Sensors & Transducers, Vol. 203, Issue 8, August 2016, pp. 69-83

Sensors & Transducers

http://www.sensorsportal.com

The Advantages of Human Milk Recognize the Spatiotemporal Locations of Toxins and Intelligently Bypass Them by Forming a *Hummingbird-Like* Hovering Neural Network Circuitry Based on an Organic Biomimetic *Choline Acetyltransferase* Memristor/Memcapacitor Prosthesis

[1] E. T. CHEN, [2] J. THORNTON, [3] P. T. KISSINGER and [*4] S-H. DUH

[1]Advanced Biomimetic Sensors, Inc., 11140 Rockville Pike, Suite 440, Unit 422, Rockville, MD 20852, USA

[2] Bruker Nano, 19 Fortune Dr., Billerica, MA 01821, USA

[3] Department of Chemistry, Purdue University, West Lafayette, IN 47906, USA

[4] University of Maryland Medical System, 22 South Greene St, Baltimore, MD 21201, USA

[*] E-mail: sduh@umm.edu

Received: 30 2016 /Accepted: 29 July 2016 /Published: 31 August 2016

Abstract: We have demonstrated a unique approach to study human milk's advantage in promoting and protecting infant early brain cognitive development by recognizing toxins and intelligently bypassing the toxin by forming *high frequency oscillation* (HFO) in the brain circuitry when compared with organic cow milk samples based on an organic memristor/memcapacitor biomimetic *Choline Acetyltransferase* (CHAT) neural network circuitry prosthesis along with a 3D *Energy-sensory* dynamic mapping method under antibody-free, radiolabeling-free, and reagent-less conditions. We also demonstrated cow milk is unfit for infant cognitive development, and it is actually harmful in terms of mutating infant brain synapse circuitry conformation, current flow direction, and energy output that lead to multiple *Pathological High Frequency Oscillation* (pHFO) formations, and further, it led to sudden infant death syndrome (SIDS) based on our prediction. *Copyright © 2016 IFSA Publishing, S. L.*

Keywords: Nanobiomimetic organic CHAT neuronal memristor/memcapacitor, Spatial-temporal orientation, 3D energy-sensory map, Pathological high frequency oscillation (pHFO), High frequency oscillation (HFO), Slow wave sleeping (SWS), Rapid eye movement (REM) sleeping, Voltage method.

1. Introduction

It is well accepted that human milk offers advantages over cow milk for babies' brain cognitive development and recommended by CDC and World Health Organization (WHO) across all populations in the United States and the world for mothers to breastfeed newborn and infant babies for the purpose of protection, promotion, and support of healthy early child development, and to prevent obesity and other chronic diseases [1-3]. However, we are still lagging far behind the CDC's 2010 goal breastfeeding rate [2]. Part of the reason may be due to the lack of in depth studies on how human milk is able to recognize toxic substances invading the neural network; how human milk has the ability to overcome this danger and maintain a healthy neural circuitry and how feeding cow milk causes danger have not put the public on alert because of this lack of study and subsequent information dissemination. We thought such study is very important and necessary, because not only will the results enhance our understanding human milk's crucial immunological advantage, it also provides first hand evidence that should draw public attention to the advantages of breastfeeding infants therefore improving urgent public health outcomes.

Acetyl co-enzyme A (AcCoA) is a leading substrate in a large variety of enzyme-catalyzed reactions, such as for choline acetyltransferase (CHAT) and acetyl cholinesterase (ACHE) [4-8]. Szutowicz's group emphasized that AcCoA is the key factor for the survival or death of cholinergic neurons during the course of neurodegenerative diseases [8]. Ivan Gout's group emphasized that the level of AcCoA is crucial to early embryonic development [9]. AcCoA is a thioester derived from catabolism of all major carbon fuels. AcCoA may play a role in energy production, metabolism, memory, cell proliferation, and early childhood development, and it is central to biological acetylation reactions. AcCoA deficiency leads to many diseases, such as diabetes, cancer, coronary disease, autism, Alzheimer's, and sudden infant death syndrome (SIDS). Abnormality of CHAT activity may lead to these diseases because CHAT represents the most specific cholinergic marker in the CNS [10-11], and the spatial temporal manifestation of CHAT has been examined at both the protein and mRNA levels in different tissues of various species [11]. Furthermore, reports revealed that the virus replications of West Nile virus (WNV), the neurotropic flavivirus that is transmitted by mosquito bites and causing meningitis and encephalitis in humans [12], involved the carboxylation of AcCoA to malonyl CoA through AcCoA carboxylase [12].

The mortality rate of SIDS has been reduced significantly worldwide; however, according to the CDC web site report, it still causes 3500 infant deaths annually in the US [13]. The American Academy of Pediatric's Task Force on SIDS fully supports breastfeeding [14]. Some literature reports that SIDS cases are more frequently reported among cow milk fed babies than breast fed babies [14-16]. More detailed literature reviews regarding the advantages of breastfeeding to reduce SIDS over feeding cow milk to infants was also reported in the literature [16]. Newborn infant screening for presynapstic congenital myasthenia syndromes (CMS) tests whether or not the babies have CHAT deficiency. Therefore, sensitive quantitation of CHAT activity, in terms of monitoring the changes of substrate AcCoA in biological specimens, is in demand for monitoring and diagnosing various diseases. Our group recently developed a nanostructured biomimetic sensor for the direct measurement of sub pM concentrations of AcCoA in milk samples under the conditions of free from antibody and free from radio labeling tracers, and the process is reagent-less. The signal changes of AcCoA over a wide range of concentrations, between 2 pM to 0.3 μM, were measured by the chronoamperometry (CA) method; it has a linear range from 2 pM to 0.4 nM. The value of Detection of Limits (DOL) is 1.2×10^{-12} M/cm^2, i.e., for our sensor of 0.031 cm^2, it is 3.7×10^{-14} M. AcCoA spiked milk specimens were measured with a recovery value of 103 %, and the method produced an imprecision error of less than 2 % (n=12) when using human milk samples [17]. From quantitation of sub pM AcCoA to seek further the possible cause of CHAT deficiency in SIDS is a challenge because the cause of SIDS is unknown [13-16]. Research reports regarding the hummingbird's unique hovering 8-shape fly pattern inspired us to develop a biomimetic neural memcapacitor device, and we tested our hypothesis of whether or not a normal brain also has a hummingbird-like hovering neuronal synapse network circuitry pattern [18]. The positive results have paved the road for our further pursuit of the goal.

Hummingbirds suffer from low thermal inertia and high heat loss. Flapping flight is energetically expensive and convective cooling due to wing and air movements could further drain their energy [19-21]. Energy conservation during flight is thus profoundly important for hummingbirds. Researchers have been interested in and fascinated by the wing's unique 8-shape quantitation and the positioning of the bird's body at about a 45 degree angle to the ground during flight that characterizes hummingbird energy conservation strategy. The hummingbird's capability of having the smallest body size with the highest wing beat frequencies among all flying vertebrates has been reported [19-21]. The hummingbird's significant asymmetry lifts the body within a stroke cycle with a ratio of 75/25 between down stroke vs. the upstroke and has enabled them to simultaneously hover and feed in the air with efficient energy conservation by forcing the resonant system of the wings and thorax to oscillate at different frequencies with an elastic restoring force [21]. However, if the bird's visual background is moving, then the hovering and lifting maneuver can fail [22]. We are wondering: if the healthy people indeed have such a pattern synapse circuitry flow as the hummingbird hovering, then what is the advantage to avoid illness? How different patterns are for peoples who have diseases? Our prior work was reported that a healthy neural circuitry indeed has a 8-shape 3D synapse fly pattern between hippocampus to neocortex using a biomimetic neural circuitry model that has advantages to avoid epilepsy [18]. Normal Slow-Wave Sleeping (SWS) waves have the highest amplitude compared with all other brain waves, because during the deep stage 3 or 4 sleeping, brain conducts consolidation of declarative memory through hippocampus to neocortical networking [23].

A normal neural network circuitry constantly fires HFO (150-200 Hz) producing synchronization within the connection between hippocampus and neocortex for long term memory storage during SWS, and where pHFO (200-600 Hz) fires randomly leading to seizures and epilepsy [24-26]. The biggest problem in epilepsy research, as the Editor Noebels explained in his book, is that researchers are "*not clear how abnormal synchrony is generated during pHFO. Clearly there is a need for additional studies that will differentiate normal from pathologic HFO in vitro and in vivo.*"[24]. Our prior published works had paved a road to identify and differentiate the difference between pHFO and the HFO by utilizing a nanostructure organic biomimetic memristor/ memcapacitor prosthesis, along with a 3D "Sensory-Energy" mapping technology, that measured and visually displayed a sub pM level β-amyloidal induced abnormal neural network circuitry with the spatiotemporal locations identified regarding the formation of pHFO compared with the formation of HFO [18, 27-29]. We decided to use this approach to identify and differentiate the formation of pHFO or HFO in a refined spatiotemporal orientation in the neuronal network circuitry challenged with AcCoA by using human milk and organic cow milk for infants; hopefully, in a multi-variable dynamic mapping setting, the human milk's extraordinary immunological and almost intelligent protection of a neural circuitry on our prosthesis would be shown under a toxic substance challenge compared with cow milk. This project is based on our prior experience in using the memristor/memcapacitor to mimic hippocampus-neocortex neuronal network circuitry [30-33]. Electrical synapses in the thalamus are known to regulate SWS for declarative memory consolidation [23, 34-35].

