages of the immunity system and the astrocytes microglia, producing myelin at the brain axons has been endowed with a toxic barrier indistinctly acting against all microorganisms, parasites and tumor cells. Hence, is a nonspecific inborn, constitutive and protective defense that could be increased by diet, including arginine.

Consequently, adds to the specific antigenic action by the reaction produces by microorganisms generating disease, which leads the immunity system to produce the corresponding recognizing anti-bodies, which can be reinforced by vaccines.

The NO could react with peroxide water (H_2O_2) to produce peroxynitrite $(ONOO^-)$.

NO in excess could damage cells and at the neuromuscular synapsis activates cAMP production, potentiating the cAMP response element binding

protein (CREB). Also, inhibits the cAMP destruction by phosphodiesterase prolonging its time action, favoring a neuronal circuit plasticity state.

Dietary nitrate as source of NO green, leafy vegetables is concentrated by about 10-fold in saliva and reduced to nitrite in the surface of the tongue by a biofilm of anaerobic bacteria [27] . In the stomach reacts reducing metabolite as vitamin C to produce a high concentration of NO. Thus, allows sterilization of swallowed food and to maintain a gastric mucosal flow into blood [28].

NO is an obligate intermediate in the denitrification pathway and it is converted to nitrous oxide by the activity of NO reductase (NRs). NRs are molybdoenzymes that reduce nitrate (NO_3^-) to nitrite (NO_2^-) in both mammals and plants.

In mammals, the salival microbes take part in the generation of the NO_2^- from NO_3^-, which further produces NO in the presence of nitrite reductases (NiRs) [29].

NO diffusion tubes could be used as a spray in absence of consumers to fumigate food locals, modifying air conditioning could add protecting ventilation, airplane, etc.

Physiological NO production by adding to diet of arginine, presently used as a dietary supplement by bodybuilders because can potentiate the physiological role of NO, dilating blood vessels, improving circulatory systems and muscular development, potentially can improve sports performance and muscle recovery.

Arginine role in aging

At the end of the eukaryotic chromosome, long repetitive DNA strands (telomeres) are configured. Aging produces its shortening, which is correlated with chronic pain and phobic anxiety.

Telomeres shortening in atherogenesis leads to investigate telomerase, a RNA-directed DNA polymerase, which extends the telomeres of eukaryotic chromosomes.

Nitric oxide (NO) is a reactive free radical that regulates transcription of genes involved in development, metabolism and differentiation. Is has been shown that NO activates telomerase and may have in endothelial cells a delay of senescence [30] [31].

Endothelial cells (ECs) undergo a limited number of cell divisions, stop dividing, and reach a replicative senescence by acting as a molecular clock. By the reactivation of telomerase, a cellular reverse transcriptase could prevent telomere shortening [32].

The endothelial isoform of the nitric oxide synthase (eNOS) [33] effect on downstream signaling of the catalytic subunit of human telomerase reverse transcriptase (hTERT, for understanding the pathogenesis and searching for therapeutic approaches) and ERs, counteract the process of endothelial cell aging [34] [35].

The telomeric repeat-binding factor 2 (TRF2) is a protein that is present at telomeres but its function, throughout the cell cycle, has been studied for possible regulatory effect by arginine methylation.

It is suggested that a restriction of senescence progress could be approach, by incubation procedures for Hb, to be used as a carrier of NO. Consequently, adapts the NO saturation of Hb for its *in situ* release to endothelial cells. Thus, allows the gas exchanges, required for vasodilation of blood vessels, in cardiovascular physiology. Exercise improves endothelial function with produce NO, which keeps blood vessels healthy.

The role of Na^+/K^+-ATPase on membrane action potential

Nascent Mg^{2+} compete by attracting water from the shells of Na^+/K^+ allow sizing translocation at the ions gates that support the membrane potential

The erythrocyte as a carrier of the kosmotropic Mg^{2+} could function signaling for the capture of water from the hydration shells of Na^+ and K^+, fitting both into their gates, allowing across the membrane the sieve effects, which confers specific pattern of an action potential, contained in neuronal junction's vesicles to activate the NA activated-adenylate cyclase (AC) located in the locus-coeruleus. A metabolic connection indicates that MgATP consumption generating inorganic phosphate (Pi) to support the level of free Mg^{2+} and phosphatase activity decreasing Mg-chelating metabolite could increase signaling to AC, its activated state of Mg^{2+} over MgATP.

This sieve effect potentiates the K^+/Na^+-translocation operating the membrane potential.

Mg^{2+} activates the Na^+/K^+ ATPase pump opening the gates for Na^+ in and K^+ out.

In response to a nervous impulse, their hydric and dipolar states can change by dynamics of the H-bonds could manifest discrete states of molecular vibration, at $36.6°C$. The brain maintains a steady state in which small changes that last between 200 and 2000 ns do not alter the frequency. Quantum mechanics describes them as wave, phonon. This could be cycled as a vectorial function of hydric-ionic translocation, participating into the active site for enzyme state turnover. The energetic contribution of the H-bond breakdown its value is about: -5kcal/mol utilized to configure a conformational change by mutual exclusion.

Ca^{2+} [36] released activates the glutamate neurotransmission [37]. Serotonin (5-hydroxytryptamine, 5-HT) produced in Raphe nuclei located in the brainstem, could induced Ca^{2+} increase and reduced the cAMP increase [38], indicating cross-talk between the 5-HT-sensitive Ca^{2+} and cAMP pathways. Ionic equilibrium controlling Ca^{2+} effects for a simultaneous dead-end by CaATP [39] [40] inhibition of adenylate cyclase (AC) and mutual exclusion activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, first glutamate receptor ion channel domain.

Turnover, with release of Mg^{2+} from the enzyme as a nascent ion Mg^{2+} acquires a stronger intrinsic charge.

The molecular kinetics synchronization that prevents microscopic reversibility, because could not be conceptually assimilated to the principle of microscopic reversibility requiring a single door, which could allow transit in both senses.

Mutual exclusion between hydrophilic and hydrophobic domains allows vectorial kinetics, which bypasses microscopic reversibility, due to the enzymes turnover has only one sense the hydrophilic changing conformation to the hydrophobic one.

Change conformation turnover of protein is supported by the activation energy of broken H-bonds, from polymeric water in cerebrospinal fluid (CSF), conversion into waste water. Astrocytes [41] could maintain the H-bond wasted state of water in a liquid phase until their release as vapor to the outside of the system, which is equivalent to entropy dissipation.

Quantum physics participation in the function of neurons depends of structures at the synaptic level, contributing to the electron spin differentiating up and down positions, with adapted angular momentum. The electrogenic membrane could allow organizing a non-polarized electron current to acquire polarity and the polarization of the current is maintained by alienation. Hence, the electrons that at the beginning do not manifest orientation are capable to reinforce electrical signals by passing through two layers of similar polarity and signal power decreased when magnetization has opposite senses.

Romero, M. et al. reported Vowel recognition with four coupled spin-torque nano-oscillators [42].

The electrogenic properties allow differential in the one neuron connective capability to maintain an average of 10^4 synapses. Hence, electric signals potentiation will decrease randomness by reinforcement of neuronal circuits. The information paths are organized in layers. Thus, signals combined as synaptic functions learned to interact and compare with experience. After iterative step a consent tendency indicates errors. Microtubules at the cytoplasmic activation step could allow a configuration with a singular conjunction of nodes reinforcing electric signals and therefore eliminating random signals.

