

# Neuro-Energetic Aspects of Cognition - The Role of Pulse-Wave-Pulse Conversion in the Interpretation of Brain Imaging Data

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**Abstract**— In the last decade, neuro-energetics has become an important research topic, which can contribute to better understanding and interpreting brain imaging data. We need to understand how the brain encodes information coming from the environment, and how this information is converted to knowledge and meaning useful for intentional action and decision making. Valuable information can be derived from both single neuron and population (*neuropil*) recording in order to investigate the cognitive cycle. Usually pulses are measured with electrodes placed intracellularly while oscillations are measured through ECoG. Our main interest here is to investigate the relationship between the creation of knowledge and meaning and the metabolic cycle in neural populations, as well as the conversion of incoming action potentials to the dendritic structure of the neuron into currents which will contribute to new action potentials. This process we call the *pulse-wave-pulse conversion*. We model the coupling the energy consumption associated with new action potentials and the metabolic cycle, and the conclusions for future large-scale neuro-energetic models.

**Keywords** - *Neuro-energetics; Metabolic Cycle; Pulse-Wave-Pulse Conversion; Cognitive Cycle; Cognition; Brain Dynamics, CAN unit.*

## I. INTRODUCTION

Perceptual and cognitive processes in the human brain are accomplished through the formation of patterns of neural activity, which can be monitored by advanced brain imaging techniques (Moseley et al., 2009; Freeman & Quiroga, 2013; Soares et al., 2016). Decades long studies by Freeman and colleagues point to the importance of amplitude-modulated (AM) patterns or frames of information in various cortical regions (Freeman, 1991; Kozma & Freeman, 2016). The AM

patterns are formed through the cooperative activity of mesoscopic cortical regions, such as the olfactory, visual, auditory, or motor cortex. These cognitive perceptual frames are coordinated spatially through synchronization-desynchronization transitions between narrow-band and broad-band (chaotic) oscillations (Tsuda, 2001; Freeman, 2003; Davis & Kozma, 2012). The spatio-temporal coordination of these AM patterns or frames is essential in the formation of perceptions, thoughts, and behaviors in the human nervous system. In this work we study the interaction of metabolic processes and spiking activity in the cortical neuropil that lay down the basis of cognitive processing and the cognitive cycle (Davis et al., 2012).

The metabolic cycle in neurons involves a set of energy transformations when electrical energy is converted into chemical energy and back into electric energy in dendritic transactions. There is an extensive literature on modeling the energy cycles in the brain; see, e.g., (Cloutier et al., 2009; Belanger et al., 2011; Joviet et al., 2015). There is less research on developing a detailed link between brain metabolism and spiking processing (Chandler & Chakravarthy, 2012; Chabria and Chakravarthy, 2016).

We aim at creating a manageable hybrid of the metabolic approach to neurobiology and the information-processing approach exemplified by the canonical single-neuron “leaky integrate and fire (LIF)” or spiking neuron models that typically eschew any discussion of energy constraints on spiking behavior. Following our previous studies (Noack et al., 2017), we consider two main group of processes in this paper: (a) the *metabolic cycle* at a very high level including astrocytes, and (b) the creation of a *new action potential* when the threshold above resting potential is met in a neuron. We

model these processes by developing a set of differential equations for the mitochondria and astrocytes in the metabolic part, and the generation of action potentials in the Izhikevich Model (Izhikevich, 2003).

The present work goes beyond previous studies by focusing on the pulse-wave and wave-pulse conversion processes in the neuropil. We connect these two components and test them, both separately and together, in order to improve our understanding of neuronal dynamics. The results on wave-pulse-wave conversion are important for the interpretation of brain imaging experiments, and to better understand neural correlates of higher cognition and consciousness.