Newborns sleep an average 16-18 hours per day, of which 50 % is spent in rapid eye movement sleep (REM), and 50 % of the time is in SWS, where sleep quality is determined [36-37]. As the literature reported, REM usually takes place more than 10 Hz (α frequency), and SWS is between 0.1-3.5 Hz (δ frequency) [36-37]. By focusing on two types of milk's biocommunication with the biomimetic neural device in the presence of AcCoA comparing their neural circuitry difference in a 3D energy-sensory map covering clinically useful frequency range without AcCoA would be a novel approach. The beauty of this approach is to eliminate the confounded factors that are beyond our scoop, such as genetic effect, environmental contamination, breastfeeding styles, food of mothers' eating, and so on, that would enable us to focus on the topic of whether or not human milk has advantage in promoting neural circuitry integrity in recognizing spatiotemporal location of toxins and bypass them compared with that of organic milk under a well-controlled experimental conditions under the hypothesis of normal human milk has no CHAT deficiency, because it produces HFOs, and the HFO promotes a neural circuitry in 8-shape flow; but organic milk induces CHAT deficiency, because it produces pHFOs and the pHFO may broke a neuron apart, eventually it leads to SIDS.

2. Experimental

2.1. Fabrication of the Nanostructure Self-Assembling Membrane (SAM) Gold Memristor Chips

The nanostructure biomimetic SAM was freshly prepared according to the published procedures based on cross linked conductive polymers of triacetyl-ß-cyclodextrin (TCD), polyethylene glycol diglycidyl ether (PEG), poly(4-vinylpyridine) (PVP) and ß-CD copolymer with appropriate amount of propositions on gold chip [38-39]. The chemicals were purchased from Sigma and went through purification procedures before use. A mixture of o-nitrophenyl acetate (o-NPA) in a molar ratio 1000:1 to the TCD mixture was incubated for 2 hrs at 35 °C; then the mixture was injected onto the gold surface and incubated for 48 hrs at 35 °C. After that, we followed the clean procedures for completion of the SAM fabrication [38-39].

2.2. Characterization of the Membrane

The morphology of the AU/SAM was characterized using an Atomic Force Microscope (AFM) (model Multimode 8 ScanAsyst, Bruker, PA). Data Collected in PeakForce Tapping Mode. Probes used were ScanAsyst-air probes (Bruker, PA). The silicon tips on silicon nitride cantilevers have 2-5 nm radius. The nominal spring constant 0.4 N/m was used. Fig. 1 depicts the 3D AFM image before the o-NPA was embedded on gold chip.

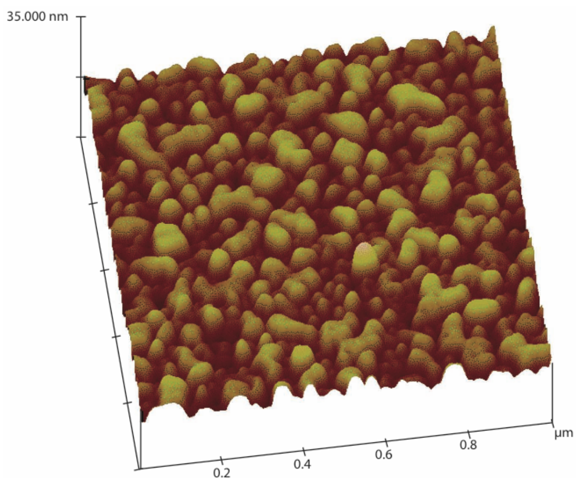

Fig. 1. 3D AFM image before adding o-NPA.

2.3. Frequency Affects on Memristor/ Memcapacitor's Performance

Evaluations of frequency affect on memristors' performance were conducted by Cyclic Voltammetric method (CV) in pH 7.0 saline solution at room temperature. The scan rate was from 1 Hz to 1 KHz in PBS pH 7.0 buffer. The data were used for comparing a fresh human milk control and a fresh organic milk control in the presence of 60 pM AcCoA and 2 mM o-NPA covering the same range of frequencies against the controls, respectively.

2.4. The Data Acquisitions

Data Acquisitions were conducted by connecting the memcapacitor sensor chips with an electrochemical station (Epsilon, BASi, IN) with the BASi software package in the computer. With the double step chronopotentiometry (DSCPO) method, we called it a voltage method, measurements were under ±10 nA with data rate 0.001s at 0.25 Hz and 2×10^{-5} s data rate over the frequency range of 40 Hz - 250Hz. AcCoA concentration was set as a fixed over dosage 60 pM concentration, as is intrinsic to a living cell according to our assumption, and was used for human milk and organic milk samples, respectively.

2.5. Mapping Energy-Sensory Image

The Energy-Sensory Matrix. From the CV profiles in PBS, human milk and organic milk without spiking AcCoA were taken as our comparative controls. We constructed each of the three types of Hippocampal-neocortical (HPC-NECOR) biomimetic neural sensory prosthesis's matrixes as controls. The "Sensory Biomarkers" components were defined: *locations of Direct Electron Transfer* (DET) [18, 40] peaks in mV (Y-axis), *the Hysteresis switch point location* in mV (X-axis) and *Frequency* in Hz (Z-axis) from 1- 300 Hz for the clinically useful range and the energy insertion data from the net pulse discharge energy were covered the frequency from 0.25 to 250 Hz. The real-time data obtained from the voltage method was converted to volumetric energy density, $E = C_s \cdot (\Delta V)^2/(2 \times 3600)$, where C_s is the specific volumetric capacitance, $C_s = [-i \cdot \Delta t/\Delta V]/L$, C_s is in F/cm^3 [41-42], Δt is the time in second, ΔV is the voltage in V, *i* is the current in Amps, and L is the volume in cm^3. The energy density data were infused into the sensory matrix sheet before AcCoA spiking and compared with that of after AcCoA was spiked, and each matrix sheet has a fixed AcCoA concentration either 0.0 or 60 pM. OriginPro 2016 software was used for statistical analysis, mapping, and imaging.

2.6. Accessing the Abnormality of Neural Circuitry of "SIDS"

To evaluate an abnormality of neural circuitry in the memcapacitor device, first use the energy-sensory mapping to observe any HFO or pHFO appearance with or without an overdose of AcCoA before and after a pulse energy infusion. The formation of an HFO indicates a sign of good memory because it promotes a flat 8-shape circuitry flow and network circuitry conformation that was confirmed by our prior work [18, 31-33]; forming pHFO indicates loss of memory because of the faulty circuitry flow direction and conformation, especially through the CR abnormality during SWS. Second, evaluate the surface smoothness of the circuitry to see whether or not any folding caused by altering the sensory spatiotemporal locations was due to invading toxins in the 3D dynamic circuitry flow map; third, is to note if there are any swellings or breaking or shrinking in either the blue area (low frequency as a representative of the neocortex area) or the red area (representing the high frequency area of hippocampus) that are reflected in the image and the contour maps.

2.7. Evaluations of Human Milk's Recognition of the Spatiotemporal Locations of Toxins

Evaluations of human milk's recognition of the spatiotemporal locations of toxins were conducted in four criteria: (1). to evaluate the spiked 60 pM AcCOA human milk samples whether or not have the ability to bypass AcCoA induced spatiotemperal locations with its cross-point and DET_{red} peak compared with that of the controls and also evaluate for whether or not the neural circuitry surface in a hummingbird-fly pattern in an enhanced light intensity in a 3D map; (2). to evaluate whether or not human milk's ability to recognize toxins can be repeated in two conditions for with a 2 mM o-NPA and 60 pM AcCoA spiked in human milk or without o-NPA in the human milk with 60 pM AcCoA. The CV profiles are recorded in 1-1000 Hz at these two conditions against controls. Of cause we only hope the recognition of toxins' "phenomena" can be repeated, we are not require the bypass spatiotemporal location are same in both conditions. (3). to observe any HFO produced due to the bypass process if any to compare with organic milk under same experimental conditions. (4). to evaluate the recognition of toxins can be extended to other toxic substances as our next step for further research. This paper only includes the evaluation of the recognition of AcCoA.

2.8. Assessing Energy Outcomes under Challenges of AcCoA

The voltage method was used for assessing energy outcomes at SWS at 0.25 Hz compared at high oscillation frequency at 250 Hz (within the seizure or epilepsy range) under the influence of AcCoA by using human milk vs. USDA certified organic cow milk for infants. It was conducted against controls. Human milk was collected from a normal subject who breastfeeds a 1 month-old newborn (Leebio Corp.,). Specimen samples run triplicates at each of the two frequencies for with or without AcCoA at ±10 nA, respectively. An electrochemical workstation was used (Epsilon, BASi, IN) with a software package from BASi.

3. Results and Discussions

3.1. Advantage of AcCoA's Rate Limiting Binding

We thought using the function groups in the SAM membrane to mimic the AcCoA's human choline acetyltransferase (CHAT) binding sites matched intrinsically to the mitochondria double membrane compartment with the structure needed may be a simplified approach as a neuronal sensor model. The model device and its function are to mimic CHAT's function in emphasizing of AcCoA's rate limiting step binding [43-47]. The possible electron-relay was proposed by the pyridine group in PVP, the COO^- group of TCD, the OH group from β-CD copolymer, and the carbonyl group from o-NPA through hydrogen bindings, to be able to mimic s540, y552, c563, c550 and h324 of AcCoA binding sites in CHAT. This innovative approach was first to directly detect AcCoA in the CHAT model's mimic binding sites without choline participating in the direct detection of AcCoA because of the nature of AcCoA's rate limiting step binding advantage [43-47].

3.2. Hummingbird's Hovering Flight Pattern

Hummingbirds are the only birds that are smaller in size and hang in the air, helicopter like, to feed and hover with wing motion supination along the long axis of the wing during upstroke, which is associated with a 'figure-8' path of the wingtip in lateral projection [19-21] as shown in Fig. 2. As we can see, a significant asymmetry of lift within a stroke cycle was depicted with a ratio of 75/25 between downstroke vs. the upstroke [19-21].