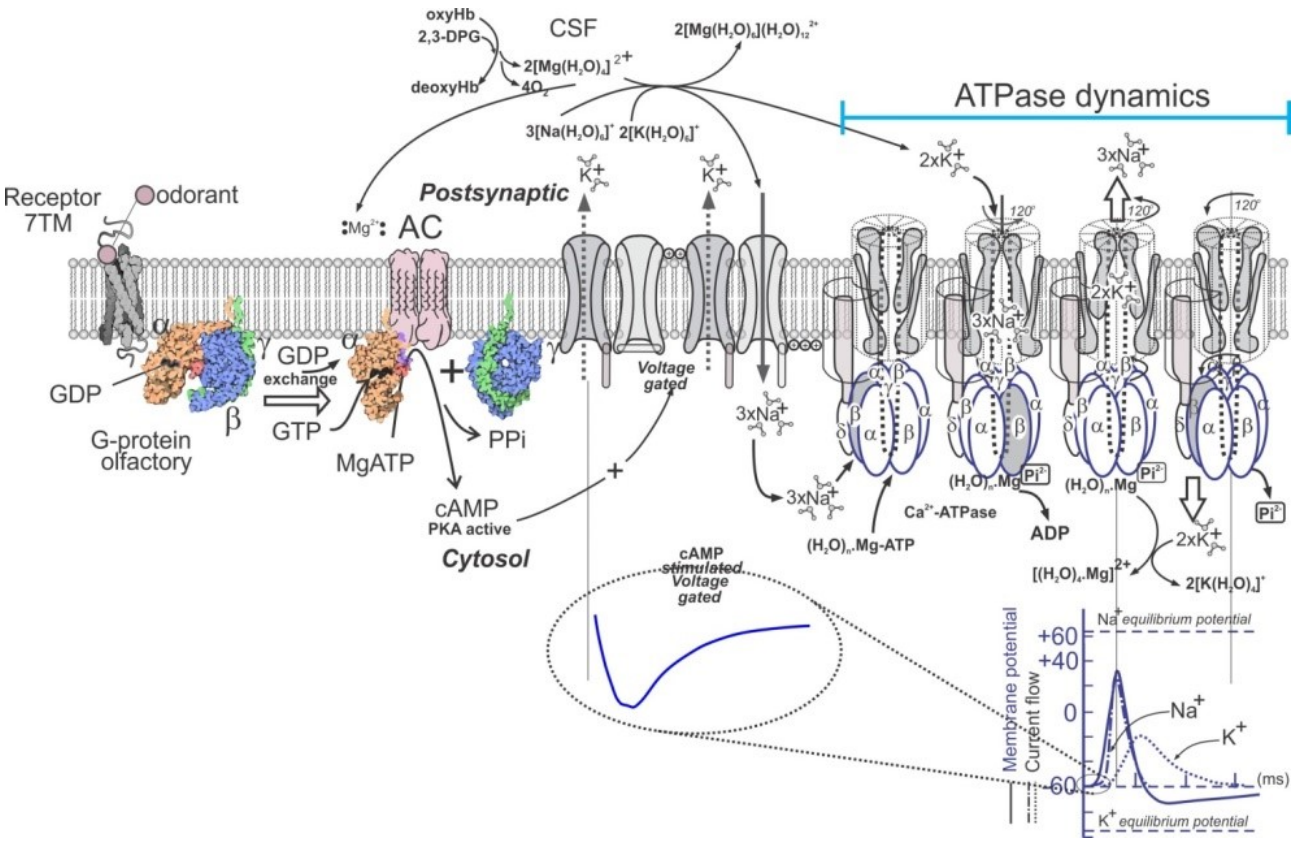


Figure 3: Mg-driven Interaction of ion-hydration shells for the coupling of Na+/K+-ATPase and AC. *The Na+-in channel and the K+-out channel open as a function of changing potential ΔV. MgATP breakdown by the ion pump-ATPase is required for releasing Mg2+, which when in excess of substrate became activatory of basal and NE stimulated AC. The differential strength between the tendencies of ions to complete their hydration shells allows directional reactivity. Moreover, the interactions of water depend of the different and variable stabilities for structuring H-bonds. Exclusion from hydrophobic regions of the protein-lipid electrogenic membrane and the proteins themselves allow one-sided distribution of ligand water sites.*

Hence, allows sequential coupling that in humans become especially reinforced by myelination. The role of spin or angular momentum of electrons will depend on the capability to orient electric impulses into polarized structures of membranes conductivity. Mg^{2+} and Ca^{2+} could coordinate R groups in a membrane of differentiable polarity, also assimilable to hydrophilic for negative R groups coordinating hydrated Mg^{2+}, with H_2O molecules, configuring folding. The latter, responds by sliding when nascent Mg^{2+} is released allow the exposing of positive R groups capable to respond to Ca^{2+} and/or the binding of negative molecules.

There is some similitude for the Na^+/K^+-ATPase pump to create polarity and action potentials by differences on access to channels and building-up of polarity, allowing the emergence of Cartesian wavelongs of differentiable wavelengths to consolidate long-term memories.

The magneto-resistance of the neuron turns modulations of electric current in voltage terminals of synaptic function. The magnetization of the outer membrane vs the inner allows spin transference.

How much current actually flows across the membrane over the course of an action potential?

A typical nerve cell contains 100Na^+ channels per square micrometer. At a membrane potential of +20mV, each channel conducts 10^7 ions per second. Assuming a cell surface $10^4 \mu m^2$ (volume of 10^4 μm^3) corresponds to an increase in the Na^+ concentration of less than 1%. A stronger action potential results very small change in the distribution of charge. Its efficient allows long distance signaling and rapid repetition rates.

Molecular Details of Ligand Selectivity

The ionic radii: 0.072 nm for Mg^{2+}, 0.067 nm for Mn^{2+} and 0.074 nm for Zn^{2+} in the octahedral and 0.060 nm in tetrahedral coordination. These ions are smaller than 0.1 nm Ca^{2+}.

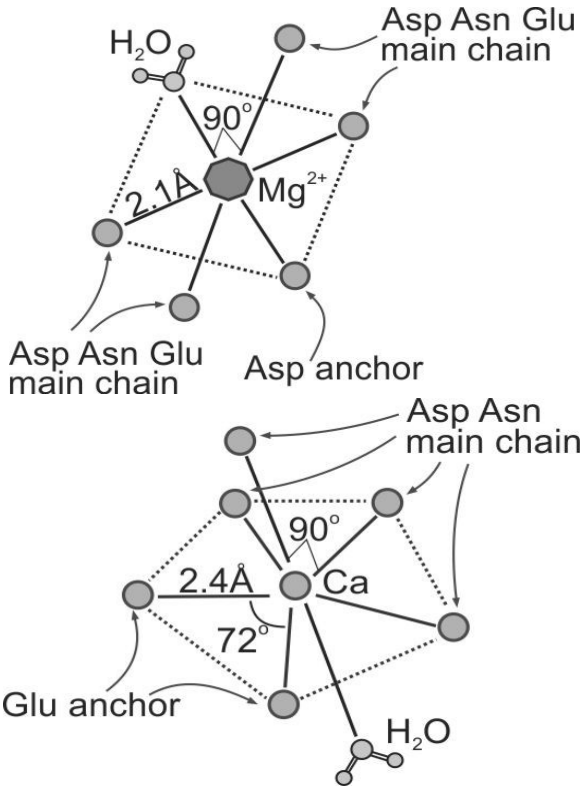


Figure 4: Molecular details of ligand selectivity. *The location of the divalent metals on a simulated protein backbone was obtained by using a program. Aspartate (Asp) with the attachment of Mg^{2+} was use as the anchor position to calculate from this one the other ligand locations. Mg^{2+} was positioned with an apical 6th R-group to constitute an Asp-H_2O axis.*

Mn^{2+} prefers octahedral ligand geometry, whereas Zn^{2+} has a preference for tetrahedral coordination. The obtained R-group configuration for a Ca^{2+}-binding site with 0.24 nm of distance configure a pentagonal-bipyramidal geometry between the divalent metal and each of the side-chains Asp or Asn (anchored to a Glu) and Glutamate (Glu) or Asp provides two atoms of oxygen for a bidentate ligand Ca binding into an EF-hand motif, troponin C (TnC), calmodulin (CaM), neuronal Ca^{2+} sensor proteins (NCS) and the S100 proteins.

At a distance of 0.21 nm between the divalent metal and each side chains: Asp, as an acidic amino acid with a pKa of 3.9, Asn, or Glu with H_2O resulted into an octahedral geometry with 5th and 6th coordinative position configuring the axis.

Hydrophilic Mg^{2+} coordinated structure by sliding allows the release of Mg^{2+}.

Kosmotropic vs chaotropic tendencies adjust the size of the hydration shells of Na^+ and K^+ ions for fitting into the gate by the dynamics of the Na^+-ion-pump

At 37°C the membrane equilibrium potential = −98mV, corresponding to [Na+]in = 14mM and [Na+]out = 143mM, potential = +62mV. For [K+]in = 157mM and [K+]out = 4mM, potential = −98mV. The enzyme is depicted as viewer from the foot of the central stalk. Only the catalytic β-subunits and the γ-subunits are shown. An action potential opens voltage-sensitive calcium channels in the presynaptic membrane, the influx of calcium lead noradrenaline (NA)-vesicles to release NA into the presynaptic cleft. In the arteriole close to the gap, oxyHb conversion to deoxyHb releases Mg^{2+} activating the NA ligand state of the postsynaptic G-protein αS-receptor linked to adenylyl cyclase.

