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A Novel Hypothesis as to the Origin of Autism: An Alteration in Biological Water Dynamics Disrupts Proton-Coupled Electron Transfer and the Organizing Function of CNS Fractones

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OVERVIEW:

- THE GOAL: Apply a chemical biology, biophysical perspective to the
  (a) pathophysiology and
  (b) prevention of Autism, Schizophrenia, and Alzheimer's

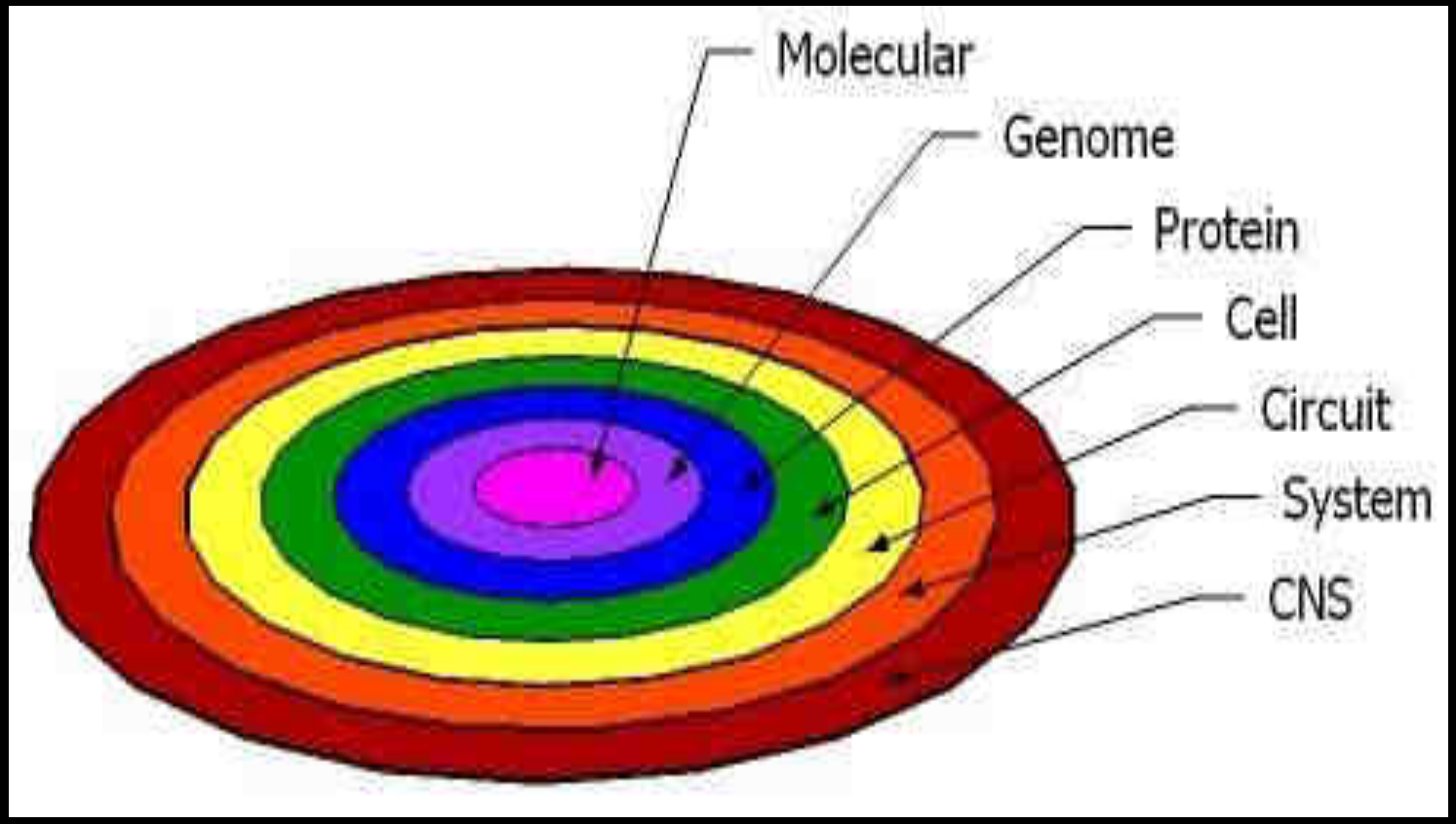
- THE HOPE: To one day find a cure, or preferably, a prevention

- Hans Selye: Most diseases are pluricausal, highly-stereotyped, and supramolecular in origin.

