Chapter 1

CALCULATING CONSCIOUSNESS CORRELATES AT MULTIPLE SCALES OF NEOCORTICAL INTERACTIONS

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ABSTRACT

A lot of what we consider Consciousness ($\mathbf{C}$) is conscious attention to short-term memories (STM). At least some STM are actively processed by highly synchronized patterns of neuronal firings, with enough synchrony to be able to be easily measured by scalp electroencephalographic recordings (EEG). Large-scale synchronous macrocolumnar EEG firings is a top-down process developed by a statistical mechanics of neocortical interactions (SMNI), depending on the associated magnetic vector potential $\mathbf{A}$. Molecular-scale Ca^{2+} waves are the affected bottom-up process that influence neuronal firings, depending on the wave momentum $\mathbf{p}$. $\mathbf{A}$ directly influences $\mathbf{p}$ via the canonical momentum $\mathbf{\Pi} = \mathbf{p} + q\mathbf{A}$ (SI units), where the charge of Ca^{2+} is $q = -2e$, e is the magnitude of the charge of an electron. Calculations in both classical and quantum mechanics approaches are consistent with this effect, and each approach yields independent testable consequences. This approach also suggests some nanosystem-pharmaceutical applications. Results (with details given in Appendix A) give strong confirmation of the SMNI model of STM, but only weak statistical consistency of $\mathbf{\Pi} = \mathbf{p} + q\mathbf{A}$ influences on scalp EEG.

1. INTRODUCTION

1.1. “Mind over matter”

“Mind Over Matter” is a stretch, but not an inaccurate, context for this project. The logic of this metaphor is based in calculations on specific processes that have specific experimental confirmation, and that have been demonstrated to have support for viable models to support this study. While results presented here show only that these processes are statistically consistent with current experimental and theoretical evidence, the importance of this study is to at least demonstrate ingredients of analysis that can be considered reasonable to approach this subject.

(1) A lot of what we consider “mind” or “Consciousness” ($\mathbf{C}$) is conscious attention to short-term memories (STM), which can develop by (a) external stimuli directly, (b) internal long-term storage, (c) new ideas/memories developed in abstract regions of the brain, etc.

(2) It is now accepted by some neuroscientists and confirmed by some experiments (Asher, 2012; Salazar *et al.*, 2012), that at least some such memories in (1) are actively processed by highly synchronized patterns of neuronal firings, with enough synchrony to be able to be easily measured by scalp electroencephalographic recordings (EEG) during activity of processing such patterns, e.g., P300 waves, etc. These minicolumnar currents giving rise to measurable EEG also give rise to magnetic vector potentials $\mathbf{A}$, for brevity commonly referred to as vector potentials. The $\mathbf{A}$ fields have a logarithmic range insensitivity and are additive over larger distances than electric $\mathbf{E}$ or magnetic $\mathbf{B}$ fields.

Only for brevity, unless otherwise stated, dependent on the context, “EEG” will refer to either the measurement of synchronous firings large enough to measurable on the scalp, or to the firings themselves.

(3) Previous papers (Ingber, 2011, 2012a; Ingber *et al.*, 2014) calculate the influence of such synchronous EEG at molecular scales of Ca^{2+} ionic waves, a process which is present in the brain as well as in other organs, but particularly as astrocyte influences at synaptic gaps, thereby affecting background synaptic activity, which in turn can be synchronized

by other processes to give rise to the large-scale activity discussed in (1). The Ca^{2+} wave have a duration of momentum $\mathbf{p}$ which is observed to be rather large, on the order of STM duration.

(4) These papers connect the influence of (1) over (3) directly via a specific interaction, $\mathbf{p} + q\mathbf{A}$, where q for a Ca^{2+} ion = $-2e$, where e is the magnitude of the charge of an electron. The $\mathbf{p} + q\mathbf{A}$ interaction is well established in both classical and quantum physics.

The direct $\mathbf{p} + q\mathbf{A}$ influence of (1) over (3) can reasonably be discussed as a "mind over matter" process. E.g., just thinking about thinking can give rise to this effect.

These SMNI models (Ingber, 1982, 1983) assume that STM responses to internal or external stimuli evoke such background-noise control to maintain maximal numbers of information states as calculated and detailed in multiple previous papers (Ingber, 1984, 1985, 1994).

1.2. Scope of research

This work is not designed to be a review of research in $\mathbf{C}$. Certainly $\mathbf{C}$ is an important component of many disciplines, not just Science. However, within the realm of Science, there still is a quite unscientific immediate negative reaction from many people focussed within their particular disciplines, ranging from neuroscience to physics, to exclude the study, even mention, of $\mathbf{C}$ from their own disciplines and journals. Within the realm of Science, there are other projects that also examine specific microscopic and quantum processes that may influence $\mathbf{C}$ (Clark, 2014; Hameroff & Penrose, 2013; Kouider, 2009; McFadden, 2007; Nunez & Srinivasan, 2006a; Pereira & Furlan, 2009; Quiroga *et al.*, 2013; Stiefel *et al.*, 2014), as well as neural correlates of reasonable models of $\mathbf{C}$ (Nacia *et al.*, 2014; Nunez & Srinivasan, 2010), but this work is focussed on a particular $\mathbf{p} + q\mathbf{A}$ mechanism.

However, by necessity, this project requires interdisciplinary contributions from neuroscience, physics, biomedical engineering, optimization, and similar disciplines. This work addresses the importance of considering topics usually focussed within physics, e.g., the vector potential $\mathbf{A}$ (Jackson, 1962), and of a specific interaction between Ca^{2+} ions and $\mathbf{A}$ developed by highly synchronous neocortical EEG. The necessity of addressing multiple scales of neuroscience has required a mathematical physics of multivariate nonlinear nonequilibrium statistical mechanics to develop aggregation of these scales (Ingber, 1982, 1983). The algebra presented by this development and the stochastic nature of EEG data has required the development of sophisticated importance-sampling algorithms like Adaptive Simulated Annealing (ASA) (Ingber, 1989, 1993), and other algorithms like PATHINT (Ingber, 1994, 2000; Ingber & Nunez, 1995) to evolve the fitted probability distributions.

1.3. $\mathbf{C}$ and Dark $\mathbf{C}$

It would be simply hubris to assume that we are even on the verge of knowing everything about our physical and human existence, including $\mathbf{C}$. Indeed, similar to current concepts of "Dark Energy" and "Dark Matter", it is possible there are aspects of $\mathbf{C}$ that we may only be able to infer existence or possibly prove we cannot know. These latter possibilities can be considered as belonging to a "Dark $\mathbf{C}$" ($\mathbf{DC}$) category, and $\mathbf{DC}$ should be researched as well as $\mathbf{C}$. However, here we are definitely examining $\mathbf{C}$ within the realm of Science, looking for viable experimental data and viable theoretical understandings of such data.

1.4. SMNI multiple-scale context of calcium waves

Although the importance of multiple scales in many physical and biological systems has been discussed (Anastassiou *et al.*, 2011; de Lima *et al.*, 2015; Nunez *et al.*, 2013), there are not yet any experiments detailing top-down processes driving bottom-up processes such as memory, attention, etc. For example, this is not the same as demonstrating that neuromodulator (Silberstein, 1995) and neuronal firing states, modify individual synaptic and neuronal activity that can give rise to large-scale synchronous firings.

This study crosses molecular (Ca^{2+} ions), microscopic (synaptic and neuronal), mesoscopic (minicolumns and macrocolumns), and macroscopic (regional scalp EEG) scales.

A statistical mechanics of neocortical interactions (SMNI) of columnar firing states has been developed in a series of 30+ papers. SMNI has calculated properties of STM — e.g., capacity (auditory 7 ± 2 and visual 4 ± 2), duration, stability , primacy versus recency rule, Hick's law — and other properties of neocortex by scaling up to macrocolumns across regions to fit EEG data (Ingber, 1982, 1983, 1984, 1985, 1994, 1997a, 2012a). Large EEG databases have been used to test scaled SMNI at relatively large regional scales.