Total cell Mg^{2+} would be in the range of 10mmol/L if it were all free in the cytosol. Hence, as cytosolic Mg^{2+} levels are reported to be 0.5 to 1 mmol/L = 90% to 95% of the cell magnesium is bound or sequestered. Ionized Mg^{2+} levels in mitochondria are reported to be in the 0.5 to 1 mmol/L range and Mg^{2+} levels in SR are reported to be 1 mmol/L5; therefore, most of the magnesium in the cell is bound, regardless of the precise location. The electrochemical gradient across the membrane with regard to extracellular [Mg^{2+}] = 1 mmol/L and cytosolic [Mg^{2+}] = 188 mmol/L involves a membrane potential of -70 mV, Mg^{2+} permeability is low and therefore Mg^{2+}-transporters do not require a high Vmax.

An action potential induces a depolarization that opens the presynaptic channel resulting in vesicular exocytosis. The neurotransmitter binds to postsynaptic receptors. The ionotropic opens the associated ionic channel and produces an ionic flux changing the membrane potential of the postsynaptic neuronal. Depolarizing membrane potential, in the glutamate (Glu) receptors, increases neuronal excitability and result in action potentials.

Hyper-polarization in the γ-aminobutyric acid (GABA) receptors decrease neuronal excitability and reduce tendency to generate an action potential.

There is 0.3 to about 5 millisecond synaptic action delay, between the arrival of the presynaptic signal and postsynaptic response. In the synapsis, the protein domains cross the neuronal membranes exhibiting an extracellular neurotransmitters recognition side.

The ionotropic receptors by association of subunits form the ionic channel that by binding the excitatory neurotransmitters: acetylcholine and Glu undergo conformational changes, which in a few milliseconds opens a channel to the cation Na^+, K^+ and Ca^{2+} or anion Cl^-. The inhibitory neurotransmitter GABA(A) and glycine act by hyper-polarization of the resting membrane. The presence of a receptor generates differential functions with an amply capability to regulation.

The Na^+/K^+-ATPase of the plasma membrane [43] is couple to a cycle in which each molecule of ATP becomes converted to ADP and Pi, moving $2K^+$ ions inward and 3 Na^+ ions outwards. This maintain a membrane potential of −50 to −70 mV (inside negative relative to outside) as result of supporting low Na^+ and high K^+ concentrations in the cell relative to the extracellular fluid.

NA favors divalent metals ligand association with the NA-enzyme with the complex conformational changes mediated by turnover of H-bonds. The protein-hydration shell turnover of broken but reconstituted through equilibrium with water cluster depletion of participating H-bonds involves about 1-7kcal/mol. This exceeds the ambiance thermic energy of about 0.8kcal/mol permitting to adapt signal to noise ratios for efficiency of the neuronal synaptic communication. The frequency transduction of a pulsatile kinetic event allows that a neuronal frequency of about 20-40MHz could be associated into an output nerve impulse.

In the red cell-Hb during deoxygenation could discharge Mg^{2+} at the synaptic cleft. From a network perspective a near simultaneously presynaptic action potential opens the voltage-sensitive calcium channels in the presynaptic membrane.

At the initiation of an action potential, a channel for Na^+ open [44] [45] and the ion moves producing a change in polarity across the axon membrane. Repolarization results from the opening of the channel for K^+ which moves out of the axon. The impulse travels unidirectional down to the axon terminal.

Voltage gated Na^+-channels [46] allow action potential lasting 1 millisecond whereas calcium-based action potentials could last for about 100 milliseconds.

In cardiac muscle cells, an initial fast sodium spike is a primer that onsets rapid calcium spike for muscle contraction.

Membrane depolarization (ΔV) activates specific voltage-operated channel (VOC) isoform voltage operated channels (VOCs) in the plasma membrane to allow a rapid influx of external Ca^{2+} to provide a Ca^{2+} trigger that then activates the ryanodine receptor 2 (RYR2) to release Ca^{2+} stored in the sarcoplasmic reticulum (SR) through a process of Ca^{2+}-induced Ca^{2+} release (CICR). This mechanism is found in cardiac muscle and neurons.

This influx of calcium into the cytoplasm leads to neurotransmitter-vesicles releasing NA to the outside of the presynaptic cleft membrane. Impulse transmission and/or NA binding to its receptor induce the depolarization of the plasma membrane. Neuronal transmission is terminated by the neurotransmitter reuptake linked to Na^+ entry. The β-receptor is present in the hormone-binding subunits of the enzyme AC. When NA binds to its receptor, this one becomes activated to bind G-protein, which is activated by GTP. As has been reported the neurotransmitter activated enzyme, increases Vmax. A network perspective allows integrating Mg^{2+} activating the responsiveness to NA of the postsynaptically located AC. The activated enzyme generates endogenous cAMP, which has the capability to induce changes in the function of ion channels within the membrane.

Postsynaptically, the activated protein kinase-A (PKA) could trigger the ion Na^+ translocation across the voltage-gated Na^+-channel, starting an action potential an completed under the ions Na^+/K^+ cotransport coupled to the Na^+/K^+-ATPase-pump, restoring the initial transmembrane potential. The ATPase itself shows an ATP hydrolysis-dependent turnaround over 3 angles of 120o each coupled to phosphorylation-dephosphorylation of a critical Asp residue in the ATPase itself [47].

ATPase activity of intact cell membranes could manifest ADP-phosphorylation by reversal of K^+ vs Na^+ ion loading or uptake [48].

The rotational properties of Na^+/K^+ ATPase

linked by these ions exchange to the electrogenic properties of neuronal membranes.

Modulation of slow inactivation by neurotransmitters acting through G-protein-coupled receptors, PKA, and protein kinase-C (PKC) is a flexible mechanism of cellular plasticity controlling the firing behavior of central neurons.

Kosmotropes ions organize water into its hydration shell and have the tendency to subtract water from chaotrope ions like $[K(H_2O)_6]^+$. To the first group belong $[Na(H_2O)_6]^+$ with hexagonal geometry in the first water layer and $[Mg(H_2O)_6](12H_2O)^{2+}$ with octahedral geometry in the first and second layers.

The nascent Mg^{2+} greater reactivity allows the ion to capture part of Hydration shell of $[Na(H_2O)_6]^+$. The less hydrated or nascent $[Na(H_2O)_3]^+$ could return to its normal hydration shell, by capturing water from $[K(H_2O)_6]^+$.

An unsaturated hydric shell of the Mg^{2+} ion is capable to subtract water from hexa-hydrated sodium ion, $[Na(H_2O)_6]^+$ to form $[Na(H_2O)_3]^+$, even if the more fully hydrated shell of Mg^{2+}, may loss water to a less hydrated specie of Na^+. The latter, chaotropic strength could capture H_2O from the kosmotropic $[K(H_2O)_6]^+$ to generate tetra-hydrated $[K(H_2O)_4]^+$ and tri-hydrated complexes $[K(H_2O)_3]^+$.

The increase in the manifest charge of Mg^{2+} leads to the capture of H_2O from the shell surrounding Na^+ at the outside of the neurons and by increasing its manifest charge to move for its inclusion at the pores/channel of the membranes. This uptake of Na^+ opens the voltage-gated channel at the beginning of the action potential.

The nerve impulse allows Na^+ from the cerebrospinal fluid (CSF) to enter in the cytoplasm side of the membrane to manifest a positive charge. Charge rearrangement may allow that the Mg^{2+} interacting with the membrane could be released as a less hydrated ion. Breaking a coordinative Mg^{2+}-membrane complex is endergonic and its forming is exergonic. This effect could couple charge exchanges with energy transduction as electrons displace within the electrogenic membrane.

If changes in hydration shells are inferred for ion translocation at the Na^+-pump and at the ATPase, these two processes may cross-couple for partial loss of the hydric shells of Na^+ and K^+ to adapt their sizes [49] to corresponding gate.