## II. CONCEPTUAL FRAMEWORK OF THE CAPILLARY-ASTROCYTE-NEURON (CAN) MODEL

Over the past several decades, remarkable advances have been made in non-invasive methods to study mammalian brain function--human brain function in particular (Bandettini, 2009; Moseley et al., 2009; Tewarie et al., 2016). With these new non-invasive techniques have correspondingly come new demands on the methods in which researchers are finding themselves having to model those brain processes. For example, for the greater part of the twentieth century, the golden age of neuroscience and neural network research, architectures built to simulate the computational intelligence of human brains relied almost exclusively on modeling the function of the individual neuron and then organizing these functional units into networks in the hope of simulating some human cognitive processes. This is no surprise—virtually the only data available to artificial intelligence modelers at the time came from single-unit neuron recordings in (mostly) rats and mice, electro-corticogram (ECoG) recording from local populations of cortical neurons in the same mammalian lab species, and electroencephalogram (EEG) scalp recording in humans. What these three recording techniques have in common is that they measure principally the electrical properties of individual and populations of interaction *neurons*, largely eschewing the contribution from the arguably equally important supporting elements of brain tissue, or *neuropil*, that the neurons are embedded in, such as neuro-glial cells and the brain’s vascular architecture.

The end result of this myopic focus on a neuron-centered approach to the computational modeling of intelligent processes in humans, reflected in the so-called “neuron doctrine” of twentieth-century neuroscience research, was the spate of intelligently designed systems that essentially used only the “integrate and fire” property of the neuron, that defined the neuron doctrine, into the core element of its computational architecture. Accordingly, the intelligent model-simulations that were purportedly based on the function of the brain in the past century were of the type that viewed the neuron as functionally equivalent to a logic gate of sorts which subsequently sums associated inputs and feeds them up and down a hierarchical cascade of “processing layers” in an effort to classify or recognize certain input stimuli. The result

of this thinking led to the emergence of the popular perceptron, backpropagation, and other artificial neural network architectures of the time. In fact, the legacy of these neural network architectures survives even today in the recently popular machine learning, deep learning and other related intelligent architectures (Bengio et al., 2013; 2015; Schmidhuber, 2015).

As popular as these new deep learning architectures have become, and despite their impressive ability for certain forms of feature recognition, natural language processing, and other predictive tasks, few of the artificial neural network models that existed in the last century, or even the ones that are around today, are biologically realistic. One of the principal reasons they are unrealistic is because they only work to model a simplified and idealized version of the functional architecture of the brain—interacting individual neurons. As stated above, what we are finding today in contemporary neuroscience study is that the fundamental units of neocortical function are composed of biologically complicated and rich interactions between the glia cells, neurons, and capillaries that make up cortical neuropil. Again, this important new discovery in neuroscience research has come about due to advances in non-invasive brain imaging that have forced researchers to relate the metabolic processes in the neuropil, such as blood flow and glucose utilization, in order to explain how recording techniques, such as the BOLD signal, influences functional magnetic resonance (fMRI) images.

In light of these recent advances in what has come to be termed “neuro-energetics” research, several recent models have emerged which attempt to describe the complex interactions of glia (astrocytes), neurons, and the brain vasculature. Some even go as far as trying to relate these neuro-energetic interactions to the information-processing of spiking behavior in individual neurons and populations of neurons (Chander & Chakravarty, 2012; Chabria & Chakravarty, 2016; Philips et al., 2016).

We developed a mathematical model and computer simulation of what we are postulating is the basic metabolic/computational functional unit within the human cerebral cortex (Noack et al., 2017). This unit, what we call the Capillary-Astrocyte-Neuron (CAN) unit is roughly equivalent in size and structure to the canonical “cortical column” first identified by Mountcastle (1997) as the primary granular or atomistic functional module/unit of cortical operation. In the CAN unit model, we attempt to replicate the complicated cycle of energy flow through the unit by simulating the fluxes of energy precursors and metabolites between the elements of the unit, the electrochemical gradients established across the unit’s constituent neuron, and the integrate-and-fire properties of the neuron in its association with other neurons in the assemblage.