Experiments verify that coherent columnar firings contain information/memory (Liebe *et al.*, 2012; Salazar *et al.*, 2012). This is independent of other candidate neural processes that code information via synchronous firings (Kumar *et al.*, 2010; Stanley, 2013) other candidate processes among neurons and astrocytes (Banaclocha & Banaclocha, 2010), including ephaptic coupling of cortical neurons (Quiroga *et al.*, 2013) and other electromagnetic interactions that contribute to the extracellular medium (Buzsaki *et al.*, 2012). It is now generally accepted that long-term memories are not only stored in individual neurons, but also in groups of neurons and macrocolumns (Quiroga *et al.*, 2013)

The neocortical electric current is taken directly from experimental data, not theoretical calculations. Thus, they include much of the contribution from these other sources. SMNI recently has included the influence of macrocolumnar EEG fields on the momentum of Ca^{2+} ions (Ingber, 2011, 2012a; Ingber *et al.*, 2014).

Ca^{2+} is generally considered to influence synaptic interactions, e.g., in modulating excitatory glutamic acid (Zorumski *et al.*, 1996), albeit not always in neocortical interactions (Adam-Vizi, 1992). Ca^{2+} waves may influence tripartite synaptic interactions of astrocytes and neuronal synapses, in neocortex (Agulhon *et al.*, 2008; Araque & Navarrete, 2010; Ross, 2012) and hippocampus (Kuga *et al.*, 2011), although this has been disputed in some contexts (Sun *et al.*, 2013). "Glissandi", another tern for Ca^{2+} waves, influences cerebral blood flow (Kuga *et al.*, 2011). Various studies examine glial cells as they affect neural information processing (Han *et al.*, 2013; Lee *et al.*, 2014).

Astrocytes are considered to influence glutamate (the main excitatory neurotransmitter in neocortex) production across synaptic gaps, by taking in some glutamate released by presynaptic neurons and converting it back into glutamate via conversion into glutamine which can enter presynaptic neurons where it can be converted into glutamine via interaction with glutaminase. In the context of SMNI calculations here, GABA (the main inhibitory neurotransmitter in neocortex) can be produced by inhibitory neurons by also utilizing glutamic acid (which when stripped of a hydrogen atom is glutamate) from astrocytes (Patel *et al.*, 2001; Walls *et al.*, 2014).

The Ca^{2+} waves considered specifically belong to a class arising from nonlinear cooperative regenerative processes from internal stores, complementary to Ca^{2+} released through classic endoplasmic reticulum channels and voltage-gated and ligand-gated Ca^{2+} transients. This class includes Ca^{2+} released from an inositol triphosphate receptor ($\mathrm{IP}_3\mathrm{R}$), requiring the presence of IP_3, acts on the same or other $\mathrm{IP}_3\mathrm{R}$ to release more Ca^{2+} while IP_3 is still present. This requires or affects additional processes, e.g., as metabotropic glutamate receptors (mGluR), muscarinic acetycholine receptors (mAChR) (Ross, 2012). A fire-diffuse-fire model is often used to describe these waves (Coombes *et al.*, 2004; Dawson *et al.*, 1999; Keener, 2006).

Columnar EEG firings develop electromagnetic fields as described by a magnetic vector potential, referred to here as the SMNI vector potential (SMNI-VP). Early discussions of SMNI-VP were suggested, including the “Smoking Gun” that implicates top-down interactions at molecular scales (Ingber, 2011, 2012a). A previous paper outlined the approach taken here in a classical physics context (Ingber, 2012b). Other papers have described detailed interactions of SMNI-VP firing states with Ca^{2+} waves, in both classical (Ingber, 2011, 2012a) and quantum contexts (Ingber *et al.*, 2014).

1.5. Review and new results

The next Section give a short review of classical and quantum considerations relevant to this project. Note that considering both classical and quantum physics approaches demonstrates that each approach yields independent testable consequences. The Section following that gives a short review of the explicit inclusion of these considerations into the SMNI model, i.e., SMNI-VP interactions with calcium waves. Much of these following two Sections paraphrase content written by the author in a previous paper (Ingber *et al.*, 2014), with additional references and discussion, which is considered relevant to developing the new context of **C** here.

The two Sections following these reviews, supported by details in Appendix A, give the methodology used for these calculations, and new results from ongoing studies. Fits to EEG data give further strong support to SMNI detailing STM. The fits are not as conclusive for the importance of the particular **A** model chosen for this study.

Appendix B gives motivation for studies to pursue STM feedback via nanosystem pharmaceutical intervention.

The final Section is the conclusion.

2. CLASSICAL AND QUANTUM CONSIDERATIONS

In classical physics, the action, which is the Lagrangian L multiplied by a time epoch Δt, defines a short-time conditional probability distribution P over a vector of variables x and time t,

$$P[x(t)|x(t-\Delta t)] = \bar{\mathrm{N}} \exp(-L\Delta t) \tag{1}$$

where $\bar{\mathrm{N}}$ is a normalization prefactor that may depend on time as well as the independent variables. P evolves in time as calculated by the path integral over all variables at all intermediate times. In quantum physics, the Lagrangian or Hamiltonian similarly generates the evolution of the wave function ψ whose absolute square is a probability distribution. There are equivalent Fokker-Planck partial and Langevin stochastic differential representations, but the Lagrangian formulation offers intuitive, algebraic and numerical advantages. This includes an associated variational principle, deriving Canonical Momenta and Euler-Lagrange equations. Powerful numerical algorithms are generally required to fit these algebraic models to data, such ASA (Ingber, 1989, 1993, 2012c), and to numerically calculate numerical the propagating probability distributions, such as Monte Carlo methods or using PATHINT (Ingber, 1994, 2000; Ingber & Nunez, 1995) and PATHTREE (Ingber *et al.*, 2001).

2.1. Canonical momentum

The canonical momentum, $\mathbf{\Pi}$, describes the dynamics of a moving particle with momentum $\mathbf{p}$ in an electromagnetic field (Feynman, 1961; Feynman *et al.*, 1964; Goldstein, 1980; Semon & Taylor, 1996). In SI units,

$$\mathbf{\Pi} = \mathbf{p} + q\mathbf{A} \tag{2}$$

where $q = -2e$ for Ca^{2+}, e is the magnitude of the charge of an electron $= 1.6 \times 10^{-19}$ C (Coulomb), and $\mathbf{A}$ is the electromagnetic vector potential. (In Gaussian units $\mathbf{\Pi} = \mathbf{p} + q\mathbf{A}/c$, where c is the speed of light.) $\mathbf{A}$ represents three components of a 4-vector (Jackson, 1962; Semon & Taylor, 1996).

$\mathbf{\Pi}$ is used here in both quantum and classical calculations (Tollaksen *et al.*, 2010).

2.2. Vector potential of wire

A columnar firing state is modeled as a wire/neuron with current $\mathbf{I}$ measured in A = Amperes = C/s,

$$\mathbf{A}(t) = \frac{\mu}{4\pi} \int \frac{dr}{r} \mathbf{I} \tag{3}$$

along a length z observed from a perpendicular distance r from a line of thickness r_0. If far-field retardation effects are neglected, this yields (Jackson, 1962)

$$\mathbf{A} = \frac{\mu}{4\pi} \mathbf{I} \log\left(\frac{r}{r_0}\right) \tag{4}$$

Note the insensitive log dependence on distance; this log factor is taken to be of order 1. The oscillatory time dependence of $\mathbf{A}(t)$ derived from $\mathbf{I}(t)$ is likely influential in the dynamics of Ca^{2+} waves.