- TODAY: Let's focus on just 3 levels of biosemiotic organization:

SUBATOMIC ←→ MOLECULAR ←→ CELLULAR

Conceptual Background: Coherent Nested Hierarchy of Biological Signalling Levels

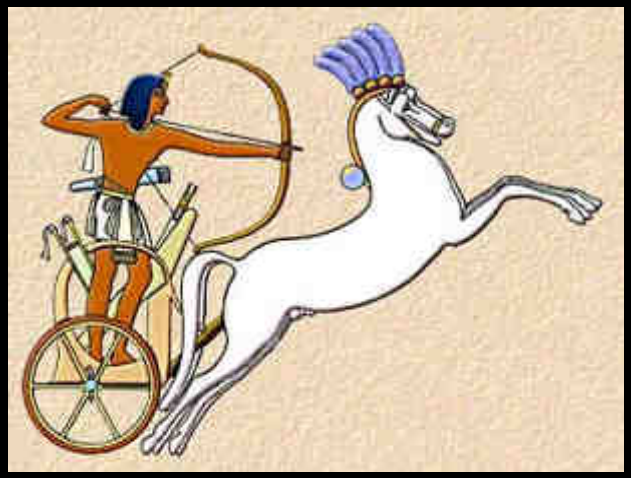


There's A New Game in Town! It's Non-Linear!

- Chemical Biology is the gateway to Quantum Biology

- Medical schools need to teach new ways of looking at
  - (a) health at the molecular level
  - (b) underlying causes of diseases

- We've got to escape the trap of "linear thinking": the "magic bullet" mentality



"A pill or shot for every malady"

A Novel Hypothesis: The Origin of the Fractal Dimension

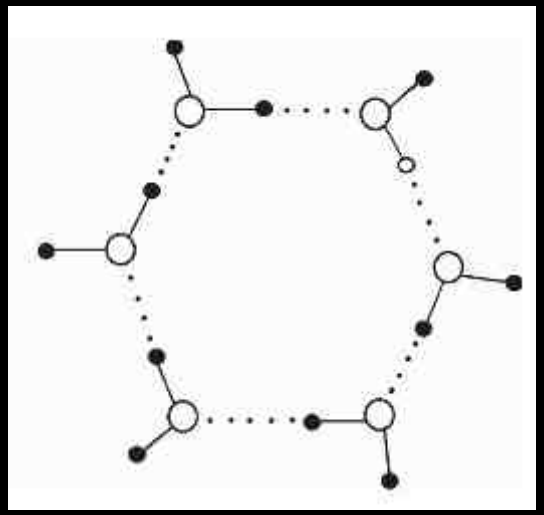
WE PROPOSE:

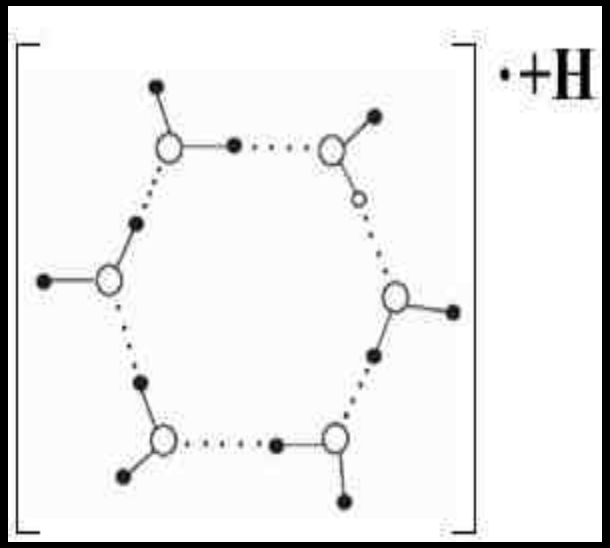
- Bipolarons represent hydrated electrons in low pH reductive environments
  - Hydrated electrons represent the "fractal dimension"
  - Redox potential and surface energy of water are pH-dependent
  - -- pH dependent speciation of e(aq's) modulates their ability to undergo Bose-Fröhlich-Einstein condensation and might play a role in quantum consciousness

- CNS fractones need a "universal sulfurylation factor" and 2-O-sulfate-L-ascorbate radical may be the universal sulfurylation factor, facilitated magnetohydrodynamically by hydrated electrons to supply sulfate to HSPGs

- Fractones are functionally maintained as stem cell "niches" via autocatalytic radical initiation, propagation, and comproportionation of the ascorbate radical