The metabolic portion of the model is inspired by (Cloutier et al., 2009; Jolivet et al., 2015) and others, the principal challenge we faced was in deciding which of the biological processes described by the multitude of equations and parameters were essential to include in the CAN model. We decided that the important features of the Cloutier et al. model

we wanted to preserve were, 1) the flux of glucose from the CBF (cerebral blood flow) to astrocyte, 2) the capacity through which the astrocyte can store this glucose energy reserve in the form of glycogen (while the neuron is unable to), 3) the “astrocyte-neuron lactate shuttle,” the mechanism whereby the astrocyte breaks down its glycogen stores to deliver energy in the form of lactate to the neuron in times of need, and 4) the process whereby the neuron metabolizes lactate in the mitochondria to produce ATP, which, in turn, powers the neuron’s sodium-potassium pumps. We reduced the dozens of equations in the Cloutier et al. model into two differential equations. The first equation describes the rate of change of the state variable,  $g$ , which is a measure of the glycogen/energy store in the astrocyte available for the neuron to utilize. The second equation describes the rate of change of the state variable,  $m$ , which is a measure of the ATP available to reset the membrane potential of the CAN unit’s representative neuron. From here, we coupled our above formulation to the canonical IZ model through a parameter in the IZ model related to the resetting of the membrane potential and the  $m$  state variable of the reduced Cloutier model; see Fig. 1 for the schematics of the model (Noack et al., 2017).

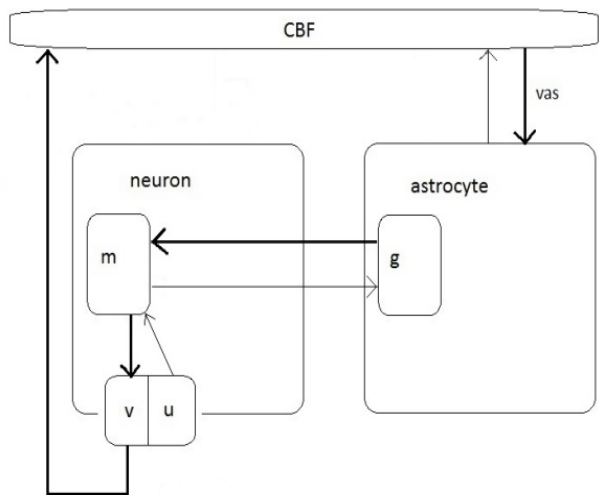


Figure 1: Schematic representation of the CAN unit model showing the flux relations between its various components; CBF – cerebral blood flow, vas – vascular connection,  $m$  – ATP level in the neuron,  $g$  glycogen/energy store in the astrocyte,  $v$  and  $u$  are state variables of the Izhikevich model; from (Noack et al., 2017).

In order to close the form of the system of equations, we added a term in the equation modeling the  $g$  variable, which represented the glutamate concentration in the interstitial matrix surrounding the CAN unit’s representative neuron. In experimental studies (Belanger et al., 2011), this concentration, which is reflective of the metabolic activity of the CAN unit neuron, is sensed by the CAN unit astrocyte and serves to compel that astrocyte to dilate the capillary portion of the CAN unit. Dilating the capillary then serves to deliver more glucose to the astrocyte in response to the increased need

for energy precursor molecules demanded via the increased activity in the CAN unit.

The tentative conclusion we have come to after working with the model and its simulation, is that the method by which the human brain is able to perform such sophisticated computational feats at such a low energy cost, is through 1) coordination of delivery of energy molecule precursors to cooperatively interacting cortical regions, and 2) the phase synchrony in the oscillations of dendritic currents in the CAN unit neuron collectives that populate these interacting cortical regions. More specifically, we put forth the argument that the coordinated delivery of nutrients to cooperatively interacting cortical regions, set a tempo of the restoral of the resting membrane potential in their constituent neurons, which in turn help facilitate the cooperative phase-synchronized, narrow-band oscillations seen between these interacting regions (Davis & Kozma, 2012; Davis et al., 2012). However, this remains a hypothesis to be tested with a finished CAN model which at the moment is a work in progress.