Evaluations of frequency affect on memristors' performance were conducted by Cyclic Voltammetric method (CV) in pH 7.0 saline solution at room temperature. The scan rate was from 1 Hz to 1 kHz in PBS pH 7.0 buffer. The data were used for comparing with a fresh human milk control and a fresh organic milk control in the presence of 60 pM AcCoA and 2 mM o-NPA covering the same range of frequencies against the controls, respectively.

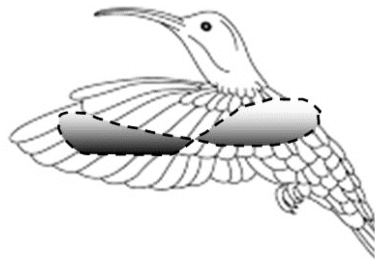

Fig. 2. Depicts the hummingbird hovering helicopter like flight in 8-shape pattern. (Obtained permission from E. Chen et al.)

3.3. Frequency Affects on Memristor/Memcapacitor's Performance

3.3.1. DET and Sensory

A memristor is a semiconductor whose resistance varies as a function of flux and charge. This allows it to «remember» what has passed through the circuit. The hysteresis pinch loop is a characteristic of this ability to remember prior states and vary resistance as a result [48-52]. A total charge of a memcapacitor is a function of a state dependent on capacitance and the potential across it [48-51]. Organic memristors and memcapacitors expanded their applications in medical and energy storage fields as compared to metal oxide thermal memcapacitors because of concerns over their heat release during electric switch. Our group developed the first organic nanomemcapcitor with negative and diverging capacitance, and achieved a superior performance in elasticity, stability and high power and energy density without environmental pollution and current leaking [37, 52].

Fig. 3A depicts a i-V hysteresis curve with a switch point at the origin (0, 0) at almost all frequencies, except at kHz high frequency in the control medium PBS only. When the perfect hysteresis behavior peaks occurred, especially at SWS frequency with a sensitive *Direct Electron Transfer* (DET), and the switch point originates at origin, it indicates a healthy "newborn single neuron" existed before feeding it any milk samples. The well accepted and commonly used terminology "Direct Electron Transfer" appeared in electrochemical sensor literature that refers to the direct transfer an electron between redox centers of an enzyme and the surface of an electrode without using a mediator or probe [53-56]. Nonlinear frequency influence on current intensity is characteristic of a memristor as reported in literature [48-51]. Fig. 3B is the controls in human milk samples with well-defined sensory DET butterfly peaks crossed near the origin at SWS.

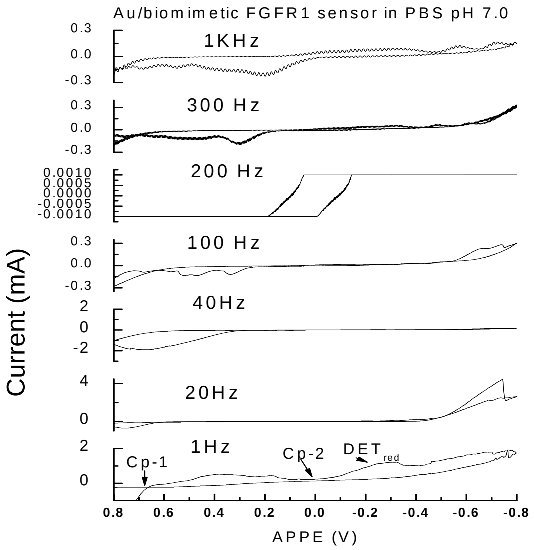

Fig. 3A. Frequency affects from 1 Hz to 1 KHz on hysteresis of the i-V curve of the memristor in pH 7.0 PBS.

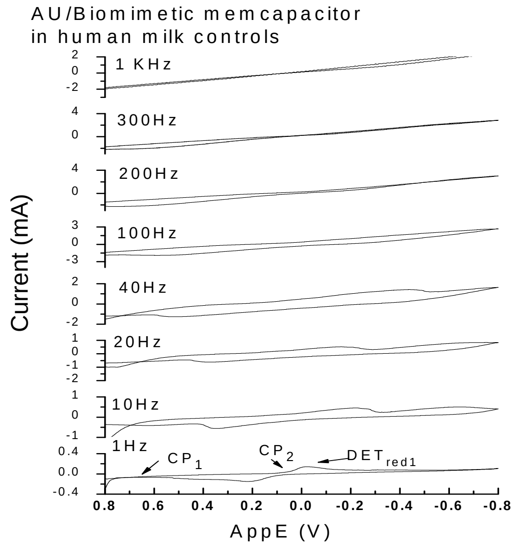

Fig. 3B. CV profiles of human milk controls.

Fig. 3C depicts the CV curves of human milk samples in the presence of 60 pM AcCoA without o-NPA with a moved cross-point location and the DET_{red} peak moved to -355 mV. Fig. 3D depicts the organic milk controls' i-V profiles. The significant difference observed among the organic milk control, the PBS control and the human milk control at SWS is the organic milk did not have a butterfly type DET_{red} peak near -0.1 to -0.2 V, where PBS and human milk have this peak and also with a cross-point near the origin. Rather, it had 2 strange DET_{red} peaks at -0.595 V and -0.365 V; 2 DET_{oxi} peaks at 0.292 V and -0.141 V with a cross point at 0.461 V. The organic milk control missed the cross-point located near zero applied potential. What substances could cause the unknown DET peaks to occur at SWS frequency along with an altered cross point? Human milk provides a critical sensory function to the single neuron at the memory consolidation stage of brain development with the reversible membrane potential in place, and ensures the normal function of direct electron-relay. One possible source may be from the contribution of the good bacteria as compared to the cow milk, which has no microbiota [57], because pasteurization of cow milk destroys both good and bad bacteria [57]. Another source which may contribute to brain development may be the unique proteins such as A2 β-casein, which is plentiful in human milk, and lacking in cow milk [34]. Fig. 3E depicts the CV profiles of organic milk in the presence of 60 pM AcCoA and without o-NPA. There is a DET peak near 70 mV and 1 cross-point occurred at 695 mV at 1 Hz.

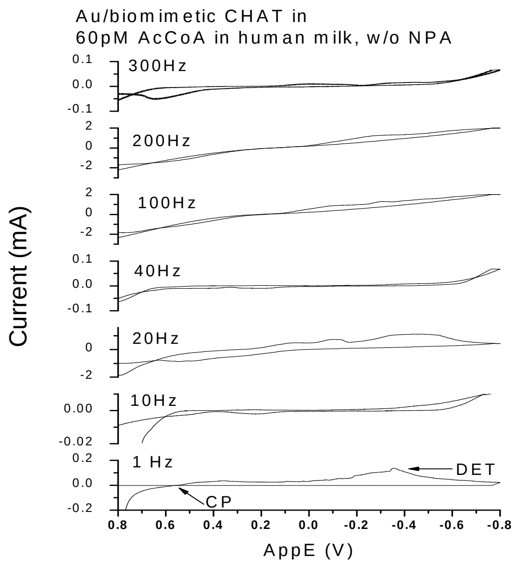

Fig. 3C. CV profiles in 60 pM AcCoA in human milk without o-NPA.

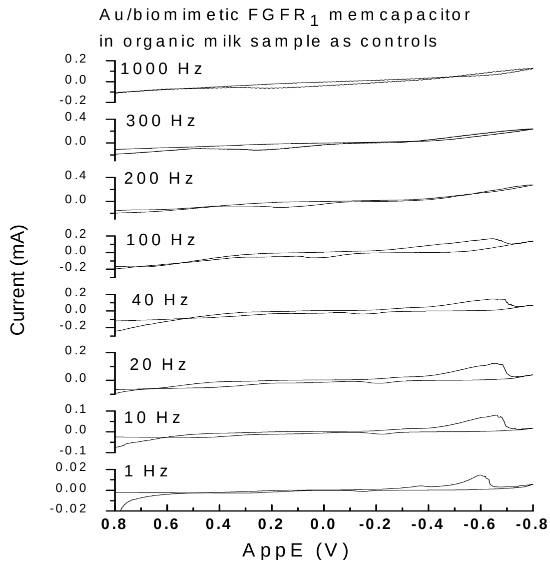

Fig. 3D. CV profiles of organic milk controls.

Fig. 3F depicts the CV profiles of organic milk in the presence of 60 pM AcCoA with o-NPA and the DET peak and the cross-point were eliminated at 1 Hz, that indicates cow milk offers a disadvantage for infant brain circuitry development when facing a toxic invader at SWS and α frequency when babies are sleeping the most at 16-18 hours at a time. Fig. 3G depicts CV profiles of human milk in the presence of 60 pM AcCoA with o-NPA. Human milk has two DET_{red} peaks and two cross-points at 1 Hz that indicates the neuron remains an appropriate function in sensing of danger, while the newborn is sleeping.

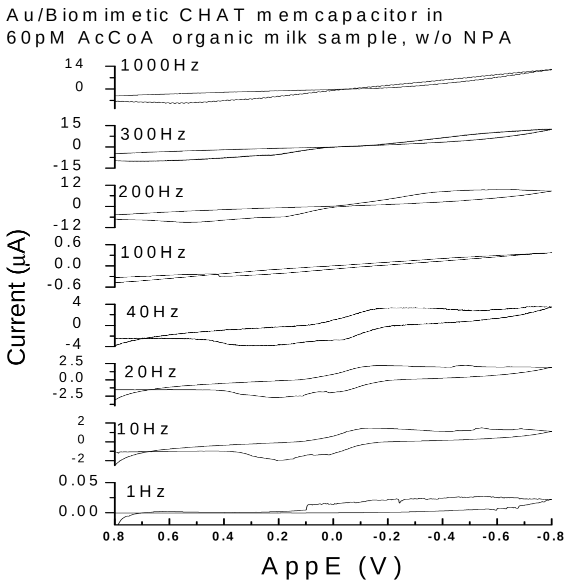

Fig. 3E. CV profiles in 60 pM AcCoA in organic milk without NPA.