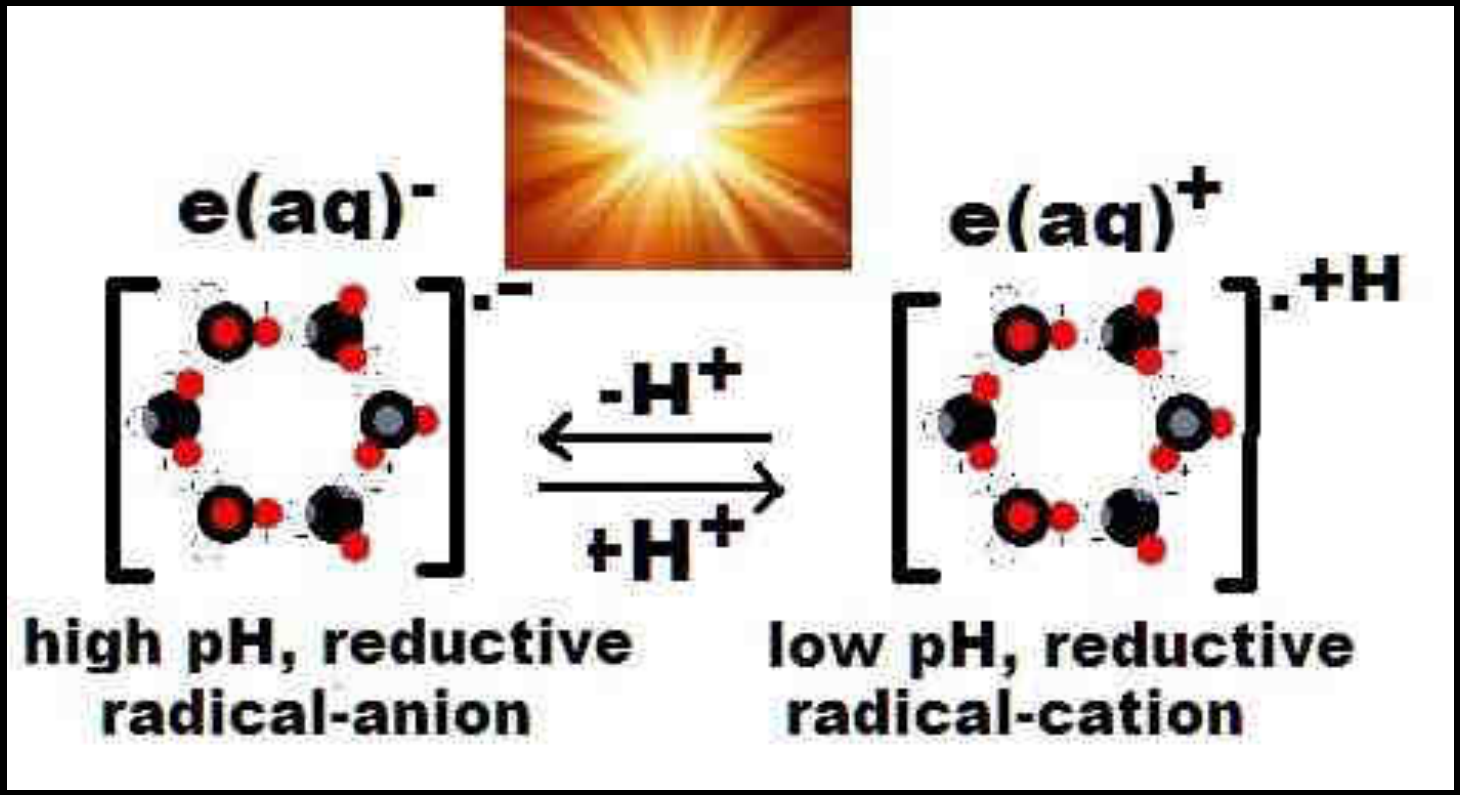
Conceptual Genesis of Our Hypothesis: The Origin of The Fractal Dimension





(1) Pang, X.F. The conductivity properties of protons in ice and mechanism of magnetization of liquid water. *Eur. Phys. J. B* **2006**, *49*, 5–23.
(2) Davidson, R.M.; Lauritzen, A.; Seneff, S. Biological Water Dynamics and Entropy: A Biophysical Origin of Cancer and Other Diseases. *Entropy* **2013**, *15*, 3822-3876.
(3) Men, Z., Fang, W., Li, Z., Sun, C., Li, Z. and Wang, X. (2015). Hydrated-electron resonance enhancement O-H stretching vibration of water hexamer at air-water interface. *Optics letters,* **40,** 1434-1437.