The ultimate goal is to build a CAN model with interacting components, which describes mesoscopic oscillations in the cerebral cortex, as documented by brain imaging. As an example, Figure 2 illustrates an amplitude-modulated (AM) pattern, which manifests a frame of cognitive processing (Freeman, 1991). Perceptual and cognitive processes in the human brain are accomplished through the formation of AM patterns, which we intend to describe through the cooperative or synchronous activity in a collection of CAN units that compose a cytoarchitectonically circumscribed and defined region of cortex such as the visual cortex (V1) or the motor cortex (M1). The spatio-temporal coordination of these AM patterns or frames is essential in the formation of perceptions, thoughts, and behaviors. Disruption of the coordination of these rhythms due to inconsistencies in the energy cycle of the CAN units, such as is witnessed in, say, hypoglycemia or diabetes, could lead correspondingly to perceptual-cognitive deficiencies as well as psycho-motor coordination problems (Rosenthal et al., 2001).

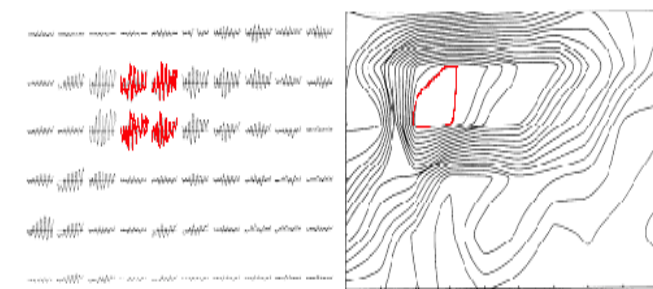


Figure 2: 6x10 micro-array of electrodes implanted on the olfactory cortex of a rabbit (left). Note the commonality of the frequency and phase of each of the sixty EEG recordings. While the frequency and phase of the oscillations are similar across the elements in the array, the amplitudes of each differ significantly (AM pattern), that can be visualized as a topographic map (right). In the current formulation, each of the 60 recordings in the array can be considered as a CAN unit coupled into a cooperative network; adopted from (Freeman, 1991).

### III. SYSTEMS THEORY APPROACH TO THE SIMPLIFIED CAN MODEL

The neuron is stimulated by electrical impulses arriving to its dendrites, and the cell body processes these impulses to derive from it new action potentials (Buzsaki et al., 2012). In the neuron there are three types of potentials: resting potential, the graded potential, and the action potential. Action potential can lead to synaptic activity on the next neuron. The resting potential can be described as a separation of charge, as in a battery, across the axonal membrane. In a typical human neuron this corresponds to  $-70\text{mV}$ . In this state the neuron has a higher percentage of potassium ( $\text{K}^+$ ) inside, as well as negatively charged anions, whilst having a higher percentage of sodium ( $\text{Na}^+$ ) and chlorine ( $\text{Cl}^-$ ) atoms on the outside. Though significantly less, there are also potassium atoms on the outside, as well as some sodium and chlorine atoms on the inside. This state, the resting potential, is known as the electrochemical gradient and it is through the collective effect of incoming pulses converted to electrical currents that the resting potential meets a threshold ( $-55\text{mV}$ ) that gives birth to a new action potential.

These conversion processes require Adenosine Triphosphate (ATP) together with the generation of new action potentials at the trigger zone near the axon. Those transactions require the replenishment of glucose coming from the blood into glycogen molecules inside astrocyte cells, where glucose is stored. When the neuron has used a certain amount of ATP through these energetic transactions then the cell replenishes the needs for more ATP by processing glucose molecules, which are taken from the glycogen present in the astrocyte cell (Belanger et al., 2011).