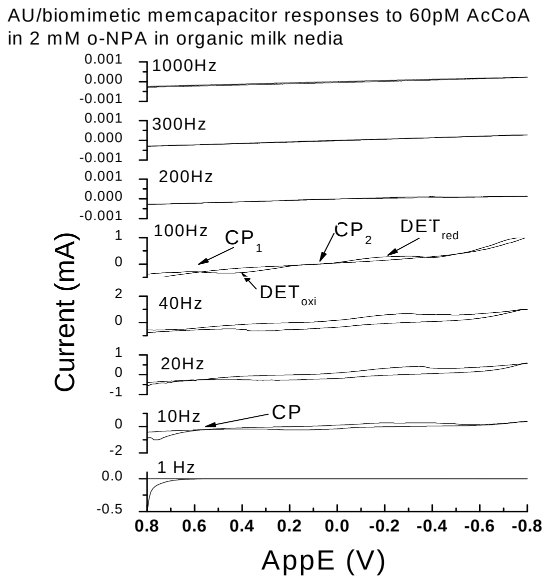

Fig. 3F. CV profiles in 60 pM AcCoA in organic milk with NPA.

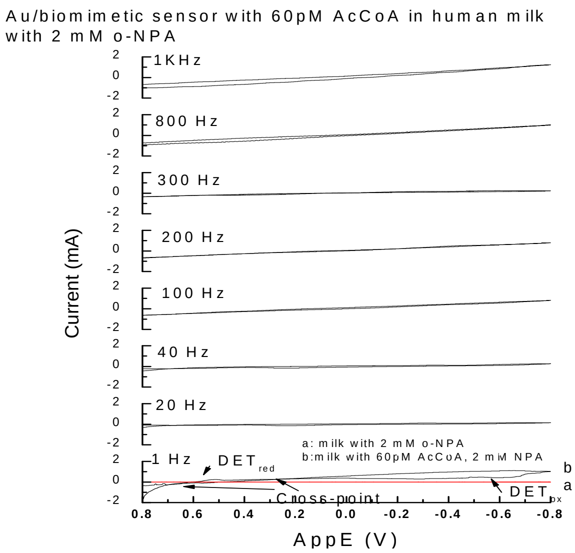

Fig. 3G. CV profiles in 60 pM AcCoA in human milk sample with 2 mM o-NPA.

3.3.2. Comparing Trafficking Patterns of the Spatiotemporal Locations of DET and Cross-point in the Frequency Domain

The purpose to study the trafficking patterns of the spatiotemporal locations of the DET_{red} and cross-point in the frequency domain for with or without AcCOA's influence is to find which sensory parameter in the milk samples has the best performance reflected in the energy-sensory maps. The study was conducted according the collected data described in Section 3.3.1. Fig. 4 depicts the effect of 60 pM AcCoA on three types of sensory parameters' trafficking patterns in human milk against the control within the frequency domain from 1 to 300 Hz. The three types of sensory categories are: Cross-point, DET_{red} and DET_{oxi} as shown in Fig. 4A, 4B and 4C, respectively compared with Fig. 5A, 5B and 5C, respectively, using organic cow milk samples. The noticeable pattern trends are observed between low frequency (1-20 Hz) and high frequency (100-300) in human milk and organic milk samples, respectively: (1), human milk at DET_{red} location trafficking pattern trends are quite contradictory between the results at the low frequency as to what is at the high frequency for with or without AcCoA. At low frequency DET_{red} peak locations moved toward more negative electric field from 1 to 40 Hz indicating a less negative capacitance occurred due to AcCoA's effect compared with the control which has a high negative capacitance from 1 to 40 Hz. A negative and diverging capacitance means that it would perpetually supply energy [48, 58-59]. However, at 100-300 Hz, the human milk controls had no DET_{red} peaks compared with human milk samples spiked with AcCoA that DET_{red} peaks speed up toward an increased negative capacitance situation. We guessed something has turned around the toxins to be unharmful. That must be the microbiota contribution in the human milk samples. In contrast, Fig 5B used an organic milk sample, in the same low frequency range, the controls have magnitude lower energy compared with human milk controls. (2). In Fig. 4C in a complete positive electric field, the controls of human milk of the $DET_{oxidation}$ peak's temporal locations moved from 219 mV at 1 Hz toward 551 mV at 100 Hz in an energy consuming state compared to the situation from human milk, that multiple DET_{oxi} peaks destroyed in the presence of AcCoA at 1 Hz, 20 Hz, 100 Hz, 200 Hz, respectively in human milk. It seems like human milk turned a toxin to good. It not only eliminates the oxidation that may cause inflammation but also increased the net energy outcome. It indicates the AcCoA in the human milk sample recognizes our biomimetic CHAT function groups in the prosthesis and it biocommunicates with the "newborn's brain neuron" in a friendly manner, so the human milk was called as "CHAT activity normal", herein it may prevent SIDS. In contrast, Fig. 5C in the same positive potential field, it shows AcCoA damaged the DET_{oxi} peak and moved toward more positive potential from 1 Hz to 200 Hz indicating organic milk has energy deficiency that may cause inflammation internally. The organic milk samples could not recognize the toxin AcCoA, it may due to an unknown substance in the organic milk that interacts with AcCoA making things worse? Because the organic milk samples could not recognize our biomiemtic CHAT function groups in the sensor membrane, so we call it as "CHAT Defecincy", herein it may be the root to cause SIDS. (3). Fig. 4A shows the temporal location of the cross-point moving pattern from human milk samples with spiked AcCoA moves in a relatively consistent manner compared with Fig. 5A of the locations of cross-point pattern in organic milk, it changed drastically, that indicates the instability nature of organic milk in a "give up mode" to allow a toxin invasion. It sounds like the predominate factor that caused problems lead to SIDS in organic milk samples is the DET_{oxi} trafficking pattern moving to a wrong direction.

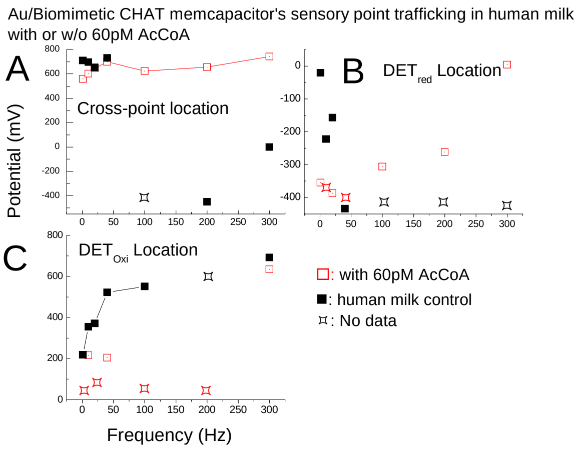

Fig. 4. Effect of 60 pM AcCoA on three types of sensory parameters' trafficking patterns in human milk vs. control in the frequency domain from 1 to 300 Hz.

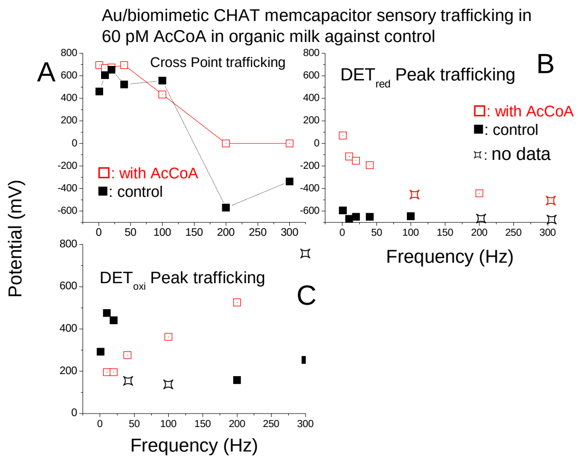

Fig. 5. Effect of 60 pM AcCoA on three types of sensory parameters trafficking patterns in organic milk vs. control in the frequency domain from 1 to 300 Hz.

3.4. Assessing Energy Outcomes

Assessing the energy outcomes was conducted by comparing human milk and the USDA certified organic cow milk for infants, both with and without 60 pM AcCoA, at 0.25 Hz and 250 Hz, respectively, using the voltage method. Fig. 6 depicts the voltage sensor control profiles compared in two media between human milk samples and PBS 7.0 buffers at multiple frequencies. Fig. 6A represents the synapse pulse discharge profiles at 0.25 Hz, Fig. 6B depicts the synapse pulse discharge profiles at 40 Hz and Fig. 6C depicts the synapse pulse discharge profiles at 250 Hz. The overlapping curves indicate human milk and PBS have a minimum difference in neural pulse energy discharge, as evidenced at SWS, they have the highest net memcapacitor voltage output compared to other higher frequencies, meaning the energy was conserved.

Fig. 7A depicts that the 60 pM AcCoA reduced the synapse voltage discharge by 94 % at 0.25 Hz in human milk as compared to milk without AcCoA. AcCoA reduced more energy outcome at SWS as compared at 250 Hz, as shown in Fig. 7B. Also shown, the good bacteria in human milk boosted the net energy of five-fold, 1.04 nWHr/cm^2 compared to the 0.19 nWhr/cm^2 of organic milk without AcCoA at 0.25 Hz; and 25.3 pWHr/cm^2 with human milk compared with 37 pWHr/cm^2 of organic milk in the presence of 60 pM AcCoA at 0.25 Hz as shown in Fig 8.