The Mg^{2+} discharged by Hb deoxygenation within the red cell could be characterized by its manifest much higher effective charge than the fully hydrated ion because during oxygenation Mg^{2+} to form a chelate with the R-group losses most of its hydration shell. Hence, when the oxyHb-Mg^{2+} and other Mg^{2+}-chelating metabolites complexes break or dissociate release Mg^{2+} surrounded only by an incompletely saturated hydric shell. The increment in the effective charge of Mg^{2+} allows the ion to seek water, altering endothelial cells tight junctions. The Mg^{2+}-discharge at the synaptic cleft resulting in simultaneous activation of the NA-receptor on adrenergic neurons and inhibition of the Glu-receptor of the glutamatergic neurons.

The sizing of the hydration shell of Na^+ is widely accepted as required for the ion to penetrate into its channel at the Na^+-pump in order to reach the interior side of the membrane. The tendency to complete ion hydration shells became synchronized for nerve impulse. In the interior surface of the membrane $[Na(H_2O)_3]^+$ should react with $[K(H_2O)_6]^+$ and the generated $[K(H_2O)_2]^+$ may be able to transit its channel. The Mg^{2+}-driven hydric coupling for ionic translocation decreases the magnitude of ΔH.

The cAMP increment could initiate a voltage-gated nerve impulse because the tendency of the more reactive Mg^{2+} to displace the outside Na^+ into pore channel.

The adenylate cyclase vectorial system

The RARE BiBi mechanism shows a second-order dependence on substrate concentration: Mg^{2+} shows an obligatory step to bind first to activate a site, allowing a binding site for MgATP. Hence, the noradrenaline (NA) activated of the hypothalamic tissue is controlled by obligatory ions Mg^{2+} exceeding the substrate concentration. The cAMP and calmodulin release of Ca^{2+} determine signaling of the amplitude, phase and period of circadian rhythms [50]. ATP^{4-} and chelating metabolites decreases CaATP, strongly activating adenylate cyclase (AC) to increment the cAMP-dependent activation of pathways for memory affirmation.

The feedback inhibitory response to Ca^{2+} occurs after cAMP product has been synthetized in

condition needing to the expulsion of water from the hydrophobic enclosure. The rupture of this enclosure by the mass action of water cluster will liberate cAMP. This leads to vectorial kinetic because prevent the reentrance of cAMP into a kinetic equilibrium, because the active site has collapsed. Restructuration requires the hydrophilic obligatory step. Thus, turnover requires various folding steps, all irreversible by consuming H-bonds. Each kinetic step configures the reorganization of new folding structures because the hydrophilic sequence is always exergonic and involves the MgATP cleavage to generate pyrophosphate and AMP- by about -8kcal/mol. The AMP cycling to generate cAMP is endergonic by about +10kcal/mol. The hydrophilic step evidently could not contribute that enthalpy, but the folding conformation of a hydrophobic cavity involves the H-bond breakdown and expulsion of water. Moreover, in order to release cAMP is needed the mass action of water cluster. The polypeptide changes in folding sum-up to several doors, mutually exclusive, because the sense changes add up as an opening step in the exergonic direction, only after H-bond has been expended to randomness, preventing a return.

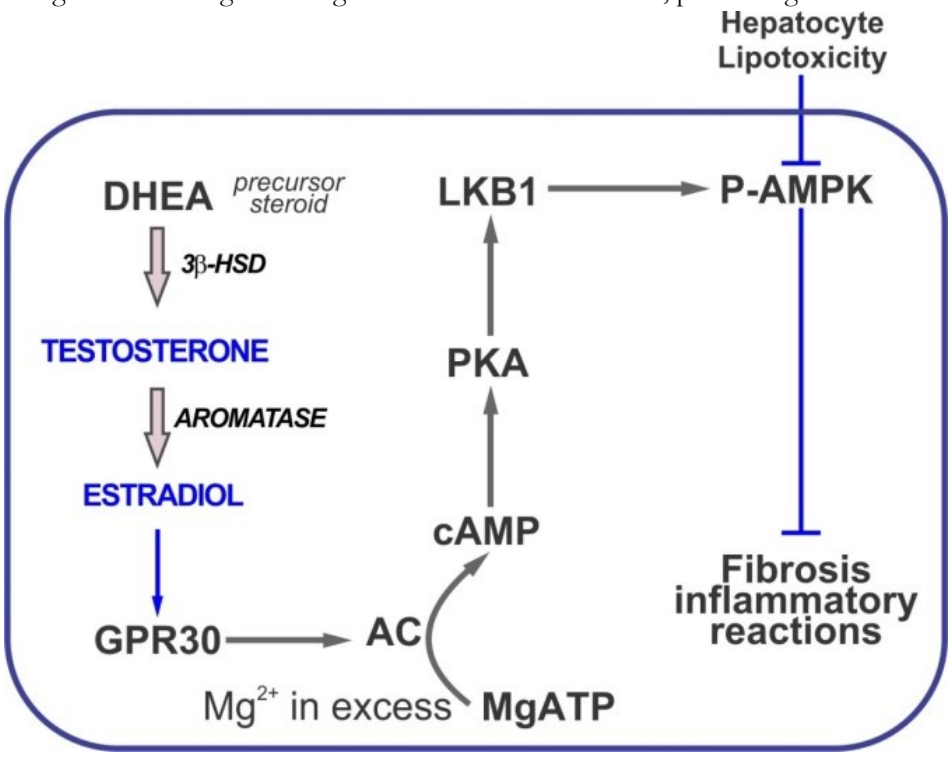


Figure 5: Dehydroepiandrosterone (DHEA) is the most abundant circulating steroid with immune and metabolic regulatory properties, and its level markedly declines with increasing age in humans. G protein-coupled estrogen receptor *(GPR30), protein kinase A (PKA), the LKB1-AMPK pathway: metabolism and growth control in tumor suppression, 5′ AMP-activated protein kinase or AMPK.*

NA (noradrenaline) release by the long axons of the corpus coerellus into the synaptic junctions also contributes to up-regulation of adenylate cyclase (AC) by Mg^{2+} and is turning off by Ca^{2+}.

As open system the accumulated mass action of substrate over dissipative product allows to a human brain to maximize neuronal transmission at a much clear potential overcoming the kinetic energy at a homeostatic temperature.

Adrenaline is coupled to the active site in transfer to AC that is coupled to 7TM G protein receptors [51] activated by a GTP cycle [52] [53]. NA is released by the long axons of neurons [54] of the locus-coeruleus into the synaptic junctions for sensorial-integrated perception between many brain areas. The activation of the Na^{+}/K^{+}-ATPase pump [55] release nascent Mg^{2+}, by decreasing $[ATP^{4-}]$, which has an inhibitory effect on AC.

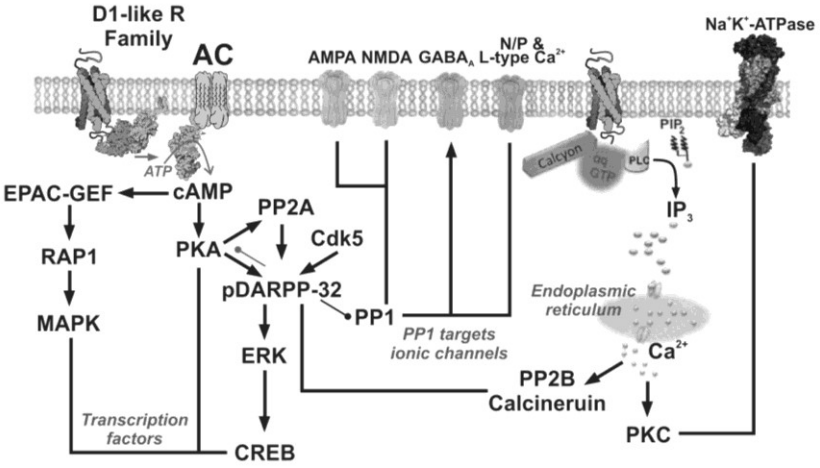


Figure 6: Producing neurotrophins and nerve growth factor, related of inducible gene expression. The D1-like dopamine (DA) receptors act signaling activatory stage to intracellular pathways. *Activation of MAP kinases in neuronal and endocrine cells is critical for cell differentiation and function. This action requires guanine nucleotide exchange factor (GEF)-mediated activation of downstream a host of Ras family small GTPases, which lead to Ras-Raf-MEK-ERK (MAPK/ERK), is a chain of proteins within cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell.*