In order to give a better description of the system in a simple manner we present in Figure 3a-b using diagrams of system dynamics. In the base model in Fig. 3a, the glucose level rises with the intake of glucose from the blood. Once it reaches a certain point the intake slows down, with a delay, until it reaches carrying capacity; when the glucose level falls to a certain point the cycle repeats beginning with a replenishment of glucose from the blood. Dendritic activity ( $\lambda(t)$ ) consumes ATP, thus triggering the cycle of glucose demand and intake from astrocyte cells. This in turn creates a reduction in the glucose level, which prompts further intake of glucose from the blood. Depending on the energy demands of the incoming action potentials into the dendrites of the neuron this model suggests that the system would replenish glucose and ATP to reach its respective carrying capacities with the possibility of displaying different dynamics, more likely oscillatory. The amount of glucose supplied to the astrocyte is a function of the energy consumed by the associated neurons' sodium-potassium pumps. Having a similar concentration of ATP in the constitutive neurons in cooperatively interacting populations is essential for the requisite synchronous brain rhythms that drive sensory and cognitive processing in those networks.

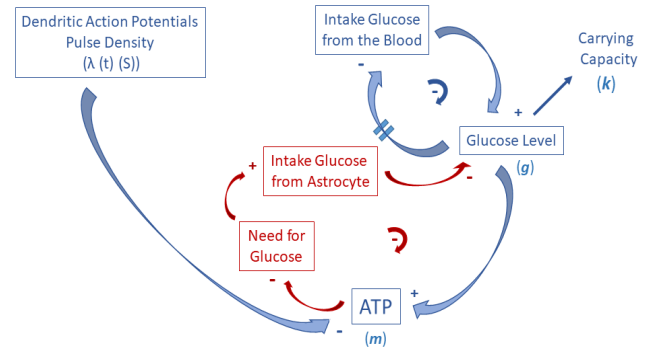


Figure 3a: Basic systems dynamics model of the Metabolic Cycle, describing the relationship between dendritic activity, glucose levels, and ATP consumption.

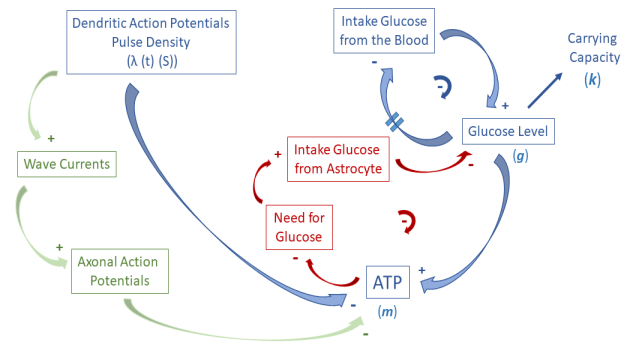


Figure 3b: Extended diagram of a systems dynamics model of the Metabolic Cycle, together with the pulse-wave-pulse conversion process.

The spiking frequency of neurons is directly affected by the immediate availability or concentration of ATP in the neuron during individual and population spiking “burst” epochs. Therefore, in order to coordinate cooperative activity in these networks, the metabolic cycling of energy precursor molecules must be coordinated between the interacting units that make up the populations.

Following the system dynamics diagram in Fig 3a-b, a set of simplified differential equations were developed for the metabolic part in conjunction with the IZ model for the production of new action potentials, with its associated energy consumption, that eventually will lead to a model that feeds back into ATP consumption. For now we only illustrate how the action potentials arriving at the dendrites ( $\lambda(t)$  in Fig. 3) and converted into an energy demand (S) will cause the consumption of ATP (m), eventually manifesting the replenishment of ATP via the intake of glucose from astrocytes when converted into ATP. The production of new action potentials is simply carried on by the Izhikevich model where (S) is converted into (I) representing the Synaptic currents or any induced dc-current via a transfer function  $I(S)$ . It is important to note that all the variables of this model are dimensionless. Following we present the set of differential equations for both the metabolic and IZ section of the model.

