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

Robert M. Davidson M.D. Ph.D. FAIS*
Ann Lauritzen, Stephanie Seneff, Stephen D. Kette, Glyn Wainwright, Anthony Samsel, and Sydney J. Bush

*Fellow, The American Institute of Stress
Physician and Medical Researcher, Kilgore, Texas, USA
Email: patrons99@yahoo.com
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


Our Proposal for pH Dependent e(aq) Speciation


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.


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.’


**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

• Al³⁺ 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.”

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.
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 membranes, (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

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

- \([\text{e (aq)}]^+ \rightarrow [\text{Asc 2-S}]^+ \rightarrow \text{sGAGs/HSPGs/F-actin filaments} \rightarrow \text{Autism/RBC phenotype}\)

- 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


Our Proposal for a Universal Sulfurylation Factor


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*?

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 in 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, facilitated 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 throughout life to maintain functionality of fractones as stem cell “niches” via autocatalytic radical initiation, propagation, and comproportionation of the ascorbate radical.