Our Proposal for pH Dependent e(aq) Speciation

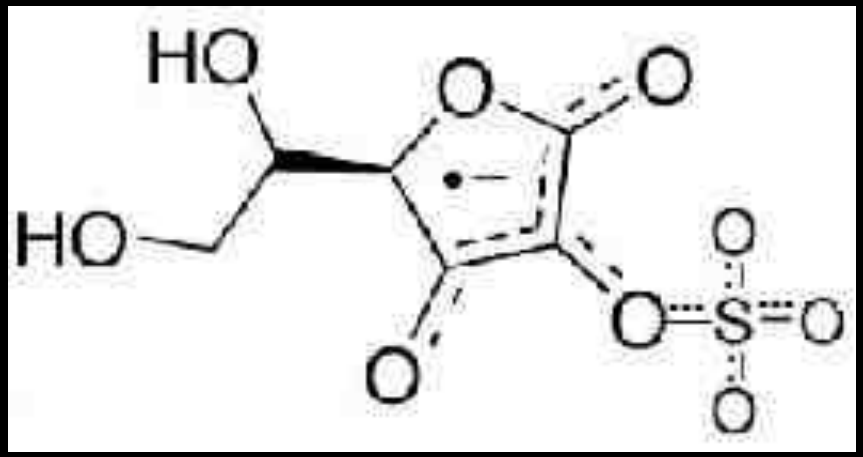


Mizuse, K. and Fujii, A. (2013). Characterization of a Solvent-Separated Ion-Radical Pair in Cationized Water Networks: Infrared Photodissociation and Ar-Attachment Experiments for Water Cluster Radical Cations (H2O)n+ (n = 3–8). *The Journal of Physical Chemistry A,* ***117, 929-938.***

Larsen, R.E., Glover, W.J. and Schwartz, B.J. (2010). Does the hydrated electron occupy a cavity? *Science,* ***329, 65-69.***

Our Proposal for a Universal Sulfurylation Factor

WE PROPOSE: 2-O-sulfate L-ascorbate radical plays a central role in the "universal nonspecific mesenchymal reaction", which has also been referred to as the Sanarelli-Shwartzman phenomenon.

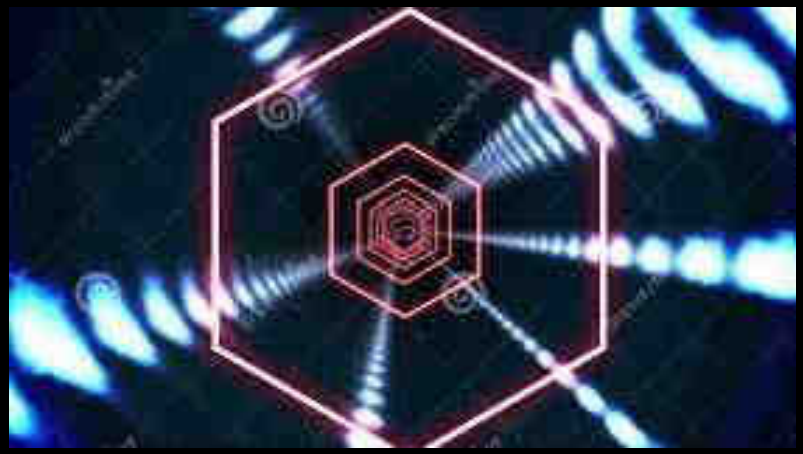


Takebayashi, J., Kaji, H., Ichiyama, K., Makino, K., Gohda, E., Yamamoto, I. and Tai, A. (2007). Inhibition of free radical-induced erythrocyte hemolysis by 2-O-substituted ascorbic acid derivatives. *Free Radical Biology and Medicine,* **43,** 1156-1164.

Verlangieri, A.J. and Mumma, R.O. (1973). In vivo sulfation of cholesterol by ascorbic acid 2-sulfate. *Atherosclerosis,* **17,** 37-48.

Cabral, J., Haake, P. and Kessler, K. (1998). Rearrangement of 3-Acyl Derivatives of L-Ascorbic Acid. *Journal of Carbohydrate Chemistry,* **17,** 1321-1329.

A Vortex of Hexagons from the Cassini Space Probe



Our Hypothesis: Dynamical Bidirectional 3-D Vortices of Interfacial Water at the Interphase

A drop of soapy molecules and water can form
a rigid gel crystal that displays more facets
than any crystal ever observed–
a phenomenon called ‘the Devil’s staircase.’

http://physics.aps.org/story/v5/st10

Pieranski, P., Sotta, P., Rohe, D. and Imperor-Clerc, M. (2000). Devil's staircase-type faceting of a cubic lyotropic liquid crystal. *Physical review letters,* **84,** 2409-2412.