For the metabolic sub model we use the logistic model for population growth ( $P$ ) with carrying capacity ( $k$ ) and a growth factor ( $r$ ) for both glucose ( $g$ ) and ATP ( $m$ ) levels:

$$\frac{dP}{dt} = r * P * \left(1 - \frac{P}{k}\right) * G(S) \quad (1)$$

Modified logistic equations are used for state variables  $g$  and  $m$  as follows, where  $r=1$ ,  $k=1$  is used:

#### Metabolic Model

$$\frac{dg}{dt} = r * g * (1 - g - g0) * G(S) \quad (2)$$

$$\frac{dm}{dt} = \gamma * g * m * (1 - m - S - S^*(v)) \quad (3)$$

The IZ sub model is used as described in (Izhikevich, 2003). An important consideration for us is that  $I$  becomes a function of  $S$ , ( $I(S)$ ) that feeds forward the generation of new action potentials. This is the Pulse-Wave conversion function (Davis, 2017). The Wave-Pulse conversion function is performed by way of the IZ model:

#### Izhikevich (IZ) Model

$$\frac{dv}{dt} = 0.04 * v^2 + 5 * v + 140 - u + I(S) \quad (4)$$

$$\frac{du}{dt} = a * (b * v - u) \quad (5)$$

$$\text{If } v \geq 30 \text{ then } \{c = v; u = u + d\}$$

We link these two sub models through the pulse-wave-pulse conversion function, whereby  $I(S)$  is a function converting the dendritic currents associated with the energy demands  $S$  into a quantity representing membrane potential fluctuations. This variable,  $I(t)$ , in turn will stimulate the IZ model in order to create new action potentials,  $S^*(v)$ . It is important to note that these new pulses will also generate their own ATP demands in the model together with the demands already present from dendritic activity.

#### IV. RESULTS OF SIMULATIONS BY THE SYSTEMS MODEL

We demonstrate five cases of simulations, where a) is a baseline without any dendritic activity where  $S = 0$ ; b) is a scenario where  $S$  is a cyclical pulse train with a certain duration, where the system has been disabled from feedback from new action potentials coming from  $v$ ; c) is the same as scenario b, however, with a step function that kicks in at  $t = 500$  representing a higher demand of energy; d) is a scenario where we add to the second one (scenario b) a function to

represent ATP ( $m$ ) consumption,  $S^*(v)$  creating a feedback that has a contribution to itself through the neuro-populations that it is linked to; and scenario e) we change the parameter  $A$  in the Izhikevich Model to create a very busy neuron rich in action potentials per millisecond.

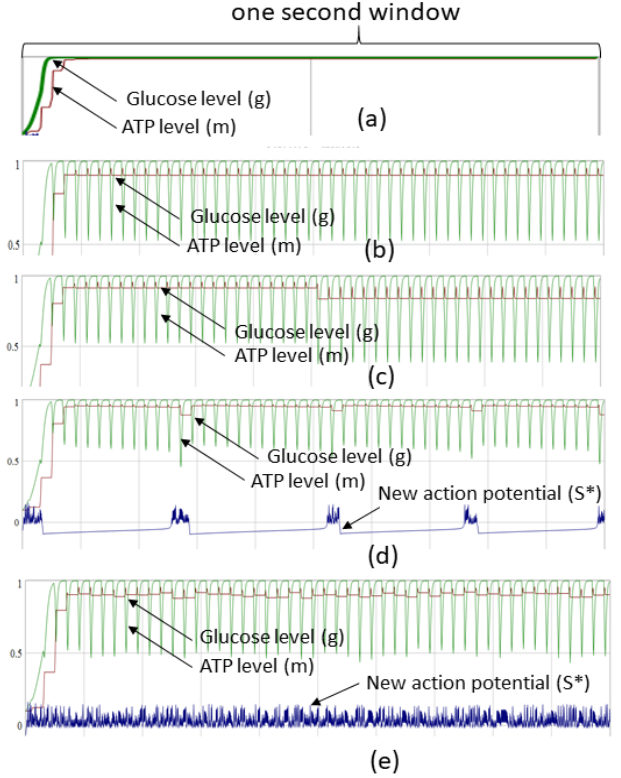


Figure 4: Shows the results for the simulation for scenario a, b, c, d and e for glucose levels, ATP levels and new action potentials for IZ model.