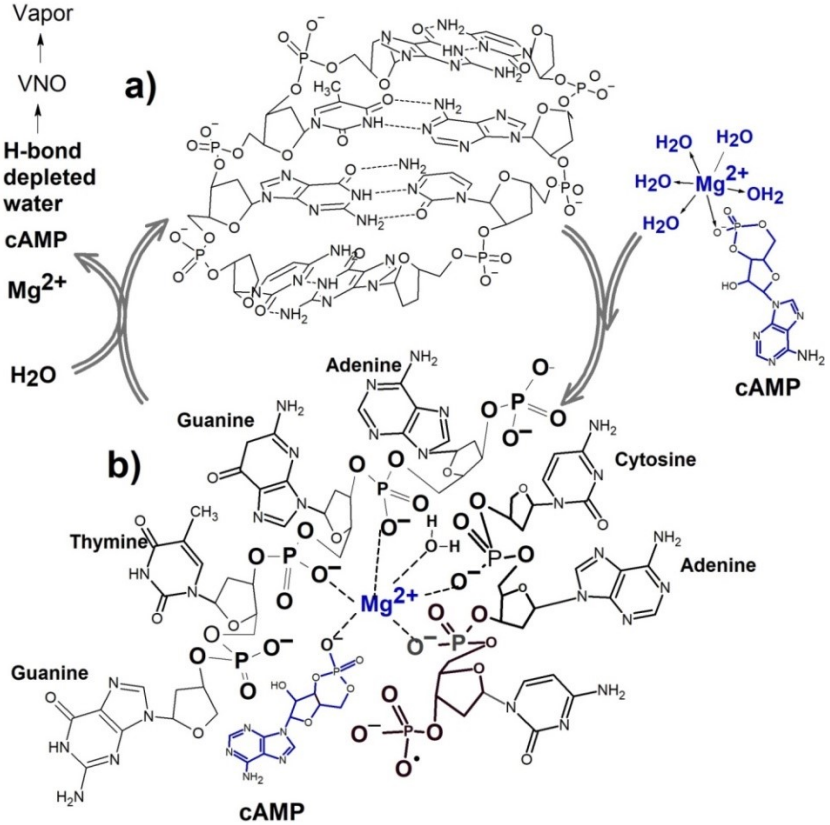


Figure 7: Physiological mechanism for cAMP fitting into the double strands unzipping of nuclear DNA. *The non-physiological treatment technic of heating DNA at* $65°C$ *allows the strands separation and transcription used experimentally. a) Base sequence of the two chains attracted to match in a double stranded binary rotational symmetry of DNA. b) cAMP unzipping mechanism opens the double-stranded DNA structure positioning the outside purines and pyrimidines bases to transcription mechanism leading to protein synthesis.*

CREB regulates transcription of genes: c-fos, BDNF, tyrosine hydroxylase, numerous neuropeptides (such as somatostatin, enkephalin, VGF, corticotropin-releasing hormone), and genes involved in the mammalian circadian clock (PER1, PER2).

Mg-cAMP inserted in domain of DNA allows a switch-on by Mg^{2+} and –off by Ca^{2+}. A dynamic

mechanism to activate gene expression in CREB by inducible gene response to dopamine phosphorylation via G protein coupled receptor. Thus, acting to synthetize brain derived growth factor, a regulator during neuronal development and synaptic plasticity.

Physiological mechanism for cAMP fitting into the double strands unzipping of nuclear DNA or the transitory structure of cffDNA. The non-physiological treatment technic of heating DNA at $65℃$ allows the strands separation and transcription used experimentally. a) Base sequence of the two chains attracted to match in a double stranded binary rotational symmetry of DNA. b) cAMP unzipping mechanism opens the double-stranded DNA structure positioning the outside purines and pyrimidines bases to transcription mechanism leading to protein synthesis.

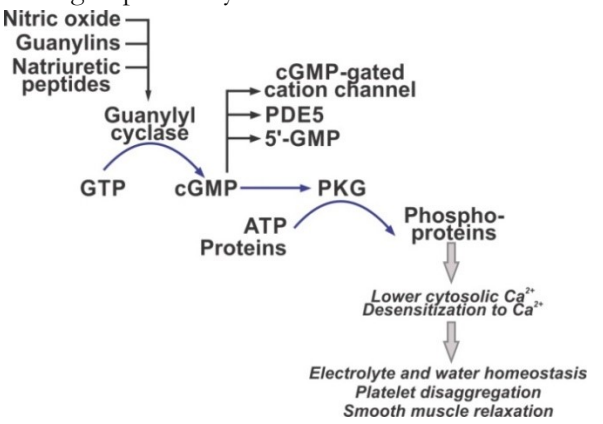


Figure 8: Cyclic GMP (cGMP) produced by guanylyl cyclases the erythrocyte transport cGMP by its uptake from extracellular fluid, without having in situ them enzyme. *Phosphodiesterases-5 (PDE5) breakdown cGMP in smooth muscle cells, platelets, gastrointestinal epithelial cells, and Purkinje cells. Also binds to cGMP to cGMP-dependent protein kinase (PKG), cGMP-gated cation channels, and allosteric sites on PDE5. Cyclic GMP binding to PKG activates the phosphotransferase to phosphorylate cellular proteins involved in Ca^{2+} homeostasis, lowering and desensitization the effects of Ca^{2+}. This effect causes relaxation of smooth muscle, decreased platelet aggregation, and altered transport of electrolytes and water in the gastrointestinal tract. PDE5 is phosphorylated in intact cells in response to stimuli that elevate cGMP, but does not response to elevation of cAMP.*

The water pair hydrophobic structure

The interaction of 2s and 2p orbitals allows a tetrahedral of 104.5° angles from two H atoms of positive charge, potential energy barrier to rotation of one of the water molecules with respect to the other.

A $O-H$ results from the 1s orbit bond strain with O to form a sp orbital. The H-bond of two water molecules, the partially positive hydrogen atom δ^+ attracts the partially 2 δ^- negative charge of one O to the other. The result in a dipole-dipole attraction mediated by the in between H-bonded distance $H-O-H--(OH_2)$ 0.177nm the polarity strength in water 104kcal/mol. The same H covalently to oxygen atom distance of 0.1nm is about 110kcal/mol. An $N-H$ and $C=O--H-N$ as between complementary pairs cytosine attracted to guanine separated by 0.27 to 0.3nm spontaneously attracted to form $H--O$ or $N--O$ by the unshared N or O electrons pairs. The water molecules detached from these intramolecular bonds within a protein become H-bonded between them, in bulk water. The dipolar state can induce transitive dipoles in other close molecules. Liquid state of water clusters show a half-life $10^{-8}s$ to $10^{-11}s$. The average number is $(H_2O)_{n=3.4}$. From liquid state (0.54kcal/g) a large number of H-bonds have to be broken to become vapor.

However, heat homeostasis at cerebrospinal fluid (CSF) hydrophobic medium at the pressure present in astrocytes, is able to maintain the release of single molecule of water by H-bonds breakdown and the hydric affinity disappears and allow a little polar state to manifest aggregated by non-polar interactions of $H_2O::OH_2$, indicating energy configuration: $(H_2O{\sim}OH_2)$, between both oxygen atoms. Thus, circulates within the astrocytes network in a metastable state of high oscillatory tension between the oxygen orbitals, between surrounding hydrogen atoms tending to maintain covalent stability. Water dimer is the most widely examined water cluster. The turnaround angle differentiates six different isomers of water dimers. Hereby, RP isomers are illustrated in figure 9, the potential planar resonance states, orbital-5 $E_{orb} = -15.15eV$ and orbital-9 $E_{orb} = -8.90eV$, with oscillatory potential $\Delta E = -6.25eV$.

Thus, determines several possible states of coherence. Hence, kinetic energy accumulates by resonance amplification. However, in the CSF the

absence of O_2 and N_2 allows coherence and their presence in the air induce a randomness decoherence, into the oral cavity, generates the exhaled vapor to the outside, decreasing entropy of the organism and allows brain to operate electrical impulses by the enthalpy potential of dissipative entropy, approaching the kinetic irreversibility of an open-system.

Ion pairs can form in the hydrophobic interiors of globular proteins. The free energy of solvation of an ion is so large (about 60kcal/mol) that an isolated charged residue is never found in the hydrophobic interior of a globular protein.