Our Hypothesis: Chiral Paramagnetic Induction Homeotropic Alignment of Water at the Interphase

- Ascorbate radical may act as inducer, nidus, or seed to chirally and paramagnetically-align biological water at the interphase [homeotropic enrichment]. Consider a chirally and paramagnetically-aligned liquid-crystalline matrix or "plasma" of spin-correlated radical pairs

- Interfacial water provides the physical basis for (a) chemotaxis and allostery, (b) a non-metabolic “fuel” source for molecular motors, (c) the ability to overcome intra- and extracellular "crowding" and thermal diffusion (kT) problems, and (d) uniquely trapping and transducing ELF EM energy from environment into charge separation and negentropy ($-\Delta S$)

- Exogenous Interfacial Water Stress (EIWS) is the disruption of normal interfacial tension between water and biomacromolecules *in vivo* by exogenous agents such as the Al^{3+} cation --- represents the root cause or initiator of inflammation and disease (Seneff *et al* 2015).

Long-Range Attractive Intermolecular Forces

- NANOASSOCIATES: Konovalov has shown that sunlight/water/hydrophilic surface sufficient to form nanoassociates of water (Konovalov *et al* 2014);
- NEGENTROPY: configurational (conformational and vibrational) entropy loss
- THIXOTROPY: pH-dependent gel-like "memory" of water (Verdel and Bukovec 2013)
- PERCOLATION THRESHOLD: the entropic, hydration, lipid, protein, and sulfur requirements for biological activity (Brovchenko *et al* 2006; Davidson *et al* 2013)
- SELF-ORDERED CRITICALITY: Biophysical quantum coherent equipoise of the CNS is disrupted by EIWS; molecular recognition, chemotaxis, and allostery are lost in the presence of EIWS (Pal and Zewail 2004; Shaw *et al* 2014)

Fractals, Anisotropy, Hydrophobic Effect

- Fractal— geometrical scaling law from math and physics
- Anisotropy— order, alignment, e.g. birefringence on intravital polarized light microscopy; e.g. loss of fractional anisotropy on DTI-MRI *precedes* anatomic and behavioral signs/symptoms of neurological disease (SDAT, ASD, MS, schizophrenia)
- Hydrophobic Effect— Lum-Chandler-Weeks theory (Lum *et al* 1997) “size matters”; "order at the edge of chaos"; Bertholet's classical experiments; Martin Gruebele's seminal "stretching water" experiment

Exogenous Interfacial Water Stress Theory

- Exogenous Interfacial Water Stress (EIWS) is the root cause or initiator leading to inflammation and disease; EIWS is the initial common pathway to all disease (Davidson and Seneff 2012; Davidson *et al* 2013; Seneff *et al* 2015)

CAVEAT: The surface energy and redox potential of water are pH-dependent. IWS subsumes redox stress, i.e. the superficial grand potential subsumes redox potential

- Al^{3+} aquo cation is a prime example of EIWS; Myelin is a preferred target of Aluminium toxicity (Verstraetten *et al* 1997); It's time to add Gadolinium to the list of EIWS sources (McDonald *et al* 2015); both Gadolinium and Aluminum are neurotropic

- EIWS *precedes* inflammation and immune activation (MIA and IL-6) which *precedes* Autism, Macrophagic MyoFasciitis (MMF), Schizophrenia, SDAT, MS, SLE, etc,

- EIWS is supramolecular, biophysically-pleiotropic, pluricausal, and highly-stereotyped

- EIWS theory provides a biophysical explanation for synergistic toxicity

The Cytoskeleton, Defined

- Dynamical combination of hydrated actin microfilaments, microtubules, and fibrils:

  (a) exquisitely sensitive to EIWS,

  (b) provides a biomechanical conduit for energy transfer between the intracellular and extracellular matrix via proton-coupled electron transfer (PCET)

- F-Actin has been shown to be associated with hypermobile water by Makoto Suzuki's group using dielectric spectroscopy (Kabir , *et al* 2003; Wazawa, *et al* 2011)

- According to the TOFT: the default cytoskeletal state is cytoproliferative and motile (Sonnenschein and Soto, *The Society of Cells*, 1999; Soto and Sonnenschein 2011)

- Under the EIWS theory: the cytoskeletal state is controlled by gradients of interfacial water tension at the interphase (Davidson*, et al* 2013); interfacial water stress subsumes redox stress

- Under the EIWS theory: interfacial water exists in a metastable, dynamical state of equipoise in a liquid-crystalline matrix, wherein the protein aggregates comprising the cytoskeleton are modulated by and *substantially* "slaved" to the dynamics of interfacial water

Fractones, Defined:

- Fractones have been referred to as stem cell "*niches*" and they are thought to regulate cytoskeletal assembly and organize the ECM of the heart, gut, brain, and bone marrow/RES. They have complex cytoarchitectures consisting of stem cells, progenitor cells, supporting cells, and laminin-rich basement membranes (Hochman-Mendez *et al* 2014).