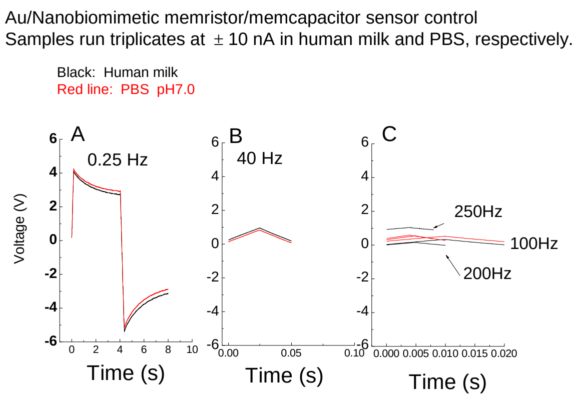

Fig. 6. Voltage sensor control profiles compared in two media between human milk control samples and samples in PBS 7.0 buffers in multiple frequencies.

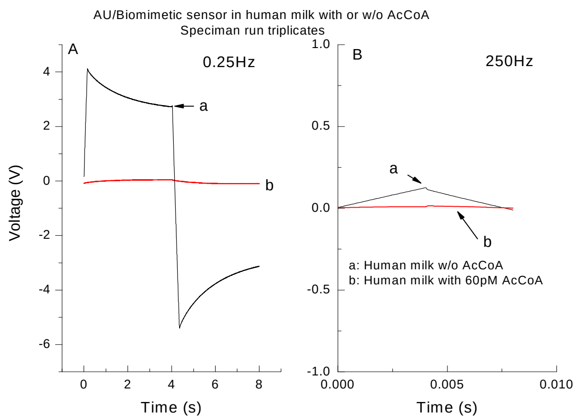

Fig. 7. Voltage profiles in the presence of AcCoA in human milk at 0.25 Hz and 250 Hz, respectively compared with controls.

From these results, human milk offers great benefits over organic cow milk for the development of neuronal cells at all frequencies studied regardless of whether it contains AcCoA. The biphasic synapse curves with the highest intensity at SWS over other frequencies are the characteristics of normal human brain function, and it originates energy for memory consolidation as demonstrated using the nanobiomimetic memristor/memcapacitor device "fed" with human milk. The same device using organic cow milk has a destroyed biphasic synapse pattern with very low energy outcome as shown in Fig. 8A at 0.25 Hz and Fig. 8B at 250 Hz, with 60 pM AcCoA against controls, respectively. That indicates there is an urgent need to enrich the probiotics in the cow milk for children.

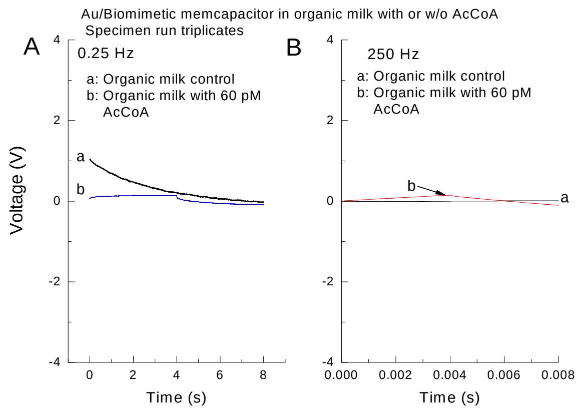

Fig. 8A. Memcapacitor voltage pulse curves in 60 pM AcCoA in organic milk at 0.25 Hz vs. control. Fig. 8B depicts the memcapacitor voltage pulse curves in 60 pM AcCoA in organic milk at 250 Hz vs. control, respectively.

3.5. Human Milk Recognizes Toxins

3.5.1. The "Normal Neural Circuitry" in Human Milk Has a *Hummingbird-like* Hovering Synapse Pattern

The goals of using *Energy-Sensory* image map are to evaluate, predict and monitor early signs of neurological diseases; here we use SIDS as an example. The energy-sensory control maps and images without a spiked AcCoA are presented in Fig. 9A, 9B and 9C. For the initial "neural network prosthesis" **before the device discharges a pulse**, the circuitry synapse networking flow is in a hummingbird-like asymmetric hovering flight "8" shape pattern on a flat 45° surface in Fig. 9A. The contour map is Fig. 9B and the optical image is in Fig. 9C, that has the original light intensity indicating the healthiness of the neocortex-hyppocampus after being put in contacted with the human milk.

3.5.2. Human Milk Recognizes the Spatiotemporal Locations of Toxins

This is the first time we observed that human milk has the ability to recognize the toxins' neural circuitry spatiotemporal location as shown in

Fig. 10A, 10B and 10C. The figures also shown human milk has the ability to bypass toxins as marked in the red circles in the maps of the prosthesis with **60 pM AcCoA with 2 mM o-NPA**. Pulse energy inserted in 0.25 Hz. AcCoA effects **at SWS only**. HFO formed with enhanced light shown as a star. The HFO located in the fast gamma frequency range. Fig. 11A, 11B and 11C depict repeatedly human milk has the ability to bypass toxins as shown in red circles in the maps of the prosthesis in **60 pM AcCoA with 2 mM o-NPA**. Pulse energy inserted in 0.25 Hz. AcCoA effects **at SWS-100 Hz.** The HFO formed with enhanced light shown as a star that indicates human milk's immunological advantage for cognitive development. Fig. 12A, 12B and 12C depict human milk has the ability to bypass toxins as shown in red circles in the maps of the prosthesis in **60 pM AcCoA without o-NPA.** Pulse energy inserted in 0.25Hz. AcCoA effects over **SWS-100 Hz.** HFOs were formed. Neural network circuitry was in an 8-shape flat circuitry surface.

3.6. Cow Milk Creates pHFO

3.6.1. Cow Milk Mutates Neural Network Circuitry

"Mutated Neural Network". The Hummingbird's hovering with an "8" shape flight pattern, like the symbol for infinity, ∞, would be destroyed if its visual background is moving [60]. Nevertheless, at the critical SWS stage, the brain-gut-microbiota axis is at resting and the electrical synapse does its best work for memory consolidation as we mentioned at the beginning; herein the neocortex-hyppocampus axis played an important role in human health at SWS. In the following section, we discuss the experimental results based on the simple model using organic milk samples both have the final 60 pM AcCoA concentration and with 2 mM o-NPA onto the same memristor/memcapacitor device under two monitoring conditions: one is the ACCoA effect on SWS vs. another condition that monitors the AcCOA effect from SWS to 100 Hz and compared the results with those from using human milk. Another condition to test the repeatability of a milk sample recognizing toxin is to test the AcCoA spiked milk with or without o-NPA under a same range of monitoring AcCoA effect frequency between SWS to 100 Hz. Fig. 13A, 13B and 13C depict the 3D **control maps** in the dynamic neural circuitry, the contour map and the image map, respectively in organic milk controls before a brain pulse was discharged. The pHFO was formed. Fig. 14A, 14B and 14C depict organic milk samples in the maps of the prosthesis in **60 pM AcCoA with 2 mM o-NPA**. Pulse energy inserted in 0.25Hz. AcCoA effects **at SWS only**. The pHFO was also formed. Surface was bended. Fig. 15A,15B and 15C depict the maps of the prosthesis in **60 pM AcCoA with 2 mM o-NPA**. Pulse energy inserted in 0.25Hz. AcCoA effects **at SWS-100 Hz.** The neural circuitry was dysfunctional with a broken neocortex. pHFO was formed. SIDS was declared. Fig. 16A, 16B and 16C depict organic milk in the maps of the prosthesis in **60 pM AcCoA without o-NPA.** Pulse energy inserted in 0.25 Hz. AcCoA effects over **SWS-100 Hz.** The neural circuitry was dysfunction with a broken neocortex. pHFO was shown in the map. SIDS was also declared. The significant difference between Fig. 9B and Fig. 13B in human milk control and organic milk control was the observation of a circular current formation caused the neocortex area swelling in organic milk. This observation is in agreement with literature that autism babies' brains experience overgrowth in early of life [61-62]. Could this observation is the first sign of CHAT deficiency evidenced by the swellingness of the neocortex and it may lead to SIDS by the unknown substance in organic milk sample? From our prior work reported in literature [17], that we estimated the Michaelis-Menton constant k_m value of the same biomimetic CHAT prosthesis memcapacitor in PBS using a CA method is 0.0164 nM by Lineweaver-Burk plot according to the result of y= 0.0026 $(\mu A/s)^{-1}$ + $4.28e^{-5}x$ for $(V_{obs}\text{-}V_{un})^{-1}$ vs. $(nM)^{-1}$ of an inversed AcCoA concentration with r = 0.983, n=15 and p<0.0001, that the CA sensor offers orders of magnitudes stronger affiliation to AcCoA compared with that of the human nerve cell's CHAT activity. It is clear evidence shown in Fig. 7A and 8A by comparing the pulse intensity at SWS frequency between human milk and organic milk that is more than 10-fold stronger. This observation indicates human milk has order of magnitude higher relative k_m strength than that of organic milk; hence the deficiency of CHAT for using organic milk to "fed" newborns has a higher likelihood vulnerable to toxin's invasion, especially at SWS that might lead to SIDS compared to human milk "fed" newborns who have the advantage of receiving higher immunological protection.