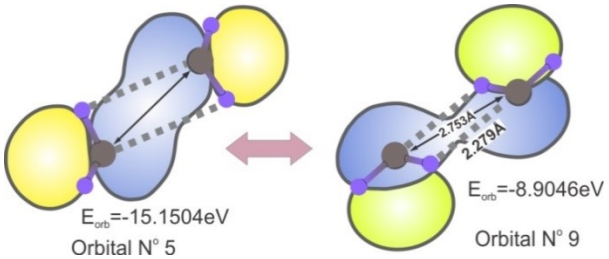


Figure 9: Two oppositely charged ions, however, can form an ion pair. *The free energy change for transfer of two oppositely charged residues from water to the monopolar interior of a protein is about -1kcal/mol. When the ion pair forms, the water molecules in the solvation sphere of each ion are released to the bulk. Each ion therefore loses its free energy of solvation, driving their force for ion-pair formation the increase in the entropy of water clusters, during formation of the ion pair.*

The microwave regions of the electromagnetic spectrum are radio waves, based in hydrogen level 1s orbital that has in energy difference of polarization change spin flip, dividing in two the energy barriers or electron density on the orbital motion. Pauli exclusion to energy density level allows movement only between tunneling is exchanges in the two pair of the H-bond donating and accepting water monomers ($H_2O{\sim}OH_2$).

A more rigorous statement is that, concerning the exchange of two identical particles, the total (many-particle) wave function is antisymmetric for fermions, and symmetric for bosons.

This means that if the space and spin coordinates of two identical particles are interchanged, and then the total wave function changes its sign for fermions.

In the dimers has been determined to begin to flip of the acceptor monomer followed by 180º rotation about oxygen-oxygen bond. The interchange orbital exclusion could be assimilated to the Pauli's exclusion resulting between energy level (barriers).

The vibrational position results from intrinsic magnetic dipole movements as carried to the hydrogen spin. These jump interactions increase in energy parallel and decrease with anti-parallel (spin flip). The frequency (ν) of the quantum relationship $E = h\nu$ detectable by this transition $\lambda = \frac{hc}{E}$.

A water dimer is capable to expand Doppler shifts and became a much broader H spectrum when cooling CSF.

In dimers when the position of the 4H became parallel (relative positions for H-bonds with differential frequency emission). The magnetic movements are antiparallel (spin flip) create harmonics in resonances kinetic energy trapped within the dimer structure. In this which of the wave function of electron and proton overlap because de e^- encompasses partially the proton location. The structure could expand the energy contend by vibration absorbing kinetic energy, trapping in resonance maintaining coherence under limit of pressure (microtubules) and temperature.

The dimers exhibit three distinct low barriers to kinetic pressures over orbital displacement. This resistance results in vibrational states, stabilized by resonance.

Analysis of H atomic closeness distance for electron and proton leads to a Pauli's resistance to configure the same quantum state and explain a vibrational state shared at H atoms, forced to partially share microscopic space at differential time to elude the exclusion. Since the magnetic dipoles unstable state represents the possibility to emit tiny current loops, structuring the high energy reached by the dipoles, within water pairs.

Discussion

Prigogine modeled life as an open system capable of decreasing entropy. However, his cosmological model was not dissipative but based on a tendency for mass action equilibrium between enthalpy and entropy.

Common knowledge describes a thermodynamics system as open to the sun and integrated to life dependent of H_2O [56]. The confluence of requirements should be evident in

terms that the sun evaporates water clusters: $(H_2O)_n$ by separating the molecules integrated in the complex and day-cycle allows the cooling for the vapor condensing as rain and return to the water cluster state.

The state of coordinative linked H-bonds became a reactant with negative and amphoteric His R groups to coordinate Me^{2+}, associated to a domain configuring a hydrophilic state to a protein.

Mutual exclusion between transitions leads the first state breakdown to become dissipated to allow for the next one molecular state. These transitions are coupled by H-bonds breakdown of the overcoming mass action of water cluster. Thus, the process characterizes vectorial cyclic kinetics for turnover of enzyme active sites, Hb, etc., overcoming the microscopic reversibility principle. This, sequence of reconfigurations allows open system to operate and a rapid dissipative axis of entropy could magnify the potential of enthalpy well about noise. Thus, allowing a restriction to indeterminism.

Mutual exclusion by H-bonds breakdown leads to. The presence of the proline in the polypeptide chains allows folding and displacement to create a competitive for amphoteric R groups and complemented by positive R groups domain to create attraction for negative molecules, like $2{,}3\text{–}DPG^{5-}$, ADP^{3-}, etc., which configures a hydrophobic or less polar state. Turnover from hydrophilic to hydrophobic state is a repetitive circular sense.

Thus, increasing rotational and vibrational kinetic activity, on the separated individual H_2O molecules, but maintaining a liquid coherence, during circulation within astrocytes until the lower pressure at the vomeronasal organ (VNO) [57] allows phase conversion to vapor, equivalent to entropy dissipation. The summation of the energy generated by metabolites and H-bond consumption allows the brain thermodynamics to support high ratios between metabolite concentrations and the electrogenic action potential in the dissipative states, within an open system.

The dissipative thermogenic H-bonds breakdown within water cluster configures a randomness increment when coupled to the proline-dependent folding of a polypeptide, but under experimental conditions the potential of an irreversible process would be undetectable because the protein concentrations could be μM whereas the mass-action of environmental water cluster would be several millions higher.

Conclusions

Maxwell predicted from a simplistic thermodynamics response to the randomness of heat distribution, the absence of vectorial kinetics. However, a role of structure and function become evident by the findings on the function of CF_1-ATPase-Synthase, when characterized by resolution-reconstitution and its purification. Thus, develops a prediction for the structural pathway for thermogenic flow from water clusters into its singular molecules, in the vapor state and its entropy exit. Thus, the opening and closing of doors is inalterable by a microscopic memory of the primary amino acid sequence of a polypeptide, and its differentiable domains in response to electrostatic and hydrophobic attractions. However, when the proline-dependent folding became coupled to water clusters functioning by H-bonds breakdown, mediates changes in the folding tertiary structure to respond to the dynamics of segment inter-sliding. These ones determine vectorial kinetics by approaching or distancing functional configurations, mediating the microscopic sequence of events within an active site. Moreover, the H-bonds twists reconfigurations, never reach energy equilibrium, because is irreversible by a dissipative exit from the system by a heat randomness of vapor.

The Pauli principle exclusion does not allow two fermions to occupy the same quantum state. Thus, within an atom, the electrons first lodge into an unoccupied lower orbital, then-on the empty levels up to threshold denominated Fermi distance. Under BCS (Bardeen-Cooper- Schrieffer) model, a within superconductor the electrons could not be treated as individually repulsive particles. Thus, each pair of particles does not behave like fermions, but as bosons, another relation between energy and matter, in which pairs of electrons could agglomerate as a Bose-Einstein condensate. The BCS derivative theories assume that in the boson state interactions could be related to the electron spins. The electron is not limited to orbiting a proton because it also turns around its axis. Accordingly, the movement of atoms became

differentiable from classical physics description as solid, liquid and gasses. Furthermore, rotational movement could take only one sense and therefore automatically allows bypassing the microscopic reversibility principle by allowing vectorial dissipative potentials rather than tendency to only relate to mass-action equilibrium.

Moreover, the rotation sense only limits one possible sense, but creates two complementary states denominated up and down. The latter, predicts water pairs by opposite alignment of spins, which could integrate shared orbitals.

Bosons have yet to be accepted for the emergence of entanglement. However, this matter to energy relationship predicts coherence-decoherence states over the whole cosmos. But, if so, the matter could be related to every characteristic of the cosmological level.

A cosmological dissipative system is far from equilibrium associated with the dissipative Planck bosons energy [58] based in quantum mechanics as inwardly open thermodynamics. This model meets the challenge implicated by primordial gravitational waves, which has only one turn around sense or vectorial dimensioning of a self-contained universe.

The flow of enthalpy into the system would be well above the generated entropy, which will exit as vapor or singular dissociated molecules. Therefore for all purposes the sliding turnover of the tertiary structure could maintain structure-functional changes, without truly affecting total free energy (ΔG). The conditions reflect the energy state of the polypeptide to have the dynamic of an open molecular thermodynamic state because it operates by the enthalpy input of a flow of H-bond breakdown, vectorial directed to the outside of the system.

Also may describe microscopic levels of entanglement linkage between quantic energy. This one allows superposition and uncertainty under a discontinuous spatial microscopic structure of energy. This becomes permissible if delocalization results from a shorter time-causality than the one required for encompassing a time coincidence of microscopic events.

A variable span of time parameter fluctuation, which delocalizes or not, the relationship between energy and space would lead to uncertainty.