The contribution to $\mathbf{A}$ includes many minicolumnar lines of current from 100's to 1000's of macrocolumns, within a region not large enough to include many convolutions, but contributing to large synchronous bursts of EEG (Srinivasan *et al.*, 2007). $\mathbf{E}$ and $\mathbf{B}$, derivatives of $\mathbf{A}$ with respect to r, do not possess this logarithmic insensitivity to distance, and therefore they do not linearly accumulate strength within and across macrocolumns.

Reasonable estimates of contributions from synchronous contributions to P300 measured on the scalp give tens of thousands of macrocolumns on the order of a 100 to 100's of

cm^2, while electric fields generated from a minicolumn may fall by half within 5-10 mm, the range of several macrocolumns.

2.3. Effects of vector potential on momenta

The momentum $\mathbf{p}$ (Ingber, 2011, 2012a; Ingber *et al.*, 2014) for a Ca^{2+} ion with mass $m = 6.6 \times 10^{-26}$ kg, speed on the order of 50 μm/s (Bellinger, 2005) to 100 μm/s (Kuga *et al.*, 2011; Ross, 2012), is on the order of 10^{-30} kg-m/s. Molar concentrations of Ca^{2+} waves, comprised of tens of thousands of free ions representing about 1% of a released set, most being buffered (Reyes & Parpura, 2009), are within a range of about 100 μm to as much as 250 μm (Bowser & Khakh, 2007), with a duration of more than 500 ms, and concentrations [Ca^{2+}] ranging from 0.1-5 μM (μM = 10^{-3} mol/m^3) (Ross, 2012).

An electric dipole moment $\mathbf{Q}$ is developed as $|\mathbf{I}|z$ where $\hat{\mathbf{z}}$ is the direction of the current $\mathbf{I}$ with the dipole spread over z. Studies of small ensembles of neurons (Murakami & Okada, 2006), give estimates of $|\mathbf{Q}|$ for a pyramidal neuron on the order of 1 pA-m = 10^{-12} A-m. Taking 10^4 synchronous firings in a macrocolumn, leads to a dipole moment $|\mathbf{Q}| = 10^{-8}$ A-m. Taking z to be $10^2\mu\mathrm{m} = 10^{-4}$ m, a couple of neocortical layers, gives $|q\mathbf{A}| \approx 2 \times 10^{-19} \times 10^{-7} \times 10^{-8}/10^{-4}$ = 10^{-28} kg-m/s,

At larger scales (Nunez & Srinivasan, 2006b) a dipole density $|\mathbf{P}| = 0.1$ μA/mm^2 is estimated. A volume of $\mathrm{mm}^2 \times 10^2\mu\mathrm{m}$ gives $|\mathbf{Q}| = 10^{-9}$ A-m. This is smaller than above due to cancellations at the scale of scalp EEG. The previous estimate is within a macrocolumn, leading to $|q\mathbf{A}| = 10^{-29}$ kg-m/s.

Estimates used here for $\mathbf{Q}$ come from experimental data, e.g., including shielding and material effects. When coherent activity among many macrocolumns associated with STM (Salazar *et al.*, 2012) is considered, $|\mathbf{A}|$ may be orders of magnitude larger. Since Ca^{2+} waves influence synaptic activity, there is direct coherence between these waves and the activity of $\mathbf{A}$.

Classical physics calculates $q\mathbf{A}$ from macroscopic EEG to be on the order of 10^{-28} kg-m/s, while the momentum $\mathbf{p}$ of a Ca^{2+} ion is on the order of 10^{-30} kg-m/s (Ingber, 2011, 2012a; Ingber *et al.*, 2014). This numerical comparison illustrates the importance of the influence of $\mathbf{A}$ on $\mathbf{p}$ at classical scales.

An experimental test at the classical molecular scale to verify the influence of $\mathbf{A}$, can be made considering that if the current lies along $\hat{\mathbf{z}}$, then $\mathbf{A}$ only has components along $\hat{\mathbf{z}}$, and

$$\mathbf{\Pi} = p_x\hat{\mathbf{x}} + p_y\hat{\mathbf{y}} + (p_z + qA_z)\hat{\mathbf{z}} \tag{5}$$

which alters momenta along $\hat{\mathbf{z}}$.

2.4. Quantum calculation

The Lagrangian L can be transformed into a Hamiltonian which defines the probability distribution in terms of the canonical energy $\mathbf{\Pi}^2/(2m)$. The magnetic vector potential field $\mathbf{A}$ is quite insensitive to a reasonable columnar spatial location, facilitating the momentum representation of a Gaussian wave function. The expectation of momentum $\mathbf{p}$ is just the classical value (Ingber *et al.*, 2014).

As developed previously (Ingber *et al.*, 2014), the wave function of a Ca^{2+} wave packet is developed from its momentum-space wave packet $\phi(\mathbf{p}, t)$

$$\phi(\mathbf{p}, 0) = (2\pi(\Delta\mathbf{p})^2)^{-3/4} e^{-(\mathbf{p}-\mathbf{p}_0)^2/(4(\Delta\mathbf{p})^2)}$$

$$U(\mathbf{p}, t) = e^{-i((\mathbf{p}+q\mathbf{A})^2 t)/(2m\hbar)}$$

$$\phi(\mathbf{p}, t) = \phi(\mathbf{p}, 0) U(\mathbf{p}, t) \tag{6}$$

The wave function in coordinate space, $\psi(\mathbf{r}, t)$ is then developed

$$\psi(\mathbf{r}, t) = (2\pi\hbar)^{-3/2} \int_{-\infty}^{\infty} d^3\mathbf{p} \phi(\mathbf{p}, t) e^{i\mathbf{p}\cdot\mathbf{r}/\hbar}$$

$$\psi(\mathbf{r}, t) = \alpha^{-1} e^{-\beta/\gamma - \delta}$$

$$\alpha = (2\hbar)^{3/2} (2\pi(\Delta\mathbf{p})^2)^{3/4} \left(\frac{it}{2m\hbar} - \frac{1}{4(\Delta\mathbf{p})^2} \right)^{3/2}$$

$$\beta = \left(\mathbf{r} - \frac{q\mathbf{A}t}{m} - \frac{i\hbar\mathbf{p}_0}{2(\Delta\mathbf{p})^2} \right)^2$$

$$\gamma = 4 \left(\frac{it\hbar}{2m} + \frac{\hbar^2}{4(\Delta\mathbf{p})^2} \right)$$

$$\delta = \frac{\mathbf{p}_0^2}{4(\Delta\mathbf{p})^2} + \frac{iq^2\mathbf{A}^2 t}{2m\hbar} \tag{7}$$

where $(\Delta\mathbf{p})^2$ is the variance of $\mathbf{p}$ in the wave packet.

During a duration of 100 ms, there is a displacement of the $\mathbf{r}$ coordinate in the real part of the ψ quantum wave function of $qAt/m = 1.5 \times 10^{-2} t$ m, on the order of 1.5×10^{-3} m = mm, the range of a macrocolumn (Ingber *et al.*, 2014). If $\Delta\mathbf{r}$ can be on the order of a synapse of a few nm (Stapp, 1993), then this spatial extent is on the order of about $\mu\mathrm{m} = 10^4$ Å(Å= Angstrom $= 10^{-10}$ m). The displacement of $\mathbf{r}$ by the $\mathbf{A}$ term is much larger than $\Delta\mathbf{r}$. If the uncertainty principle is close to saturation, $\Delta\mathbf{p} \geq \hbar(2\Delta\mathbf{r})$ = $1.054 \times 10^{-34}/(2 \times 10^{-6}) = 5 \times 10 - 29$ kg-m/s. This would make $\Delta\mathbf{p}$ on the order of $\mathbf{p}$.