Literature reported that cow milk fed babies are more frequently seen in SIDS than are seen in breast milk fed babies [14-16]. SIDS also appeared in young type 1 diabetes infants and toddlers reported everywhere [63]. This SIDS phenomena also hurts type 1 biabetes infants reported in literature [64-65]. The cause is still unknown till to this day. It is our desire to find a means for solving this unknown problem. In this report, the results revealed there are unknown substances in cow milk that may have mutated the normal brain sensory and altered the connectivity in the brain network circuitry. One of our prior works had proved the vertex toroid force existed in the mutated ACHE gorge cavity; herein the bad reentrant circuitry forming perpendicular conformational surfaces [66]. Fig. 14A, 14B shows a vertical gap between neocortex and hippocampus, that causes challenge to circuitry current flowing freely. Fig. 15A, 15B and 15C and Fig. 16A, 16B and 16C depict the number of vertical cliff increases, and the pHFO caused the neocortex broken down in the presence of 60 pM AcCoA that effects over SWS to 100 Hz regardless with or without NPA in the prosthesis. The neural circuitry was dysfunctional with the broken neocortex. SIDS was predicted at this stage. From Fig. 13's neocortex brain volume increase to Fig. 15 and Fig. 16 brain's neocortex broken indicates SIDS, and may be a sign that sudden infant death from either heart or breathing failure, that is unavoidable. In summary, the figures show when using cow milk samples, the unknown substances in cow milk played a crucial role in altering brain synapse circuitry in surface conformation, flow direction, and poor energy that may hamper an infant's early normal brain cognitive development.

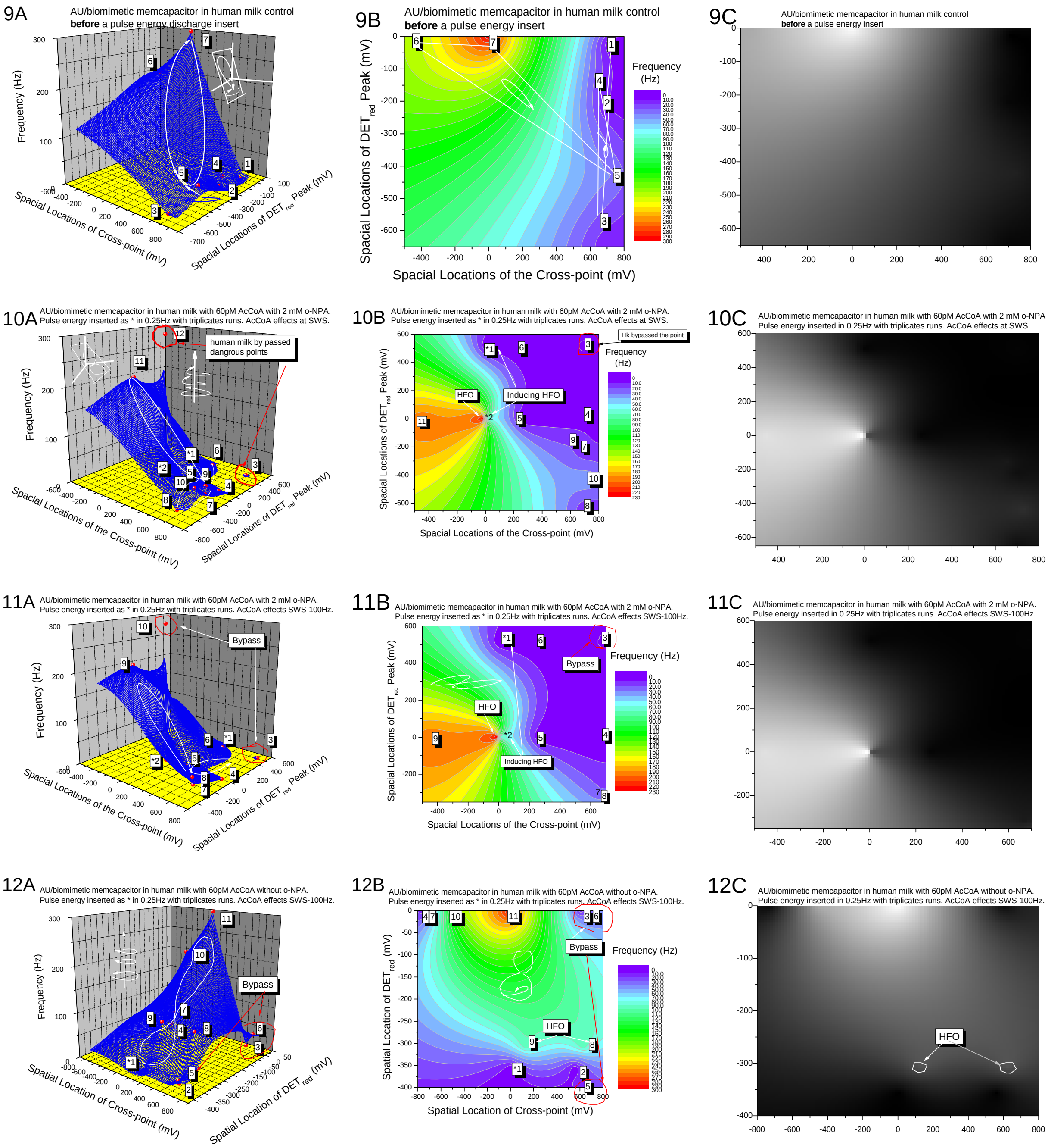

Fig. 9A, 9B and 9C. 3D control maps in neural circuitry map, contour map and image map, respectively in human milk controls before brain pulse was discharged. **Fig. 10A, 10B and 10C.** Human milk has the ability bypass toxins in red circles in the maps of the prosthesis in 60 pM AcCoA with 2 mM o-NPA. Pulse energy inserted as * in 0.25 Hz averaged by triplicates runs. AcCoA effects at SWS only. HFO formed with enhanced light shown as a star. **Fig. 11A, 11B and 11C** Human milk has the ability bypass toxins in red circles in the maps of the prosthesis in 60 pM AcCoA with 2 mM o-NPA. Pulse energy inserted as * in 0.25 Hz averaged by triplicates runs. AcCoA effects at SWS-100 Hz. The HFO formed with enhanced light shown as a star. **Fig. 12A, 12B and 12C.** Human milk has the ability bypass toxins in red circles in the maps of the prosthesis in 60 pM AcCoA without o-NPA. Pulse energy inserted as * in 0.25 Hz averaged by triplicates runs. AcCoA effects over SWS-100 Hz. HFOs were formed. Neural network circuitry was in an 8-shape flat surface.

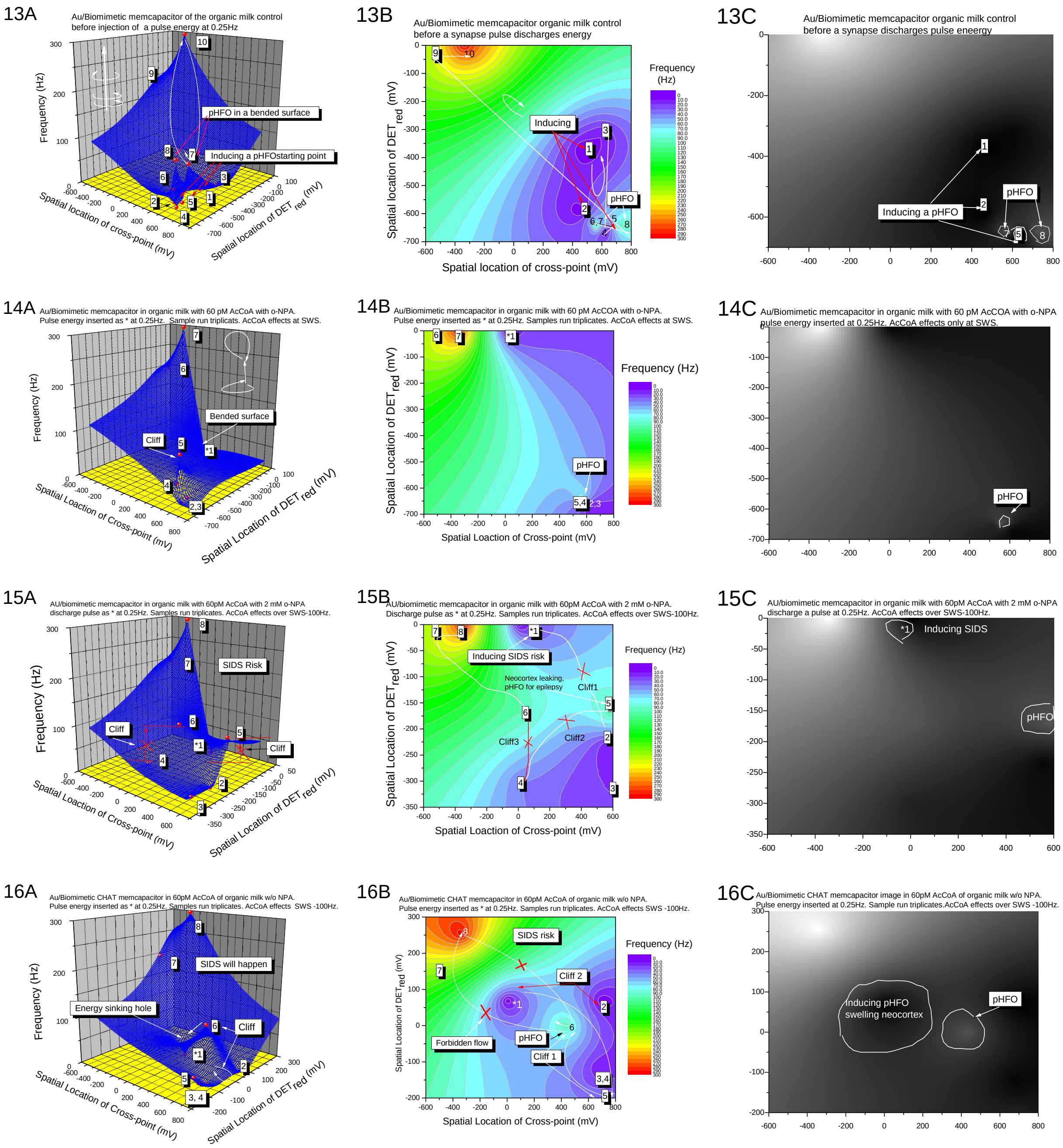

Fig. 13A, 13B and 13C. 3D control maps in neural circuitry, the contour map and the image map, respectively in organic milk controls before brain pulse was discharged. The pHFO was formed. **Fig. 14A, 14B and 14C.** Organic milk samples in the maps of the prosthesis in 60 pM AcCoA with 2 mM o-NPA. Pulse energy inserted as * in 0.25 Hz averaged by triplicates runs. AcCoA effects at SWS only. The pHFO was formed. Surface was bended. **Fig. 15A, 15B and 15C.** Maps of the prosthesis in 60 pM AcCoA with 2 mM o-NPA. Pulse energy inserted as * in 0.25 Hz. AcCoA effects at SWS-100 Hz. The neural circuitry was dysfunction with broken neocortex. pHFO was formed. SIDS was predicted. **Fig. 16A, 16B and 16C.** Organic milk the maps of the prosthesis in 60 pM AcCoA without o-NPA. Pulse energy inserted as * in 0.25 Hz. AcCoA effects over SWS-100 Hz. The neural circuitry was dysfunction with broken neocortex. pHFO was formed. SIDS was predicted.