We show the results of the different scenarios in Figs 4-5, where we can appreciate for scenario: a) how both the levels of glucose and ATP reach their carrying capacity following a logistic function behavior; b) we can see how for this cyclical slow pulse train, both the levels of glucose and ATP oscillate showing us a behavior related to the cycle of replenishment for both ATP and glucose; c) we can see the same cyclical pattern, however the amplitude of the oscillations grows after  $t = 500$  due to the extra input provided to the system; for d) we can observe an extra drop in glucose level and ATP caused by the creation of the new action potentials which feedback into the process of glucose and ATP consumption; and finally in e) we can see the effects of very rich and dense action and potential processes with its repercussion of the ATP and glucose consumption and replenishment cycles.

In order to have a better insight into how the Izhikevich model couples with the demands of energy induced by  $\lambda(t)$  we show a set of graphs in Fig. 5, where we also modeled a number of scenarios, as follows: no feedback; energy demands pattern one (1); energy demands pattern two (2); feedback to dendrites; and feedback to dendrites and ATP demands.

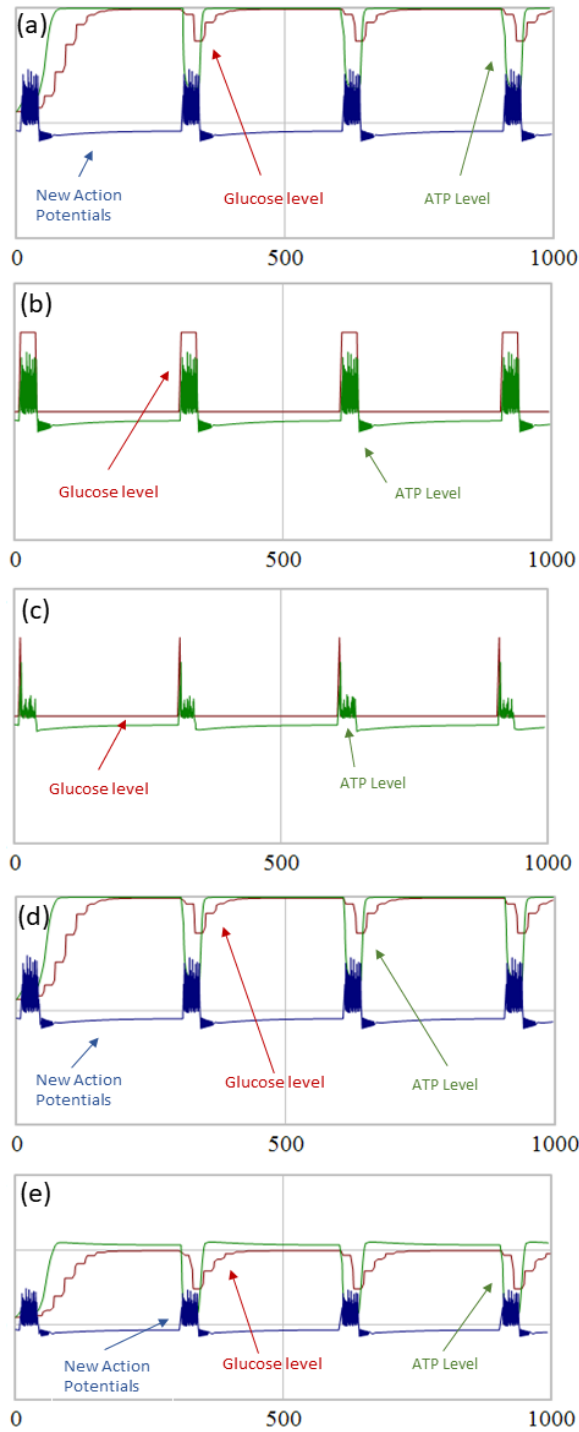


Figure 5: Illustration of the results for the simulation for scenario a, b, c, d and e for energy demand ( $S$ ), and new action potentials  $S^*(v)$ .