- Frederic Mercier and his associates have studied neural stem cell niches and described fractones as:

  "particulate extracellular matrix structures that I previously characterized in both the developing and adult brain". --- F. Mercier (personal statement)

  "In the neural stem cell niche of the adult brain, I have demonstrated that fractone-associated heparan sulfate proteoglycans serve as captors and activators of growth factors to regulate neural stem cell proliferation."

Mercier, F., Kitasako, J.T. and Hatton, G.I. (2002). Anatomy of the brain neurogenic zones revisited: fractones and the fibroblast/macrophage network. *J Comp Neurol,* **451,** 170-188.

Polymerized Laminin is Hexagonal !
Is PolyLM the structural basis for CNS Fractones?

- Fractal nature and hexagonal symmetry of polylaminin (polyLM) has been noted on confocal fluorescence microscopy (CFM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) (Hochman-Mendez *et al* 2014)

- "SEM and AFM analyses revealed that the seed unit of polyLM was a flat polygon formed in solution whereas the seed structure of LM was highly heterogeneous, intercalating rod-like, spherical and spread lamellar deposits." (emphasis added)

- "A search for the Hausdorff dimension in images of the two matrices showed that polyLM, but not LM, presented fractal dimensions…" (emphasis added)

- "…the intrinsic fractal nature of polymerized laminin can be the structural basis for the fractal-like organization of basement membranes in the neurogenic niches of the central nervous system." (emphasis added)

Structural Basis for the Organizing Functions of CNS Fractones

WE PROPOSE:

Hydrated electrons, specifically bipolarons in low pH, reductive environments, represent the fractal dimension. (Davidson *et al* 2013). Support for this proposal was found by Hochman-Mendez *et al* 2014.

"…key signaling properties of laminin were preserved and even augmented after the acid-induced assemblage, which was demonstrated mainly for neurons [8], but also for other cells types as glial [9] and thyroid cells [19]." (emphasis added)

- In low pH, reductive environments, fractones and hydrated electrons (*bipolarons*) provide:

  (a) a water-mediated physical basis for chemotaxis and allostery of signalling molecules, molecular motors, and,

  (b) a coherent bidirectional electromagnetic "connection" or "conduit" for PCET between the ECM, fractones, caveolae of the plasma membranes, the cytoskeleton, and mitochondria.

Fractone-Plasma Membrane-Cytoskeletal "Connection"

WE PROPOSE:

A coherent liquid-crystalline "connection" between the subatomic and cellular (mesoscopic) levels of biosemiotic organization consisting of:

(a) *Josephson-like* QM tunneling effects, (b) hydrated electrons, (c) PCET, (d) mitochondrial membranes, (e) cytoskeletal actin, (f) lipid rafts (caveolae) of plasma membrances, (g) integrins, and (h) laminin-rich basement membranes

- Cell morphology is highly-correlated with biomechanical, functional, hemorheological properties of cells
- Cellular polarization occurs when cell energy flows, either in centrifugal or centripetal direction, in the resting and proliferative states, respectively
- WHEREAS, the default cytoproliferative and motile state is typically kept in check, at times, EIWS disinhibits and "unleashes" the default state

CNS Fractones Need Sulfur

- GAGs and HSPGs need a UNIVERSAL SULFURYLATION FACTOR, e.g. 2-O-sulfate-L-ascorbate radical might preempt and supercede PAPS/SULTS
- CNS fractones need BOTH ascorbate and sulfur
- HSPGs have been shown to be low in sulfur at autopsy of CNS fractones in Autism

Corley *et al* (2012); Mercier *et al* (2012); Meyza *et al* (2012); Pearson *et al* (2013); Mercier *et al* (2011)

Autism as a Sulfate and/or Ascorbate Deficiency

- MOUSE MODEL of **Autism** and a GUINEA PIG MODEL of **Scurvy**
- Jones-Ray Effect: biphasic concentration dependent surface enhancement; Riddick Effect: biphasic concentration dependent zeta potential enhancement
- A New Triad in Classical Autism: abnormal RBC shape, oxidative damage, β-Actin (Ciccoli *et al* 2013); EIWS is very likely to *precede* the Autism Triad; Sulfate Deficiency may be a cause of EIWS
- A Plausible scenario: Sulfate deficiency → EIWS → Autism Triad → Autism phenotype
- SEM studies of RBCs by Bleau, *et al* (1975) suggest that Ch-S supplementation might reverse the RBC morphological and hemorheological abnormalities in Autism
- Both sulfate and ascorbate deficiency may represent synergistic consumptive sequelae of EIWS

Multiple Scales of Time and Space

- "There's plenty of room at the bottom" – Richard Feynman (1959); both Feynman and Irving Langmuir observed "like-likes-like" physical and biophysical behavior, a phenomenon familiar to colloid chemists. Our blood can be thought of as a colloidal suspension that flows.