Table 1 is a summary for comparison of neural circuitry characteristics between human milk and organic milk for with or without AcCoA under different conditions. The results show human milk offered multiple advantages in fighting toxins invasion: to bypass the toxin's spatiotemporal locations; to lower the high frequency surface of the circuitry to a healthy frequency domain and to avoid the epilepsy frequency domain possible; to form HFOs for enhancing the energy; to form a humming-bird-like 8-shpe circuitry. In contrast, organic milk does not offer these advantages due to the possible CHAT deficiency and may be caused by unknown substances in the milk.

Table 1. Comparison of neural circuitry characteristics between human milk and organic milk with or without AcCoA under different conditions.

Situation		Human milk				Organic Milk			
		Number of HFO	**Number of pHFO**	**Bypass toxins**	**Circuitry Integrity**	**Number of HFO**	**Number of pHFO**	**Bypass toxins**	**Circuitry Integrity**
1	Control	0	0	-	Asymmetry 8-chape	0	2	No	Neocotex swelling
									Circular current
									Surface folded
2	60 pM AcCoA with o-NPA. It effects SWS	1	0	yes	Asymmetry 8-chape	0	1	No	cliff
		Star Enhanced light intensity			Lower surface cover from sws-200 Hz. Bypass toxin; Avoiding 300 Hz				Surface vertically tiled
3	60 pM AcCoA with o-NPA. It effects SWS-100 Hz	1	0	yes	Asymmetry 8-chape	0	1	No	3 cliff
		Star			Lower surface cover sws-200Hz; Bypass toxin				Circular current
		Enhancing Light intensity			Intentionally avoid 300 Hz				Neocortex broken
4	60 pM AcCoA w/o o-NPA. It effects on SWS-100 Hz	2	0	yes	Asymmetry 8-chape	0	1	No	3 cliff
		Enhancing Light intensity			Flat surface				Neocortex broken, swelling
					Bypass toxin				Circular current

[1] All pulse discharge energy was inserted in the map at 0.25 Hz, except the controls are before discharge pulses.

4. Conclusion

We have demonstrated a unique approach to study human milk's advantage in promoting and protecting infant early brain cognitive development based on the organic memristor/memcapacitor Biomimetic neural network circuitry prosthesis along with the Energy-sensory mapping method under an antibody-free, radiolabel-free and reagent-less conditions. We also demonstrated cow milk is unfit for infant cognitive development and is actually harmful in terms of mutating the circuitry conformation, current flow direction and energy output that leads to neocortex broken down and blocked the information flow from neocortex to hippocampus and vice versa that further led to SIDS according to our predictions.

Acknowledgement

We would like to thank Matt Lee and his team for recruiting breastfeeding mothers and providing human milk samples as gifts for our projects. The authors want to thank Valarie Kitts for editing the manuscript.

References

[1]. K. R. Shealy, R. Li, S. Benton-Davis, L. M. Grummer-Struwn, The CDC guide to breastfeeding interventions, Atlanta: *U. S. Department of Health and Human Services, (DHHS), Center for Disease Control and Prevention*, 2005. www.cdc.gov/breastfeed.

[2]. U. S. DHHS, Healthy people 2010, 2nd ed., 2 volumes, *U. S. Government Printing Office,* Washington DC, November, 2000. www.healthypeople.gov/publications

[3]. Chapter five of breast feeding, J. of Tropical Pediatrics, Mother and Child Nutrition in Tropics and subtropics, World Health Organization: Breastfeeding: A brochure for ready reference, WHO, Geneva, 1981.

[4]. U-M. Bilhardt, P. Stein and G. M. Whitesides, Enzymatic methods for the preparation of acetyl-coA and analogs, *Bioorganic Chemistry*, 17, 1989, pp. 1-12.

[5]. A. B. A. Prempeh, A. K. Prince and E. G. J. Hide, The reaction of acetyl-coenzyme A with choline acetyltransferase, *Biochem. J.*, 129, 1972, pp. 991-994.

[6]. T. Kato, Enzymatic determination of choline acetyltransferase by coenzyme A cycline and its

application to analysis of single mammalian neurons, *J. of Neurochemistry,* 42, 4, 1984, pp. 903-909.

[7]. A-R. Kim, R. j. Rylett, B. H. Shilton, Substrate binding and catalytic mechanism of human choline acetyltransferase, *Biochemistry,* 45, 2006, pp. 14621-14631.

[8]. A. Szutowicz, H. Bielarczyk, A. Jankowska-Kulawy, T. Pawetczyk, A. Ronowsa, Acetyle-CoA the key factor for survival or death of cholinergic neurons in course of neurondegenerative diseases, *Neurochem Res,* 38, 2013, pp. 1523-1542.

[9]. Y. Tsuchiya, U. Pham, W. Hu, S-I. Ohnuma, I. Gout, Changes in acetyl coA levels during the early embryonic development of xenopus laevis, *PLOS One,* 9, 5, 2014, p. e97693.

[10]. Y. Oda, Choline acetyltransferase: the structure, distribution and pathologic changes in the central nervous system, *Pathology International,* 49, 1999, pp. 921-937.

[11]. D. Wu and L. B. Hersh, Choline acetyltransferase: celebrating its fiftieth year, *J. Neurochemistry,* 62, 1994, pp. 1653-1663.

[12]. T. Merno-Ramos, A. Vazquez-Calvo, J. Cacas, et. al., Modification of the host cell metablism induced by hypolipidemic drugs targeting the acetyl coenzyme A carboxylase impairs west nile virus replication, *Antimicrobial Agent and Chemotherapy,* 60, 2015, pp. 307-315.

[13]. http://www.cdc.gov/sids/data.htm

[14]. R. A. Darnall, M. H. Goodstein, F. R. Hauck, R. Y. Moon, American Academy of Pediatric's Task Force on SIDS fully supports breastfeeding, *Breastfeeding Medicien,* 9, 9, 2014, pp. 486-487.

[15]. W. Sears, Eight reasons breastfeeding reduces SIDS www.askdrsears.com

[16]. B. Alm, G. Wennergren, P. Mollborg, H. Lagercrantz, Breastfeeding and dummy use have a protective effect on sudden infant death symdrum, *Acta Pediatrica,* 105, 2016, pp. 31-38.

[17]. S-H. Duh, J. Thornton, P. T. Kissinger and E. T. Chen, Nanobiomimetic memristor/memcapacitor devices used for direct and reagent-less detection of sub pM acetyl coenzyme A in milks, *Sensors, Diagnostics & Imaging, TechConnect Briefs,* 4, 2016, pp. 136-139.

[18]. E. T. Chen, J. T. Thornton and C. Mulchi, Jr., Early forming a hummingbird-like hovering neural network circuitry pattern with reentrant spatiotemporal energy-sensory orientation privileged to avoid, epilepsy, based on a biomimetic acetylcholinesterase memcapacitor prosthesis, *Sensors & Transducers,* Vol. 191, Issue 8, August 2015, pp. 84-99.

[19]. B. W. Tobalske, D. R. Warrick, C. J. Clark, Three-dimensional kinematics of hummingbird flight, *Journal of Experimental Biology,* 210, 2007, pp. 2368-2382.

[20]. (a) J. Song, H. Luo, T. L. Hedrick, Three-dimensional flow and lift characteristics of a hovering ruby-throated hummingbird, *Journal of the Royal Society Interface,* 11, 98, 2014, (b). web/Stanford.edu/group/ stanfordbirds/text/essays/Hovering_Flight.html.

[21]. P. A. Chai, Flight thermogenesis and energy conservation in hovering hummingbirds, *J Exp Biol.,* 201, Pt 7, 1998, pp. 963-968.

[22]. B. Goller and D. L. Altshuler, Hummingbirds control hovering flight by stabilizing visual motion, *Proceedings of the National Academy of Science,* 111, 51, 2014, pp. 18375–18380.

[23]. G. Buzsáki, C. A. Anastassiou, C. Koch, The origin of extracellular fields and currents — EEG, ECoG, LFP and spikes, *Nature Reviews Neuroscience,* 13, 2012, pp. 407-420.

[24]. Jasper's Basic Mechanisms of the Epilepsies, J. L. Noebels, M. Voli (Eds.), 4th edition, *Oxford Press Publisher,* NY, 2012.

[25]. L. Marshall, S. Binder, Transcranial oscillatory stimulation to research on neural networks, an emphasizes on hippocampus-neocortical rhythms, *Frontiers in Human Neuroscience,* 7, 614, 2013, pp. 1-6.

[26]. The hippocampus book, Anderson P., Morris R., Amaral D., Bliss T. and O'Keefe J. (Eds.), *Oxford University Press,* 2007.