There may be specific interactions between $\mathbf{A}$ and $\mathbf{p}$ within neocortex, e.g., perhaps requiring explicit frequency dependence of $\mathbf{A}$. For example, processing speeds of information at quantum scales may be influenced by Ca^{2+} waves, e.g., via Grover's algorithm giving a quantum square-root versus a classical linear search (wherein the search is processed by the wave function instead of its square, the associated probability function) (Clark, 2014; Mukherjee & Chakrabarti, 2014), in turn influenced by $\mathbf{A}$, providing a feedback loop between states of attention at regional scales and control of STM information at molecular scales.

2.5. Quantum coherence of calcium waves

Ca^{2+} waves have durations up to 500 ms (Ross, 2012). Quantum coherence times on the order 100 ms are not yet experimentally observed in real neocortex. However, $\mathbf{A}$ exerts strong quantum influences on $\mathbf{r}$ via its relative influence on $\mathbf{p}$. Even if the $\mathbf{p}$ wave packet may not survive long coherence times, there is evidence of free Ca^{2+} ions surviving for hundreds of ms, and these ions will be affected by $\mathbf{A}$ during this time.

Arguments that quantum coherence cannot be maintained at high temperatures (Davies, 2004), may not necessarily apply to many biological systems (Aharony *et al.*, 2012; Chin *et al.*, 2013; Fleming *et al.*, 2011; Hartmann *et al.*, 2006; Lloyd, 2011). Quantum coherence in potassium ion channels has been proposed (Vaziri & Plenio, 2010). The cooperative regenerative process underlying Ca^{2+} waves is similar to free ion passing over two bound charges via Coulomb interactions, and this may mediate extended entanglement with free ions (Buscemi *et al.*, 2007, 2011).

Ca^{2+} waves of coherent free ions (Pereira & Furlan, 2009), may develop pulsed-dynamical decoupling, generalizing the quantum Zeno effect (QZE) and “bang-bang” (BB) decoupling of ions from their environment, promoting long coherence times (Facchi *et al.*, 2004; Facchi & Pascazio, 2008; Giacosa & Pagliara, 2014; Wu *et al.*, 2012; Zhang *et al.*, 2014) as the system receives n “kicks” during time t. The QZE is described by the evolution

$$U_n(p,t) = [U_{k(n)} U(p, t/n)]^n \tag{8}$$

The kicks $U_{k(n)}$ may come from other quantum systems, e.g., other Ca^{2+} ions in the same wave developed in the regenerative processes discussed previously, wherein these processes are essentially “weak measurements” of wave packets, projecting the combined system of new few Ca^{2+} ions and waves consisting of many Ca^{2+} ions onto new wave packet states during each “kick”. Similar phenomena are investigated in quantum computation (Rego *et al.*, 2009; Yu *et al.*, 2012). These systems include distinguishable particles which can exhibit quantum coherence and entanglement via collisions (Benedict *et al.*, 2012; Harshman & Singh, 2008). Other studies calculate how environment noise may lead to extended entanglement (Zhang & Fan, 2013).

Recent work has clarified differences between continuous QZE and BB effects, the latter typically causing a collapse/decoherence of the wave-function at each short time kick into a sub-space of the original state, but ultimately also often greatly extending coherence times of the basic original state (Giacosa & Pagliara, 2014; Zhang *et al.*, 2014). However, the elongation of coherence times in many cases is the same whether calculating using the BB or the QZE approach. The regenerative processes Ca^{2+} wave processes are in the class of BB models, wherein kicks from new individual/few ions at time t_n are “weak measurements” projecting the previous wave-packet onto a subspace of a weakly modified wave-packet. Kicks may add to or subtract from the total number of Ca^{2+} ions, or add to or subtract from the vector momentum, in the wave packet. Each projection starts a new wave-packet at t_n that starts its own evolution according to the equations described above from the previous wave-packet $\phi(\mathbf{p}_{n-1}, t_{n-1})$ in momentum space or $\psi(\mathbf{r}_{n-1}, t_{n-1})$ in coordinate space, thereby prolonging the effective coherence time of the physical system into a new wave-packet $\phi(\mathbf{p}_n, t_n)$ in momentum space or $\psi(\mathbf{r}_n, t_n)$ in coordinate space.

For example, if we consider the above wave packet in momentum space, $\phi(\mathbf{p}, t)$ is "kicked" from $\mathbf{p}$ to $\mathbf{p}+\delta\mathbf{p}$, and simply assume that repeated kicks of $\delta\mathbf{p}$ result in $<\delta\mathbf{p}>\approx 0$, and each kick keeps the variance $\Delta(\mathbf{p}+\delta\mathbf{p})^2 \approx \Delta(\mathbf{p})^2$, then the overlap integral at the moment t of a typical kick between the new and old state is

$$< \phi^*(\mathbf{p}+\delta\mathbf{p},t)|\phi(\mathbf{p},t) >= e^{\frac{i\kappa+\rho}{\sigma}}$$

$$\kappa = 8\delta\mathbf{p}\Delta\mathbf{p}^2\hbar m(q\mathbf{A}+\mathbf{p}_0)t - 4(\delta\mathbf{p}\Delta\mathbf{p}^2 t)^2$$

$$\rho = -(\delta\mathbf{p}\hbar m)^2$$

$$\sigma = 8(\Delta\mathbf{p}\hbar m)^2 \tag{9}$$

where $\phi(\mathbf{p}+\delta\mathbf{p},t)$ is the normalized wave function in $\mathbf{p}+\delta\mathbf{p}$ momentum space. Note that the time dependence of this overlap is only in κ which affects only the phase of the projection.

A crude estimate is thereby obtained of the survival time $A(t)$ and survival probability $p(t)$ (Facchi & Pascazio, 2008),

$$A(t) =< \phi^*(\mathbf{p}+\delta\mathbf{p},t)|\phi(\mathbf{p},t) >$$

$$p(t) = |A(t)|^2 \tag{10}$$

As given above, $q\mathbf{A}$ can be on the order of 10^{-28}, a wave packet of 1000 Ca^{2+} ions can have $\mathbf{p}_0 = \Delta\mathbf{p} = 10^{-27}$ kg-m/s, $\hbar = 1.0546 \times 10 - 34$ J-s (J = kg-m^2/s^2), and the mass of such a Ca^{2+} packet is $m = 6.6 \times 10^{-23}$ kg. With a kick from a single Ca^{2+} ion, $\delta\mathbf{p} = 10^{-30}$ kg-m/s. These numbers yield:

$$< \phi^*(\mathbf{p}+\delta\mathbf{p},t)|\phi(\mathbf{p},t) >= e^{i(1.67\times10^{-1}t-1.15\times10^{-2}t^2)-1.25\times10^{-7}} \tag{11}$$

Even many repeated kicks do not appreciably affect the real part of ϕ, and these projections do not appreciably destroy the original wave packet, giving a survival probability per kick as $p(t) \approx \exp(-2.5 \times 10^{-7}) \approx 1 - 2.5 \times 10^{-7}$. Note that both time-dependent phase terms in the exponent are sensitive to time scales on the order of 1/10 sec, the same scales prominent in STM and in synchronous neural firings measured by EEG. This suggests that $\mathbf{A}$ effects on Ca^{2+} wave functions may maximize their influence on STM at frequencies consistent with synchronous EEG during STM.

Models still must consider interactions of Ca^{2+} ions in the wave packet with its immediate surroundings. Any degree of quantum coherence among ions in Ca^{2+} waves can only be resolved by experiment, but as yet there is no such evidence.

3. SMNI-VP INTERACTIONS WITH CALCIUM WAVES

3.1. SMNI dipoles

SMNI develops a dipole model for collective minicolumnar oscillatory currents, flowing in ensembles of axons (Ingber & Nunez, 2010). The vector potentials produced by these dipoles survive far from the axons (Feynman *et al.*, 1964; Giuliani, 2010), and this leads to effects at the molecular scale.