Unstable coincidence within available energy flowing into available space could develop from the Pauli's principle of classic physics if could be integrated with a quantum mechanics treatment.

Let's consider that this means that orbitals trajectories intertwine by compression at temperatures compatible with life. This condition allows evaluation of the kinetic energy absorbed to form dimers ($H_2O{\sim}OH_2$) from H-bond depleted ones and circulates in liquid state, before that released as vapor.

Analysis of closeness H atomic distance for electron and proton leads to a Pauli's resistance to configure the same quantum state and explain a vibrational state shared at H atoms level, forced to partially share space at differential time eluding the exclusion. Since the magnetic dipoles overlap, represents the possibility to emit tiny current loops, structuring the high energy reached by the dipoles, within water pairs.

The conclusion is that the resonance between two isomers of the dimer orbitals keeps energy into the opposition between compressions and distensions by quantum mechanism, preserving vectorial kinetics.

The results should be lacking H-bonds dissipated from water clusters: $(H_2O)_n$, gain in the degree of randomness and the system as a whole pulled by opening the organismal system thanks to entropy release.

The kinetics energy solvation provides a polarity scale for unidirectional unitary sense of the circulatory flow for the thermogenic transitions for dissipation into the exit of organismal entropy.

Thermodynamically the complete process is a cyclic one. A turnover from solar thermogenesis, generating vapor, the kinetic equivalent of entropy (S), which is dissipated by cooling and generates enthalpy (H), an Gibbs free energy: $\Delta G = \Delta H - T\Delta S$. Hence, ΔG would be potentiated by dissipative entropy, which results in an open system out of the equilibrium.

Structure and function thermodynamics show that chemical transitions are coupled by mass-action, leading to equilibrium in a closed system. A symmetry breaking has to appear to prevent coupling between two differential forms of energy. Thus, chemical affinity could not couple with the randomness of the dissipative vector potential of heat. The heat expulsion-out of the system, or entropy, allows dissipative events, a characteristic of

open-system.

The dead-end kinetic inhibition of adenylate cyclase activity [59] [60] [61], which involves H-bond breakdown of intermediates, does not manifest a singular characteristic of a direct irreversibility, but rather the incompatibility of dead-end inhibition with the obligatory step because the active site could not respond to a bidirectional transit at the same time.

The turn-on, or turn-off, involves the continuous reconstruction of the active site itself, an obligatory step, or specific path for turnover, in addition to the reactions intermediates to form cAMP. Turnover involves an Mg^{2+} activatory site before binding the substrate Mg-ATP. The integration with the coupling of Ca^{2+}, generating the dead-end inhibition could not occur simultaneously. The integration does require a microscopic time vector to operate under differentiated microscopic spatial relationships and requires additional inputs of enthalpy.

References

[1] Bennun, A. and Avron, M. Light-dependent and light-triggered adenosine triphosphatases in chloroplasts, Biochimica et Biophysica Acta, 79, 646-648 (1964).

[2] Bennun, A. and Avron, M., The relation of the light-dependent and light-triggered adenosine triphosphatases to photophosphorylation, Biochimica et Biophysica Acta, 109, 117-127 (1965).

[3] Bennun, A., Hypothesis for coupling energy transduction with ATP synthesis or ATP hydrolysis, Nature New Biology, 233 (35), 5-8 (1971).

[4] Bennun, A., A model mechanism for coupled phosphorylation, Proceedings 3rd International Congress on Photosynthesis, Rehovoth (M. Avron, ed.), , Vol. 2, pp. 1107-1120 (1974), Elsevier Sciences Pub. Co., Amsterdam.

[5] Bennun A. Interaccion de factor acomplante del cloroplasto con protons y agua. Recientes Adelantos en Biologia (página 254) Editores Raul H. Megia y Jaime A. Moguilevsky, simposia Buenos Aires, 1971 (Titration with glycerol allow to determine the number of water molecules involved in the turnover of the active site of CF1-ATPase).

[6] Bennun, A. and Bennun, N., Hypothesis for a mechanism of energy transduction. Sigmoidal kinetics of chloroplast's heat-activated ATPase, Proceedings 2nd International Congress on Photosynthesis Research (G. Fortí, M. Avron and A. Melandri, eds.), Vol. 2, 1115-1124, (1972). Dr. W. Junk N.V. Pub., The Hague.

[7] Bennun, A., The unitary hypothesis on the coupling of energy transduction and its relevance to the modeling of mechanisms, Annals of the New York Academy of Sciences, 227, 116-145 (1974).

[8] Bennun, A., Hypothesis on the role of liganded states of proteins in energy transducing systems, Biosytems, 7, 230-244 (1975).

[9] Bennun, A. Interacción de factor acomplante del cloroplasto con protones y agua. Recientes Adelantos en Biologia (página 254) Editores Raul H. Megia y Jaime A. Moguilevsky, simposia Buenos Aires, 1971 (Titration with glycerol allow to determine the number of water molecules involved in the turnover of the active site of CF1-ATPase).

[10] Bennun, A., Hypothesis for coupling energy transduction with ATP synthesis or ATP hydrolysis, Nature New Biology, 233, 35, 5-8 (1971).

[11] Bennun, A. and Bennun, N., Hypothesis for a mechanism of energy transduction. Sigmoidal kinetics of chloroplast's heat-activated ATPase, Proceedings 2nd International Congress on Photosynthesis Research (G. Fortí, M. Avron and A. Melardri, eds.), 2, 1115-1124, (1972). Dr. W. Junk N.V. Pub., The Hague.

[12] Bennun, A. The unitary hypothesis on the coupling of energy transduction and its relevance to the modeling of mechanisms, Annals of the New York Academy of Sciences, 227, 116-145 (1974).

[13] Bennun, A. Hypothesis on the role of liganded states of proteins in energy transducing systems, Biosytems, 7, 230-244 (1975).

[14] Yitian Gao, Hongwei Fang and Ke Ni. A hierarchical clustering method of hydrogen bond networks in liquid water undergoing shear flow. Scientific Reports. 11(9542) (2021).

[15] Perutz, M. F. Stereochemistry of cooperative effects in heamoglobin. Nature, 228, 726-739 (1970).

[16] Bennun, A. A coupling mechanism to inter-relate regulatory with haem-haem interactions of haemoglobin. Biomed. Biochim. Acta, 46 (2/3), 314-319 (1987).

[17] Bennun, A., Needle, N.A. and De Bari, V.A. Infrared spectroscopy of erythrocyte plasma membranes. Biochemical Society Transactions, 13, 127-128 (1985).