[27]. E. T. Chen, J. Thornton and C. Mulchi Jr, Nanobiomimetic Memcapacitor Memory Devices Identify Circadian Rhythm Dysfunction and Predict Early Signs of, Epilepsy, Using Reentrant Energy-Sensory Images, *Advanced Manufacturing, Electronics and Microsystems: TechConnect Briefs,* 2015, pp 200-203.

[28]. J. Thornton, C. Mulchi, Jr., P. T. Kissinger and E. T. Chen, Acetylcholine Repairs the Amyloid-beta Damage on Brain Circuitry and Memory Loss From a, Mutated Biomimetic Acetylcholinesterase, Neuronal Memcapacitor During Slow-Wave Sleeping, *Advanced Manufacturing, Electronics and Microsystems: TechConnect Briefs,* 2015, pp. 226-229.

[29]. J. T. Thornton, C. Mulchi, Jr., P. T. Kissinger, E. T. Chen, In Vitro Restoration of an Amyloid-Beta Altered Network Circuitry in a 'Mutated Biomimetic Acetylcholinesterase' Memristor/Memcapacitor Neural Prosthesis, *Sensors & Transducers,* Vol. 191, Issue 8, August 2015, 2015, pp 100-113.

[30]. S-H. Duh, J. Thornton, P. T. Kissinger and E. T. Chen Nanobiomimetic Memristor/memcapacitors' Function as a Voltage Sensor for Direct and Reagent-free Detection of sub pg *Lipopolysaccharide* (LPS) in Different Types of Milks for Infants, *Sensors, Diagnostics & Imaging, TechConnect Briefs,* 4, 2016, pp. 140-143.

[31] E. T. Chen, J. Thorten, C. Ngatchou, S-H Duh, P. T. Kissinger, Nanostructured biomimetic pyruvate dehydrogenase complex (PDC) sensors selectively detect single brain cancer cell having the ability to mimic the, ATP Lid, *NSTi-NanoTech* 2, 2013, pp. 107-110.

[32]. E. T. Chen, J. Thornton, C. Ngatchou and S-H Duh, Nanostructured memristor sensor mimics acetylcholinesterase (ACHE) active sites in the gorge for fM detection of acetylcholine, *NSTi-Nanotech,* 2, 2014, pp. 169-172.

[33]. E. T. Chen, Nanostructured biomimetic-enzyme sensing and energy storage, first volume, Third Edition, S. E. Lyshevski, *Dekker Encyclopedia of Nanoscience and Nanotechnology, CRC,* March 20, 2014.

[34]. G. Buzsáki, C. A. Anastassiou, C. Koch, The origin of extracellular fields and currents — EEG, ECoG, LFP and spikes, *Nature Reviews Neuroscience,* 13, 2012, pp. 407-420.

[35]. A. E. Pereda, Electrical synapses and their functional interactions with chemical synapses, *Nature Reviews Neuroscience,* 15, 2014, pp. 250-263.

[36]. R. Wang, Ontogenetic development of the human sleep-dream cycle, *Science,* 152, 1966, pp 604-619.

[37]. F. Simion, G. Butternworth (Eds), The development of sensory, motor and cognitive capacities in early infancy: from perception to cognition, *Psychology Press*, 1998.

[38]. E. T. Chen, J. Thornton, C. Ngatchou, S-H. Duh, P. T. Kissinger, Study of the correlations between direct electron transfer rate constants and the effectiveness of cancer inhibitors using nanobiomimetic sensors, *NSTi-Nanotech*, 3, 2013, pp. 115-118.

[39]. E. T. Chen and C. Ngatchou, Study of the factors that effect on the power storage and generation of a nano-biomimetic membrane electrode-assembling (NBMEA) for battery/fuel cell dual applications, *Clean Technology*, 3, 2011, pp. 204-207.

[40]. E. T. Chen, J. Thornton and C. Mulchi Jr. Mapping Circular Current for a Single Brain Cancer Cell's Spatial-Temporal Orientations Based on a Memristor/Memcapacitor, *Sensors & Transducers,* Vol. 183, Issue 12, December 2014, pp. 72-83.

[41]. M. F**.** El-Kady, V. Strong, S. Dubin, R. B. Kaner, Laser Scribing of High-Performance and Flexible Graphene-Based Electrochemical Capacitors, supplement materials, *Science,* 335, 2012, pp. 1326-1330.

[42]. J. R. Miller, R. A. Outlaw, B. C. Holloway, Graphene double-layer capacitor with ac line-filtering performance, *Science*, 329, 2010, pp. 1637-1639.

[43]. U-M Bilhardt, P. Stein and G. M. Whitesides, Enzymatic methods for the preparation of acetyl-coA and analogs, *Bioorganic Chemistry*, 17, 1989, pp. 1-12.

[44]. A. B. A. Prempeh, A. K. Prince and E. G. J. Hide, The reaction of acetyl-coenzyme A with choline acetyltransferase, *Biochemistry. J.,* 129, 1972, pp. 991-994.

[45]. T. Kato, Enzymatic determination of choline acetyltransferase by coenzyme A cycline and its application to analysis of single mammalian neurons, *J. of Neurochemistry*, 42, 4, 1984, pp. 903-909.

[46]. A-R. Kim, R. j. Rylett, B. H. Shilton, Substrate binding and catalytic mechanism of human choline acetyltransferase, *Biochemistry,* 45, 2006, pp. 14621-14631.

[47]. A. Szutowicz, H. Bielarczyk, A. Jankowska-Kulawy, T. Pawetczyk, A. Ronowsa, Acetyle-CoA the key factor for survival or death of cholinergic neurons in course of neurondegenerative diseases, *Neurochemistry Research*, 38, 2013, pp. 1523-1542.

[48]. Martinez-Rincon, M. D. Ventra, Y. V. Pershin, Solid-state memcapacitive system with negative and diverging capacitance, *Physical Review B*, 81, 19, 2010, pp. 195430-195437.

[49]. M. D. Pickett, G. Medeiros-Ribeiro and R. S. Williams, A scalable neuristor built with Mott memristors, Nature Materials, 12, 2012, pp. 114-117.

[50]. R. Kozma, R. E. Pino, G. E. Pazienza, Advances in neuomorphic memristor science and applications, *Springer Publisher*, 2012.

[51]. M. D. Ventra, Y. V. Pershin, On the physical properties of memristive, memcapacitive and meminductive systems, *Nanotechnology*, 24, 2013, p. 255201.

[52]. E. T. Chen, C. Ngatchou, An electron-relay prototype supercapacitor mimics electrophorus electricus's reversible membrane potential for a high rate discharge pulse, *Sensors & Transducers*, Vol. 15, Special Issue, 2012, pp. 42-48.

[53]. L Goorton, A. Lindgren, T. Larsson, F. D. Munteanu, T. Ruzgas and L Gazaryan, Direct eletrontransfer between heme-containing enzymes and electrodes as basis for third generation biosensors, *Analytica Chimica Acta,* 400, 1, 1999, pp. 91-108.

[54]. E. T. Chen, S-H Duh, C. Ngatchou, J. T. Thornton and P. T. Kissinger, Selectivity study for a reagent-less and enzyme-free nanopore glucose sensor against interferences from non-glucose sugars and other substances, *Nanotech,* 3, 2011, pp. 101-104.

[55]. E. Chen, Nanopore structured electrochemical biosensor, *U. S. Patent* 8/083,926, December 27, 2011.

[56]. E. Chen and R. Fenkelstien, Development of an electrolyte-free, oxygen-free, high-performance, single direct methanol fuel cell (DMFC) in *Proceedings of the 44th Power Sources Conference,* 2010, pp. 333-336.

[57]. M. L. Marin, R. Avrovo et. al., Cold storage human milk: effect on its bacteria composition, *J. Pediatric. Castroenterol. Nutrition,* 49, 3, 2009, pp. 343-348.

[58]. E. T Chen, J. Thorten, Nanostructured Acetylcholinesterase (ACHE) Memristor/ Memcapacitor Mimicks *Brachyhypopomus* Electric Fish's Signal-Cloaking Behavior, in *Proceedings of the CTSi-Cleantech,* 2014, pp. 63-66.

[59]. Negative resistance, http://en.wikipedia.org

[60]. B. Goller and D. L. Altshuler, Hummingbirds control hovering flight by stabilizing visual motion, in *Proceedings of the National Academy of Science,* 111, 51, 2014, pp. 18375–18380.

[61]. A. Park, Brain size, early growth: clues to Autism's causes, May 3, 2011, www.Healthland.time.com.

[62]. M. H. Johnson, T. Gliga, E. Jones, T. Charman, Annual research review: infant development, autism, and ADHD-early pathways to emerging disorders, *Journal of Child Psychology and Psychiatry*, 56, 3, 2015, pp. 228-247.

[63]. G. Sartor, G. Daulquist, Short-term motality in childhood onset insuline-dependedt diabetes mellitus: a high frequency of unexpected death in bed, *Diabetic Medicine*, 12, 7, 1995, pp. 607-611.

[64]. E. Chen, J. Nichols, S-H Duh and G Hortin A study of the factors that affect the performance of the blood glucose monitoring devices, *Clinical Chemistry* 47, S6, 2001, pp. A189.

[65]. E. Chen, J. Nichols, S-H. Duh and G. Hortin. Evaluation of performance of self- monitoring blood glucose meters, *Diabetes Technology & Therapeutics* 5, 5, 2003, pp. 749-768.

[66]. E. T. Chen, J. Thornton and C. Mulchi Jr. Mapping Circular Current for a Single Brain Cancer Cell's Spatial-Temporal Orientations Based on a Memristor/Memcapacitor, *Sensors & Transducers,* Vol. 183, Issue 12, December 2014, pp. 72-83.