Approaches other than SMNI also describe dendritic presynaptic activity as inducing large scale EEG (Nunez, 1981), or axonal firings directly affecting astrocyte processes (McFadden, 2007). SMNI specifically models electromagnetic fields in collective axonal firings, which directly applies to columnar STM phenomena in SMNI calculations.

3.2. SMNI Lagrangian

SMNI develops time-dependent and nonlinear multivariate drifts and diffusions. This was calculated in the mid-point (Stratonovich or Feynman) representation, and all Riemannian contributions were calculated and numerically estimated for neocortex, as the nonlinear multivariate diffusions present a curved space (Ingber, 1982, 1983). Derivations of the mathematical physics are in texts (Langouche *et al.*, 1982) and compact derivations have been given in several papers (Ingber, 1991).

EEG data is fit to SMNI, using data collected at several centers in the United States, sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) project. that the author made public in 1997 (Ingber, 1997b; Zhang *et al.*, 1997a,b, 1995), This project examines the influence of $\mathbf{A}$ on the B synaptic parameters in the SMNI Lagrangian L (given below), using sensitive canonical momenta indicators (CMI) derived from the N-dimensional L to develop graphical results (Ingber, 1996, 1997a, 1998; Ingber & Mondescu, 2001; Ingber *et al.*, 2014). The CMI are a natural method of combining N first moments and $N(N+1)/2$ second moments (with their correlations) into N indicators to fit to data. They are derived from the SMNI Lagrangian Euler-Lagrange equations

$$\mathrm{Mass} = g_{GG'} = \frac{\partial^2 L}{\partial(\partial M^G/\partial t)\partial(\partial M^{G'}/\partial t)}$$

$$\mathrm{Momentum} = \Pi^G = \frac{\partial L}{\partial(\partial M^G/\partial t)}$$

$$\mathrm{Force} = \frac{\partial L}{\partial M^G}$$

$$\mathrm{F} - \mathrm{ma} = 0 : \ \delta L = 0 = \frac{\partial L}{\partial M^G} - \frac{\partial}{\partial t}\frac{\partial L}{\partial(\partial M^G/\partial t)} \tag{12}$$

where $G = \{E, I\}$ is the index representing columnar-averaged chemically-independent excitatory (E) and inhibitory (I) induced synaptic polarizations. The SMNI CMI are the Π^G above, not to be confused with the canonical momenta $\mathbf{\Pi}$ at the scale of Ca^{2+} waves (which also can be derived from different Lagrangians at those scales).

3.3. Coupling calcium waves with SMNI Lagrangian

There are studies that take quite different and complementary approaches to that considered here. Some studies have examined influences of Ca^{2+} on large-scale EEG (Kudela *et al.*, 2009). For example, time dependence of Ca^{2+} wave momenta should be examined, e.g., as calculated with rate-equations (Li & Rinzel, 1994) as a Hodgkin-Huxley model (Hodgkin & Huxley, 1952), including contributions from astrocytes (Bezzi *et al.*, 2004; Larter & Craig, 2005; Lavrentovich & Hemkin, (2008).

Eventually, the functional form of these dynamics should be established by quantum molecular models fit to data — a major task even in a semi-classical setting (Miller, 2006; Nyman, 2014; Wong, 2014; Yang *et al.*, 2006), but for now at least their parameterized influences can be included.

In the prepoint (Ito) representation the SMNI Lagrangian L is

$$L = \sum_{G,G'} (2N)^{-1} (\dot{M}^G - g^G) g_{GG'} (\dot{M}^{G'} - g^{G'})/(2N\tau) - V'$$

$$g^G = -\tau^{-1}(M^G + N^G \tanh F^G)$$

$$g^{GG'} = (g_{GG'})^{-1} = \delta_G^{G'} \tau^{-1} N^G \mathrm{sech}^2 F^G$$

$$g = \det(g_{GG'}) \tag{13}$$

where $M^{G'}$ and $N^{G'}$ in F^G are afferent macrocolumnar firings scaled to efferent minicolumnar firings by $N/N* \approx 10^{-3}$, and $N*$ is the number of neurons in a macrocolumn, about 10^5. τ is usually considered to be on the order of 5-10 msec. The threshold factor F^G is derived as

$$F^G = \sum_{G'} \frac{\nu^G + \nu^{\ddagger E'}}{\left((\pi/2)[(v_{G'}^G)^2 + (\phi_{G'}^G)^2](\delta^G + \delta^{\ddagger E'})\right)^{1/2}}$$

$$\nu^G = V^G - a_{G'}^G v_{G'}^G N^{G'} - \frac{1}{2} A_{G'}^G v_{G'}^G M^{G'}$$

$$\nu^{\ddagger E'} = -a_{E'}^{\ddagger E} v_{E'}^E N^{\ddagger E'} - \frac{1}{2} A_{E'}^{\ddagger E} v_{E'}^E M^{\ddagger E'}$$

$$\delta^G = a_{G'}^G N^{G'} + \frac{1}{2} A_{G'}^G M^{G'}$$

$$\delta^{\ddagger E'} = a_{E'}^{\ddagger E} N^{\ddagger E'} + \frac{1}{2} A_{E'}^{\ddagger E} M^{\ddagger E'}$$

$$a_{G'}^G = \frac{1}{2} A_{G'}^G + B_{G'}^G \,,\; a_{E'}^{\ddagger E} = \frac{1}{2} A_{E'}^{\ddagger E} + B_{E'}^{\ddagger E} \tag{14}$$

where $\{A_{G'}^G, B_{G'}^G, A_{E'}^{\ddagger E}, B_{E'}^{\ddagger E}\}$, $A_{G'}^G$ is the columnar-averaged direct synaptic efficacy, $B_{G'}^G$ is the columnar-averaged background-noise contribution to synaptic efficacy. $A_{G'}^G$ and $B_{G'}^G$

have been scaled by $N*/N \approx 10^3$ to keep F^G invariant. Other values taken are consistent with experimental data, e.g., $V^G = 10$ mV, $v^G_{G'} = 0.1$ mV, $\phi^G_{G'} = 0.03^{1/2}$ mV. In this study Ca^{2+} wave activity affects the A and B synaptic parameters, while the $\mathbf{A}$ EEG fields affect the Ca^{2+} waves.

Ca^{2+} ions regulate synaptic interactions (Manita *et al.*, 2011). In SMNI, the Ca^{2+} affect the columnar-averaged synaptic parameters, and a "centering mechanism" (CM) is used to model changes in background synaptic activity which develop multiple columnar minima representing collective firing states, by adjusting $B^G_{G'}$ to center the numerator of the firing threshold function F^G about $M^G = 0$, bringing in a maximal number of minima, similar to changes in synaptic background observed during selective attention (Briggs *et al.*, 2013; Mountcastle *et al.*, 1981). It has been observed that changes in $[\mathrm{Ca}^{2+}]$ appear to influence release of glutamate and postsynaptic firing (Sharma & Vijayaraghavan, 2003). It is reasonable to consider that Ca^{2+} waves from tripartite interactions contribute to the B's.

The CM models changes in background synaptic activity which develop multiple columnar minima representing collective firing states. Since the SMNI columnar distribution has a functional form similar to firing distributions of individual neurons, SMNI properly includes effects of a vector potential.

These CM minima lie along a line in a trough in M space, $A^E_E M^E - A^E_I M^I \approx 0$, where it is noted that in F^I $I - I$ connectivity is observed to be small relative to other pairings, so that $(A^I_E M^E - A^I_I M^I)$ typically is small only for small M^E.