[18] Bennun, A., Seidler, N. and De Bari, V.A. Divalent metals in the regulation of hemoglobin affinity for oxygen. Annals of the New York Academy of Sciences, 463, 76-79 (1986).
[19] De Bari, V.A., Novak, N.A. and Bennun, A. Cyclic nucleotide metabolism in the human erythrocyte, Clinical Physiology and Biochemistry, 2, 227-238 (1984).
[20] Bennun, A., Seidler, N. and De Bari, V.A. A model for the regulation of haemoglobin affinity for oxygen, Biochemical Society Transactions, 13, 364-366 (1985).
[21] Novembre, P., Nicotra, J., De Bari, V.A., Needle, N.A. and Bennun, A. Erythrocyte transport of cyclic nucleotide, Annals of the New York Academy of Sciences, 435, 190-194 (1984).
[22] De Bari, V.A. and Bennun, A., Cyclic GMP in the human erythrocyte. Intracellular levels and transport in normal subjects and chronic hemodialysis patients, Clinical Biochemistry 15(4), 219-221 (1982).
[23] Taqui-Khan, M. M. and Martell, A. E. Metal chelates of adenosine triphosphate. J. Phys. Chem., 66, 10-15 (1962).
[24] Vicario, P.P., Saperstein, R. and Bennun, A. Role of divalent metals in the activation and regulation of insulin receptor tyrosine kinase. BioSystems, 22, 55-56 (1988).
[25] Rivière, S., Challet, L., Fluegge, D., Spehr, M., Rodriguez, I. Formyl peptide receptor-like proteins are a novel family of vomeronasal chemosensors. Nature., 459 (7246), 574-577 (2009 May 28).
[26] Liberles, S.D., Horowitz, L.F., Kuang, D., Contos, J.J., Wilson, K.L., Siltberg-Liberles, J., Liberles, D.A. and Buck, L.B. Formyl peptide receptors are candidate chemosensory receptors in the vomeronasal organ. PNAS, 106 (24), 9842-9847 (June 16, 2009).
[27] Lundberg, J.O., Eddie Weitzberg, E; Gladwin, MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nature Reviews Drug Discovery. 7 (2), 156-167 (2008).
[28] Green, S.J. Nitric oxide in mucosal immunity. Nature Medicine. 1 (6), 515-517 (1995).
[29] Abraini, J.H., David, H.N., Lemaire M. Potentially neuroprotective and therapeutic properties of nitrous oxide and xenon. Annals of the New York Academy of Sciences. 1053 (1), 289-300 (2005).
[30] Mojiri, A. et al. Telomerase therapy reverses vascular senescence and extends lifespan in progeria mice. Eur Heart J. 42(42), 4352-4369 (2021 Nov 7).
[31] Vasa, M., Breitschopf, K., Zeiher, A.M. and Dimmeler, S. Nitric oxide activates telomerase and delays endothelial cell senescence. Circ. Res. 87(7), 540-2 (2000 Sep 29).
[32] Sinha-Datta, U. *et al.* Transcriptional activation of hTERT through the NF- B pathway in HTLV-I-transformed cells. Blood 104(8), 2523-31 (November 2004).
[33] Azadeh Haghighitalab, Maryam M Matin, Ahmad Amin, Shima Minaee, Hamid Reza Bidkhori, Thorsten R Doeppner and A. Reza Bahrami. Investigating the effects of IDO1, PTGS2, and TGF-β1 overexpression on immunomodulatory properties of hTERT-MSCs and their extracellular vesicles. Sci Rep. 11(1), 7825 (2021 Apr 9).
[34] Meireson, A., Devos, M. and Brochez, L. IDO expression in cancer: Different compartment, different functionality?. Front. Immunol. 11, 531491 (2020).
[35] Antonella Farsetti, Annalisa Grasselli, Silvia Bacchetti, Carlo Gaetano and Maurizio C Capogrossi. The telomerase tale in vascular aging: regulation by estrogens and nitric oxide signaling. J Appl Physiol, 2009 Jan, 106(1), 333-7 (1985).
[36] Guerra-Gomes, S., Sousa, N., Pinto, L., Oliveira, J.F. Functional roles of astrocyte calcium elevations: from synapses to behavior. Front Cell Neurosci., 11, 427 (2018 Jan 17).
[37] McEntee, W.J. and Crook, T.H. Glutamate: its role in learning, memory, and the aging brain. Psychopharmacology (Berl)., 111 (4), 391-401 (1993).
[38] Amireault, P., and Dubé, F. Intracellular cAMP and calcium signaling by serotonin in mouse cumulus-oocyte complexes. Mol. Pharmacol. 68 (6), 1678-1687 (2005 Dec).
[39] Harris, R., Cruz, R. and Bennun, A. The effect of hormones on metal and metal-ATP interactions with fat cell adenylate cyclase. *BioSystems*, 11, 29-46 (1979).
[40] Bennun, A. and Racker, E. Partial resolution of the enzymes catalyzing photophospharylation IV. Interaction of coupling factor I from chloroplast with components of the chloroplast membrane. J. Biol. Chem., 244, 1325-1331 (1969).
[41] Oberheim, N.A., Nedergaard, M., et al. Uniquely hominid features of adult human astrocytes. J Neurosci., 29 (10), 3276-3287 (2009

Mar 11).
[42] Romero, M. et al. Vowel recognition with four coupled spin-torque nano-oscillators. Nature. 563, 230-234 (November 2018).
[43] Gerber, G., Berger, H., Janig, G.R. and Rapoport, S.M. Interaction of haemoglobin with ions. Quantitative description of the state of magnesium, adenosine 5'-triphosphate, 2,3-disphosphoglycerate, and human haemoglobin under simulated intracellular conditions. Eur. J. Biochem., 38, 563-571 (1973).
[44] Rodrigues, T.B. and Cerdán, S. The cerebral tricarboxylic acid cycles. In Handbook of Neurochemistry and Molecular Neurobiology, Eds. Lajtha, A., Gibson, G. and Dienel, G. (New York: Springer), 63-91 (2007).
[45] Rodrigues, T.B., Valette, J. and Anne-Karine Bouzier-Sore. 13C NMR spectroscopy applications to brain energy metabolism. Front. Neuroenergetics, 5, 9 (2013).
[46] Morris, P. and Bachelard, H. Reflections on the application of C-13-MRS to research on brain metabolism. NMR Biomed. 16, 303-312 (2003).
[47] Bennun, A., Seidler, N. and De Bari, V.A.. A model for the regulation of haemoglobin affinity for oxygen. Biochemical Society Transactions, 13, 364-366 (1985).
[48] Vicario, P.P. and Bennun, A. Separate effects of Mg2+, MgATP, and ATP4- on the kinetic mechanism for insulin receptor tyrosine kinase. Archives of Biochemistry and Biophysics, 278, 99-105 (1990).
[49] Sutherland, E.W., Rall, T.W. and Menon, T. Adenylyl cyclase. I. Distribution, preparation, and properties. J. Biol. Chem., 237, 1220-7 (1962).
[50] O'Neill, J.S. and Reddy, A.B. The essential role of cAMP/Ca^{2+} signaling in mammalian circadian timekeeping. Biochem Soc Trans. 40 (1), 44-50 (2012).
[51] Ramms, D.J., Raimondi, F., Arang, N., Herberg, F.W., Taylor, S.S. and Gutkind, J.S. Gαs-Protein Kinase A (PKA) Pathway Signalopathies: The Emerging Genetic Landscape and Therapeutic Potential of Human Diseases Driven by Aberrant Gαs-PKA Signaling. Pharmacol Rev. 73(4), 155-197 (2021 Oct).
[52] Efeyan, A., Zoncu, R., Chang, S., Gumper, I., Snitkin, H., Wolfson, R.L., Kirak, O., Sabatini, D.D. and Sabatini, D.M. Regulation of mTORC1 by the Rag GTPases is necessary for neonatal autophagy and survival. Nature, 493(7434):679-83 (2013 Jan 31).
[53] Ren, M., Zeng, J., De Lemos-Chiarandini, C, Rosenfeld, M., Adesnik, M. and Sabatini, D.D. In its active form, the GTP-binding protein rab8 interacts with a stress-activated protein kinase. Proc Natl Acad Sci USA. 93(10), 5151-5 (1996 May 14).
[54] Sanchez-Arias, J.C., Liu, M., Choi, C.S.W., Ebert, S.N., Brown, C.E. and Swayne, L.A. Pannexin 1 Regulates Network Ensembles and Dendritic Spine Development in Cortical Neurons. eNeuro. 6(3), ENEURO.0503-18 (2019 Jun 6).
[55] Omori, K., Omori, K., Morimoto, T., Takada, T., Akayama, M., Yoshimori, T., Sabatini, D.D. and Tashiro, Y. Expression, localization, and function of an N-terminal half fragment of the rat Na,K-ATPase beta-subunit in HeLa cells. J Biochem., 109(2), 267-75 (1991 Feb).
[56] Bennun, A. The Thermodynamic Inwardly Open System by Locally Decreasing Entropy Originates Life. viXra.org > Relativity and Cosmology > viXra:2104.0155 https://vixra.org/abs/2104.0155 (2021-04-25).
[57] Trotier, D. Vomeronasal organ and human pheromones. European Annals of Otorhinolaryngology. Head and Neck Diseases, 128 (4), 184-190 (2011).
[58] Bennun, A. and Ledesma, N. The Photon Structure in Interference Processes, Quantum Entanglement and Self-Organized Cosmos. viXra.org > Relativity and Cosmology > viXra:2109.0214 (2021-09-30).
[59] Brydon-Golz, S., Ohanian, H. and Bennun, A. Effects of noradrenaline on the activation and the stability of brain adenylate cyclase, Biochem. J. 166, 473-483 (1977).
[60] Ohanian, H., Borhanian, K., De Farias, S. and Bennun, A. A model for the regulation of brain adenylate cyclase by ionic equilibria, Journal of Bioenergetics and Biomembranes, 13(5/6), 317-355 (1981).
[61] Ohanian, H., Borhanian, K. and Bennun, A. The effect of manganese on the regulation of brain adenylate cyclase by magnesium and adenosine triphosphate, Biochemical Society Transactions. 6, 1179-1182 (1978).