- Medical schools need to teach a multidisciplinary vocabulary to accommodate the "new" science of biophysics, soft matter physics, chemical biology, redox biochemistry, liquid-crystal chemistry, magnetohydrodynamics, and quantum biology: this is where we will find the cipher…the Rosetta Stone

EIWS – Exogenous Interfacial Water Stress

TOFT – Tissue Organization Field Theory

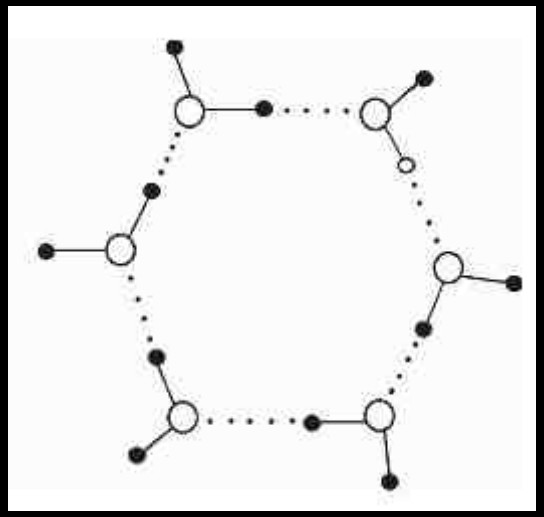
SCRPM - [electron] spin coupled radical pair mechanism
EPR - electron paramagnetic resonance
PCET - proton coupled electron transfer
CPET - concerted proton electron transfer
NQMT - nuclear quantum mechanical tunneling
KIE - kinetic isotope effect, mass independent KIEs
HFI - hyperfine interaction (electron spin - nuclear spin interaction)
DTI-MRI - diffusion tensor imaging magnetic resonance functional imaging; includes calculated measures of [fractional] anisotropy and diffusion OF WATER !

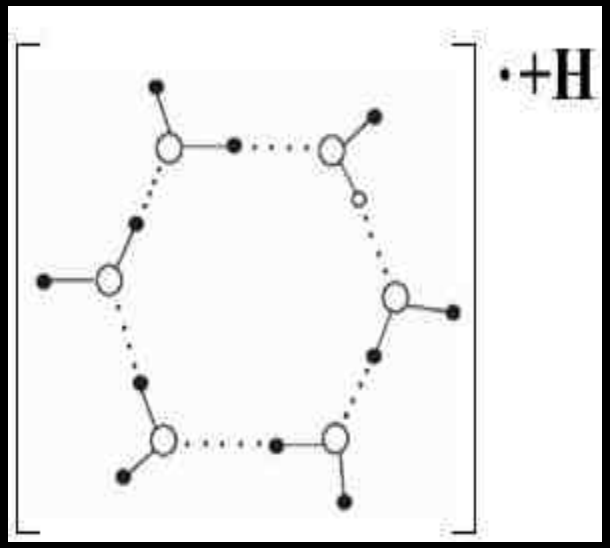
Summary

- [e (aq)] $^{\bullet+}$ → [Asc 2-S] $^{\bullet-}$ → sGAGs/HSPGs/F-actin filaments → Autism/RBC phenotype
- Hydrated electrons represent the physical basis for the "fractal dimension"
- We propose pH dependent speciation of e(aq's) as a requirement for quantum consciousness
- Autism and Other Brain Disorders may represent Sulfate and/or Ascorbate Deficiency Syndromes which sensitizes via EIWS to inflammation, microvascular ischemic, hemorheologic, and thrombohemorrhagic phenomena
- Autism may represent an EIWS-induced loss of self-ordered criticality and molecular recognition which leads to maternal immune activation and autoimmunity
- Autism may be result from EIWS-induced disturbance of a CNS fractone function, anywhere along the cytoskeletal energy "connection" between mitochondria and CNS fractones
- The Autism Triad may be explained in terms of sulfate and ascorbate deficiency, both of which may represent synergistic consumptive sequelae of EIWS
- Fractones of the brain, heart, gut, and bone marrow require a **"**universal sulfurylation factor**" and** we have proposed the structure for such a factor, i.e. the 2-O-sulfate-L-ascorbate radical

THANK YOU !