3.4. Experimental verification

The momenta of Ca^{2+} ions are influenced during EEG events like N100 and P300 potentials, with latencies on the order of 100 ms and 300 ms, resp., common in selective attention tasks (Srinivasan *et al.*, 2007). Previous SMNI fits to EEG data (Ingber, 1997a, 1998), were used as a template for this study. In recent work, the influence of Ca^{2+} waves is tested by parameterizing B synaptic parameters to be dependent on Ca^{2+} wave activity. Parameters are fit/trained to a portion of the EEG data, the in-sample set. These trained parameters are tested in out-of-sample EEG data.

The background parameters are modeled as a Taylor expansion in $|\mathbf{A}|$,

$$B^G_{G'} \to B^G_{G'} + |\mathbf{A}| B'^G_{G'} + \dots \,,\; B^{\ddagger E}_{E'} \to B^{\ddagger E}_{E'} + |\mathbf{A}| B'^{\ddagger E}_{E'} + \dots \tag{15}$$

The electric potential Φ is experimentally measured by EEG, not $\mathbf{A}$, but both are due to the same currents $\mathbf{I}$. Therefore, $\mathbf{A}$ is linearly proportional to Φ with a simple scaling factor included as a parameter in fits to data. Additional parameterization of $B^G_{G'}$ and $B^{\ddagger E}_{E'}$ modify previous work. To handle the otherwise recursive calculation of $|\mathbf{A}|$ multiplying $B'^G_{G'}$ and $B'^{\ddagger E}_{E'}$, $|\mathbf{A}|$ is calculated as a multiple of means/drifts of L over epochs defined by the experimental data. The data used for this study, is spaced about 3.6 ms ($< \tau$) between 150-400 ms after presentation of stimuli (Ingber, 1997a, 1998).

Since the data fit is within the duration of P300 EEG waves, the inclusion of the time-dependent B' terms, i.e., including $|\mathbf{A}|$, requires a "dynamic centering mechanism" (DCM), i.e., re-calculating CM during each epoch in the EEG data, to model continued access to maximum memory states. Future studies will simulate/test the contribution of other models of Ca^{2+} waves developed via tripartite synaptic interactions.

There can be a trade-off in having the background noise increase in the simple Taylor expansion model above: While lower noise generally leads to sharper narrower peaks of multiple STM states, higher noise especially from E connections within and among macrocolumns can increase the main difference in F^G numerators between the threshold voltage for columnar firing and the other efficacy terms.

Experiments at the classical molecular scale can consider that if the current lies along $\hat{\mathbf{z}}$, then $\mathbf{A}$ only has components along $\hat{\mathbf{z}}$, and

$$\mathbf{\Pi} = p_x \hat{\mathbf{x}} + p_y \hat{\mathbf{y}} + (p_z + qA_z)\hat{\mathbf{z}} \tag{16}$$

This classical physics prediction considers the large value of $|q\mathbf{A}|$, arising from many minicolumns during periods of large synchronous columnar firings, relative to $|\mathbf{p}|$ of each ion in the $\mathbf{A}$ field, e.g., such that direct interactions $q\mathbf{A} \cdot \mathbf{p}/m$, arising from canonical kinetic energy $(\mathbf{p} + q\mathbf{A})^2/(2m)$, is on the order of $\mathbf{p}^2/(2m)$. The context of the quantum physics calculations above is similar, even within short coherence times, since the bias of $\mathbf{A}$ is present at the early times of the formation of wave packets.

This methodology of using EEG data is useful as a future testbed to possibly discern among neocortical models of synaptic activity that include detailed molecular processes. It has been pointed out in the Results Section that this testbed should be used on new EEG data.

This methodology also may be useful with imaging data collected under different experimental paradigms and different imaging techniques (Ingber, 2009). For example, some studies strongly suggest circuitry among brain regions influential in cognitive-emotional interactions (Pessoa, 2013). If good quality imaging data during STM also included tests under different emotive states, then this premise could be similarly measured.

4. METHODOLOGY OF COMPUTATIONS

4.1. Cost functions fit to data

SMNI cost functions are defined by minus the log of the product of conditional probabilities over all epochs considered for a given run, i.e., minus the log of the “effective action” which is the sum over $L\Delta t$ plus the normalization prefactor which includes the log of the determinant of the metric which is the inverse covariance matrix. This maximizes the probability fit to the data for a given model. Typically, for this system, the normalization prefactor contributes over half of the total cost function, but since it has a log insensitivity to changes in variables and parameters, the Lagrangian L is most influential to the fit.

These SMNI cost functions are fit to data from 10 control and 10 alcoholic subjects, each set containing data from 6 electrode sites (selected from 64 in the original data set) with 10 trials of 69 epochs between 150 and 400 msec after presentation of 3 paradigms {stimulus 1, match, no-match} (Ingber, 1997a). Parameters include connectivity and time delays to model information flow among these electrodes (Ingber, 1997a, 1998). Each set of results is labeled as [{alcoholic | control}, {stimulus 1 | match | no-match}, subject, {potential | momenta}], where match or no-match was performed for stimulus 2 after 3.2 sec of a presentation of stimulus 1 (Zhang *et al.*, 1997a,b, 1995). Data used for most of this study includes 10 subjects, 10 trials per subject, per paradigm per Test/Train.

This is sparse data. Because of this, two independent research co-authors examined all raw data and CMI graphical results to see which patterns best represented the data (Ingber *et al.*, 2014). They did a very detailed analysis of all the input and output data, for all paradigms, which was included in the supplemental material with that paper, and which also can be retrieved from the http://ingber.com/smni14_eeg_ca_supp.pdf file. They concluded that the $\mathbf{A}$ model marginally best represented the data in most cases. However, just looking at CMI graphs generated from ASA fits to EEG data with the $\mathbf{A}$ SMNI model versus the no-$\mathbf{A}$ SMNI model were not very conclusive.

Given the relatively subjective nature of examining graphs (as is often the case with human patients/subjects in clinical settings), future progress should depend more on statistical measurements, albeit the use of statistical evidence using models fit to data also often verges on subjective choices and applications of models, even accepting verification within 5 standard deviations (Franklin, 2013, 2014; The-CMS-Collaboration, 2014). In many disciplines, a theory of physical phenomena is tested by fitting data to derived models at multiple scales or fitting different data to derived models (Ingber, 1968).

In this context, results can be summarized by the first four moments of the data distribution of n points, in terms of the

$$\{\text{STAT}\} = \{\text{mean, standard-deviation, skewness, kurtosis}\}$$

The conventions used give skewness as the third moment about the mean, and kurtosis as the fourth moment about the mean, with deviations from 0 of the skewness measuring asymmetry and deviations of 3 from the kurtosis measuring deviations from Gaussian distributions (Perlman & Horan, 1986). All STATs below have been simply truncated to 3 significant figures for presentation purposes. Fitted cost functions for this system typically typically fall between 10 and 20, while unfitted cost functions have values of at least several hundred, reflecting that SMNI models STM processes as taking place in a trough of multiple minima embedded in a “sea of noise”.

In addition to considering the overall STATs of Train and Test sets, another important set of STATs is how well the models do on Test sets of data per classification/paradigm, i.e., in terms of how much the same cost function calculated with the Test sets varies from the fitted cost function of the Train sets. This could be important for clinical applications.

The CM for the no-$\mathbf{A}$ model and the DCM at each epoch for the $\mathbf{A}$ model modify the background noise parameter independently. Also, a parameter b' ranging between $\{0, 1\}$ multiplies B' terms in the $\mathbf{A}$ model, and this typically fell between 1/3 and 1/2 in ASA fits, yielding a possible total background noise consistent with the no-$\mathbf{A}$.

4.2. ASA optimization

The use of ASA for optimizing fitting EEG to 28 parameters of the regional SMNI model were similar to those used previously (Ingber *et al.*, 2014). However, for these recent calculations, the ASA_FUZZY Option was used (Ingber, 2012c), which kept the cost temperature at more reasonable scales throughout the runs. This did not make any difference in the final fits, as tested using the previous as well as the current calculations, but it did give more confidence in the ASA process for this system.