In Scenario (1), we observe the output of the IZ model coupled with the energy demand pulses. In Scenario (2) we observe a similar pattern to Scenario (1), however, the duration of the pulse in energy demand is much shorter also reflecting in the pulse trains of the new action potentials

generated by the IZ model. In the Scenario (3), we can observe the effect of the new pulse train pattern generated by the IZ model and its energetic impact in ATP availability, as well as glucose levels. Scenario (4) shows the effect of feeding back a contribution of the new set of action potentials generated by the IZ model, both in energy demands on ATP and glucose levels. Scenario (5) shows an extra level of ATP demand with its associated drop in glucose levels due to the feedback of the contribution of the simulated new action potential in the pulse density dendritic network.

## V. DISCUSSIONS

The CAN model presents a system whereby the metabolic and spiking neuron dynamics of mammalian neuropil are merged into a single interactive framework in the effort to describe both the mesoscopic dynamics of neuron populations and the microscopic dynamics of individual “spiking” neurons. At its core, the metabolic equation models two state variables,  $g$  and  $m$ , which represent, respectively, the level of glucose concentration in astrocyte cells and ATP concentration in neuron cells. The dynamics of both the  $g$  and  $m$  variables are represented foundationally by a logistic function with a carrying capacity that tends to unity absent of systems constraints, yet showing biologically realistic oscillatory behavior when the various parameters and constraints of the model are placed on the system. These constraints represent the chemical fluxes and feedback loops between the neurons, astrocytes and capillaries that make up each individual CAN unit.

In simulation runs of the CAN unit model, we demonstrated biologically realistic behavior reflecting the dependence of: a) blood glucose delivery from the vasculature, b) glucose level fluctuations in the astrocyte and c) ATP level fluctuations in the neuron comprising the CAN unit. The interdependency of these fluctuations is observed in the oscillatory coupled behavior of the  $g$  and  $m$  state variables, and these oscillations in turn, result in biological approximations of new action potentials manifested in the neuron and neuropil as observed by (Buzsaki et al., 2012; Werbos & Davis, 2016).

It is important to state that we consider the present work as an initial, very crucial step towards a comprehensive theory of neuro-energetics. We are confident that this work will support future breakthroughs in understanding and interpreting brain behavior, as we advance in the challenging adventure of unravelling the mysteries of cognition and brain dynamics.

## VI. CONCLUSIONS AND FUTURE PERSPECTIVES

During the process of the creation of knowledge and meaning, the brain needs to consume energy which derives mainly from glucose in order to produce electrical chemical signals that are the carriers of action potentials (*pulses*) and, in a broad sense, dendritic currents (*waves*) that are usually described as oscillations in broad frequency bands between 2Hz and 120Hz. This study breaks new grounds in modeling

these conversion processes, thus embedding the pulse transfer and propagation into the electromagnetic field domain produced by the immense complexity of currents and associated biochemical processes. Progress in this field helps to interpret experiments on brain dynamics and better understand the relation between the creation of knowledge and meaning for decision making, through intentional actions (Davis et al., 2013; 2015). These models will allow us to explore the hypothesis on the presence of cycles in the brain (Werbos & Davis, 2016). The results can lead to the development of computers that are energy-aware, and thus capable of mimicking the energy constraints crucial in the emergence of human intelligence.

Potential benefits include better understanding of energy and stress management for health and the prevention of diseases through healthy diets, exercise and the practice of relaxation and meditation. All of this could also improve our capacity for sustained inner peace and its positive repercussions for social harmony; ultimately better understanding ourselves and understanding between each other contributing for a bright future of humanity.

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