Conceptual Genesis of Hypothesis: The Fractal Dimension





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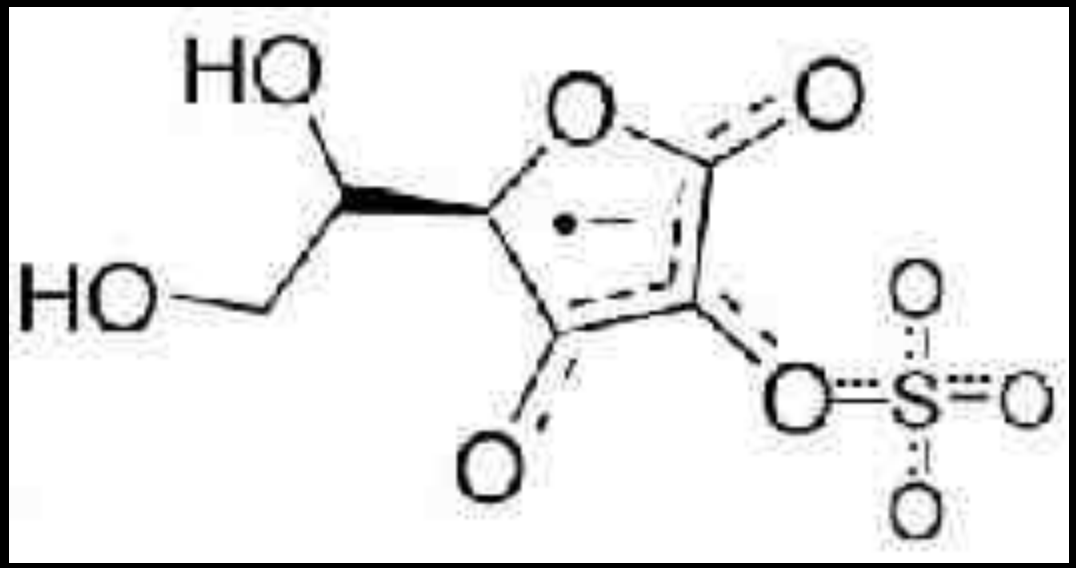
Our Proposal for a Universal Sulfurylation Factor



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Cabral, J., Haake, P. and Kessler, K. (1998). Rearrangement of 3-Acyl Derivatives of L-Ascorbic Acid. *Journal of Carbohydrate Chemistry,* **17,** 1321-1329.

Our Speculation: Frequency-Locked Vortices?

- A cubic lyotropic liquid-crystal of surfactant and water demonstrated an infinite number of facets to suggest “Devil’s Staircase” frequency-locking (Pieransky *et al* 2000)
- Are hydrated electrons involved?
- Are spin-correlated, frequency-locked, hydrated electrons involved? *In vivo*?
- Is a frequency-encoded hydrated electron the singularity at the apex of vortices? *In vivo*?

Pieranski, P., Sotta, P., Rohe, D. and Imperor-Clerc, M. (2000). Devil's staircase-type faceting of a cubic lyotropic liquid crystal. *Physical review letters,* **84,** 2409-2412.

A Novel Hypothesis: The Origin of the Fractal Dimension

WE PROPOSE THE FOLLOWING:

- Protomeric/electromeric cyclic hexamer radical-cations of water (bipolarons) represent hydrated electrons, and vehicles for PCET in low pH, reductive environments, *in vivo*
- Hydrated electrons, i.e. electrons solvated by cyclic water hexamers, represent the "fractal dimension", the singularity at the apex of 3-D dynamical vortices of biological water, both i*n vivo* and *in vitro*.
- The need by HSPGs of CNS fractones for sulfate, implies that CNS fractones have a need for a "universal sulfurylation factor"
- 2-O-sulfate-L-ascorbate radical may be a universal sulfurylation factor which is attracted by water-mediated chemotaxis to CNS fractone, faciliated magnetohydrodynamically by dynamical vortices of hydrated electrons, so as to affect the sulfurylation of HSPGs
- 2-O-sulfate-L-ascorbate radical has a kinetically-transient lifetime sufficient to act as a post-translational "sulfurylation factor" of GAGs and HSPGs
- In liquid-crystalline lyotropic phases of biological water at the interphase, the transulfurylation transition-state would be stabilized by on-water heterogeneous catalysis, PCET, and by facile formation of resonance-stabilized cyclic trigonal bipyramidal intermediates which can undergo Berry pseudorotation.
- Our proposal might be repeated through-out life to maintain functionality of fractones as stem cell "niches" via autocatalytic radical initiation, propagation, and comproportionation of the ascorbate radical.