4.3. Computer resources

Computations used Message Passing Interface (MPI) to parallelize code that fits EEG data to a model that includes the dynamic influence of a $\mathbf{p} + q\mathbf{A}$ interaction on background synaptic activity, embedded in a Statistical Mechanics of Neocortical Interactions (SMNI) coded model, to assess the viability of EEG activity influencing this interaction (Gibson, 2014; Ingber *et al.*, 2014; Zverina, 2014). This now provides a testbed for future models of such interactions. Each parallel job constitutes a set of 120 runs taking about 6-9 hrs real-time CPU, equivalent to over a CPU-month, which includes 60 no-$\mathbf{A}$ model and 60 $\mathbf{A}$ model runs, each with Train runs with 4 million generated states and subsequent Test runs. Train runs were done with 10 million generated states to be sure of getting the best final results.

Results presented in Appendix A represent a sampling of about two CPU-years of calculations on two XSEDE.org (Towns *et al.*, 2014) platforms: Trestles is a cluster of 324 compute nodes; each compute node contains four sockets, each with a 8-core 2.4 GHz AMD Magny-Cours processor, for a total of 32 cores per node and 10,368 total cores for the system, yielding a theoretical memory bandwidth of 171 GB/s and a theoretical peak performance of 100 TFlop/s (1 TF = 10^{12} FLoating-point Operations Per Second). Stampede is a 10 PFLOPS (1 PF = 10^{15} FLoating-point Operations Per Second) Dell Linux Cluster based on 6400+ Dell PowerEdge server nodes, each outfitted with 2 Intel Xeon E5 (Sandy Bridge) processors and an Intel Xeon Phi Coprocessor (MIC Architecture); the aggregate peak performance of the Xeon E5 processors is 2+PF, while the Xeon Phi processors deliver an additional aggregate peak performance of 7+PF. Each platform has additional features built into the platform.

4.4. Discussion of results

Appendix A makes it clear that using the simple Taylor expansion for B' or A' efficacies will give about the same results, i.e., many STATs for these variations of the $\mathbf{A}$ model are statistically similar, even though some {a, c} and {1, m, n} runs do better than others with variations in the $\mathbf{A}$ model.

New models, based on other neuroscience modeling research, need to be tested. This SMNI model will be a testbed for future models of tripartite synaptic interactions of astrocytes and neuronal synapses, that directly lead to other functional models of the influence of EEG-developed $\mathbf{A}$ on background synaptic activity.

Consideration also must be given to the SMNI model's dependence on the A and B efficacies. Each set of efficacies, albeit the B's are modified by the CM or DCM, are sufficiently nonlinear that they can represent a different model of the data. The DCM, modifying the B's at each epoch, can represent a string of such models, e.g., for varying degrees of fits at different stages of P300 present in EEG. Since the no-$\mathbf{A}$ and $\mathbf{A}$ models are within the same statistical ranges, some additional functional dependence of the $\mathbf{A}$ model on Ca^{2+}-wave influences may be required to better describe these multiple scales of interaction.

Differences between the $\mathbf{A}$ model and no-$\mathbf{A}$ model are very much smaller that the differences noted when CM and DCM are turned off completely, giving strong confirmation of SMNI describing STM with CM and DCM mechanisms.

5. CONCLUSION

An SMNI model has been developed to calculate coupling of molecular scales of Ca^{2+} wave dynamics with $\mathbf{A}$ fields developed at macroscopic regional scales measured by coherent neuronal firing activity measured by scalp EEG, during tests of STM. This requires crossing molecular, microscopic (synaptic and neuronal), mesoscopic (minicolumns and macrocolumns), and macroscopic regional scales.

Over the past three decades, the SMNI approach has yielded specific details of STM and LTM phenomena, likely components of other phenomena like attention and $\mathbf{C}$, not present in molecular approaches (Ingber, 2012a).

More recently, SMNI calculations detail information processing of patterns of columnar firings, e.g., as observed in scalp EEG (Salazar *et al.*, 2012), in terms of an SMNI vector potential $\mathbf{A}$ that influences molecular Ca^{2+} momentum $\mathbf{p}$, in turn influencing synaptic interactions. Explicit Lagrangians serve as cost/objective functions that are fit to EEG data (Ingber *et al.*, 2014).

Considerations of both classical and quantum physics give predictions of the influence of $\mathbf{A}$ on the momenta of Ca^{2+} waves during STM processing as measured by scalp EEG. Since the spatial scales of Ca^{2+} wave and macro-EEG are quite disparate, an experiment would have to be able to correlate both scales in time scales on the order of tens of milliseconds.

This study is robust against much theoretical modeling, as experimental data is used wherever possible. The theoretical construct of the canonical momentum $\mathbf{\Pi} = \mathbf{p} + q\mathbf{A}$ is firmly entrenched in classical and quantum mechanics.

The SMNI model supports a process of $\mathbf{p} + q\mathbf{A}$ interaction at tripartite synapses, via the DCM to control background synaptic activity, which acts to maintain STM during states of selective attention. Results of fits to EEG data presented here only demonstrate that fits to an $\mathbf{A}$ model are within reasonable statistical ranges of fits to a no-$\mathbf{A}$ model. While these fits are not conclusive for the importance of the $\mathbf{A}$ model, this study presents a testing methodology and code to further test the $\mathbf{p} + q\mathbf{A}$ interaction with future better EEG data.

However, other fits reported in Appendix A do demonstrate the importance of the CM for the no-$\mathbf{A}$ model and the importance of the DCM for the $\mathbf{A}$ model, giving further support to SMNI detailing STM.

This study likely sheds some light on the multiple scales of neocortical interactions underlying $\mathbf{C}$, and how models can be developed faithful to experimental data. The scientific focus on computational models that include experimental data opens these ideas to testable hypotheses. This approach also suggests some nanosystem-pharmaceutical applications. Results give strong confirmation of the SMNI model of STM, but only weak statistical consistency of $\mathbf{\Pi} = \mathbf{p} + q\mathbf{A}$ influences on scalp EEG.

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APPENDICES

A. RESULTS

A..1. Previous constraints

An early constraint in the previous paper (Ingber *et al.*, 2014) was that the B' terms not exceed the value of any of the initialized B terms, and that only excitatory presynaptic connections could contribute to B' terms, i.e., added to terms $B^{\ddagger E}_{E'}$ as well as to $B^G_{E'}$, $G = \{E, I\}$. (In $B^G_{G'}$ terms, presynaptic contributions from neurons indexed with G' subscript, affect postsynaptic neuron indexed with G superscript.)

Using these previous constraints, the STAT of the Train set no-**A** model was

{no-A, Train} = {12.6, 1.25, -0.118, 2.61}

while the STAT of the Train set **A** model was

{A, Train} = {13.7, 1.39, -0.444, 2.60}

The STAT of Test-Train (STAT of differenced cost functions) for the no-**A** model was

{no-A, Test-Train} = {0.770, 1.07, 1.38, 4.60}

while the STAT of Test-Train for the **A** model was

{A, Test-Train} = {1.00, 1.90, 3.24, 16.8}

The data can be drilled down further. For example, each model can be assessed among the three paradigms presented to each subject, according to whether the subject was classified as {a = alcoholic, c = control (non-alcoholic)}, and according to paradigm {1 = single stimulus, m = attempt to match second stimulus to first, n = no second stimulus matched first}.

STATs for model no-**A** for Test-Train data are:

{no-A, Test-Train, a, 1} = {0.967, 1.34, 0.937, 2.43}
{no-A, Test-Train, a, m} = {1.20, 1.50, 1.01, 2.49}
{no-A, Test-Train, a, n} = {0.712, 1.01, 0.515, 1.65}
{no-A, Test-Train, c, 1} = {0.763, 1.08, 1.28, 4.06}
{no-A, Test-Train, c, m} = {0.936, 1.25, 1.30, 3.89}
{no-A, Test-Train, c, n} = {0.613, 0.883, 0.869, 2.54}

STATs for model **A** for Test-Train data are:

{A, Test-Train, a, 1} = {1.04, 1.55, 0.947, 2.26}
{A, Test-Train, a, m} = {1.36, 1.53, 0.508, 1.37}
{A, Test-Train, a, n} = {2.17, 3.79, 1.47, 3.89}
{A, Test-Train, c, 1} = {0.644, 1.18, 1.73, 5.29}
{A, Test-Train, c, m} = {0.889, 1.28, 1.03, 2.84}
{A, Test-Train, c, n} = {1.47, 2.79, 2.45, 8.85}

A..2. Selection of connections

As mentioned previously, Ca^{2+} is generally considered to influence synaptic interactions by modulating excitatory glutamic acid (Zorumski *et al.*, 1996).

Instead of focusing on net presynaptic excitatory models (Ingber *et al.*, 2014), for all remaining runs reported here, models set contributions from B' only from excitatory postsynaptic connections (which could be influenced directly by tripartite glutamic acid enhancements), i.e., added to terms $B^{\ddagger E}_{E'}$ as well as to $B^{E}_{G'}$, $G' = \{E', I'\}$, and that each B' term not exceed the value of its associated initialized B term. This approach includes contributions to postsynaptic sites from both excitatory and inhibitory presynaptic interactions, considering the discussion in the Introduction that both GABA and glutamate may be influenced by presynaptic processes involving glutamine in astrocytes, i.e., with opposite contributions from $\mathbf{A}$ influences on excitatory versus inhibitory postsynaptic sites.

{A, Train} = {13.7, 1.56, -0.495, 2.95}
{A, Test-Train} = {1.16, 1.95, 2.13, 7.01}
{A, Test-Train, a, 1} = {1.26, 1.97, 1.15, 2.82}
{A, Test-Train, a, m} = {2.04, 2.65, 1.29, 3.54}
{A, Test-Train, a, n} = {1.01, 2.06, 1.96, 5.56}
{A, Test-Train, c, 1} = {0.845, 1.48, 1.96, 6.37}
{A, Test-Train, c, m} = {1.58, 2.44, 1.70, 4.82}
{A, Test-Train, c, n} = {1.07, 1.82, 1.95, 5.84}

giving similar Train and Test cost functions for the $\mathbf{A}$ model as from the previous study. The results for the no-$\mathbf{A}$ model are the same as immediately above.

Results also were obtained modifying the ceiling constraint on B', e.g., reducing the initialized B parameters by a ceiling C, and constraining the additional B' parameters to not exceed $(1 - 1/C)B$, thereby keeping the maximum noise available to the $\mathbf{A}$ model the same as for the no-$\mathbf{A}$ model. Similar results were obtained using $C = 2$:

{A, Train} = {13.8, 1.00, -0.420, 2.70}
{A, Test-Train} = {1.38, 2.19, 2.74, 11.2}
{A, Test-Train, a, 1} = {1.68, 2.10, 1.26, 3.50}
{A, Test-Train, a, m} = {1.81, 3.40, 2.03, 5.85}
{A, Test-Train, a, n} = {1.26, 1.80, 1.29, 3.67}
{A, Test-Train, c, 1} = {1.39, 1.73, 1.54, 5.12}
{A, Test-Train, c, m} = {1.34, 2.44, 3.24, 13.3}
{A, Test-Train, c, n} = {1.42, 2.44, 2.16, 7.28}

The results for the no-$\mathbf{A}$ model are the same as immediately above.

A..3. Modification of firing efficacies

The influence of Ca^{2+} on modulating excitatory glutamic acid, was tested differently, to see if there was any large-scale influence on the $A^{G}_{G'}$ contribution to efficacies. The $B^{G}_{G'}$ contribution to efficacies was still modified with the DCM, but the Taylor-expansion $\mathbf{A}$ model was applied to the A's, leading to A' terms with parameterized coefficients a' ranging between {0, 1}. Similar to tests with B', the constraint was that each A' term not exceed the value of its associated initialized A term.

The results with the Taylor-expanded $\mathbf{A}$ model applied to A' was about the same as the application to B':

{A, Train} = {13.6, 1.42, 0.0599, 2.45}
{A, Test-Train} = {1.20, 2.74, 5.39, 36.8}
{A, Test-Train, a, 1} = {0.860, 1.50, 1.28, 3.32}
{A, Test-Train, a, m} = {2.54, 6.15, 2.24, 6.48}
{A, Test-Train, a, n} = {0.781, 1.38, 0.803, 1.91}
{A, Test-Train, c, 1} = {0.846, 1.28, 1.20, 3.61}
{A, Test-Train, c, m} = {1.94, 4.41, 3.39, 14.0}
{A, Test-Train, c, n} = {0.816, 1.17, 0.949, 2.45}

The results for the no-$\mathbf{A}$ model are the same as immediately above.

The results with the Taylor-expanded $\mathbf{A}$ model applied to both A' and B', using just one parameter/coefficient for both sets, was also about the same:

{A, Train} = {13.6, 1.35, -0.244, 3.23}
{A, Test-Train} = {1.23, 3.32, 5.85, 40.9}
{A, Test-Train, a, 1} = {1.22, 1.69, 0.668, 2.10}
{A, Test-Train, a, m} = {3.29, 7.58, 2.19, 6.31}
{A, Test-Train, a, n} = {0.954, 1.18, 1.54, 4.41}
{A, Test-Train, c, 1} = {0.775, 1.31, 1.39, 4.52}
{A, Test-Train, c, m} = {1.79, 5.45, 3.65, 15.4}
{A, Test-Train, c, n} = {1.13, 1.52, 1.55, 4.56}

The results for the no-$\mathbf{A}$ model are the same as immediately above.

A..4. Smoothing drifts

The drifts have been calculated at each epoch based on g^G terms in the Lagrangian. This can cause some volatility affecting fits, and a remedy borrowed from regularizing covariance matrices is to simply perform short-term averaging (Litterman & Winkelmann, 1998). Therefore, the drifts were averaged over the last few epochs, e.g., over the last 4 epochs reported here.

Applying the Taylor-expanded $\mathbf{A}$ model to just A' terms gave:

{A, Train} = {13.5, 1.16, -0.0447, 2.18}
{A, Test-Train} = {1.17, 2.03, 3.27, 16.7}
{A, Test-Train, a, 1} = {2.45, 4.00, 1.44, 3.91}
{A, Test-Train, a, m} = {1.43, 1.98, 1.61, 4.63}
{A, Test-Train, a, n} = {1.18, 1.47, 0.592, 1.80}
{A, Test-Train, c, 1} = {1.37, 2.99, 2.57, 9.38}
{A, Test-Train, c, m} = {1.07, 1.49, 2.36, 9.36}
{A, Test-Train, c, n} = {1.08, 1.25, 0.751, 2.48}

The new results for the no-$\mathbf{A}$ model are:

{no-A, Train} = {12.6, 1.18, -0.0169, 2.47}
{no-A, Test-Train} = {1.03, 2.02, 3.19, 13.8}
{no-A, Test-Train, a, 1} = {1.35, 2.53, 1.85, 5.26}
{no-A, Test-Train, a, m} = {1.85, 3.38, 1.91, 5.38}
{no-A, Test-Train, a, n} = {0.833, 1.28, 1.48, 4.09}
{no-A, Test-Train, c, 1} = {0.896, 1.84, 3.01, 12.1}

{no-A, Test-Train, c, m} = {1.49, 2.79, 2.31, 7.55}
{no-A, Test-Train, c, n} = {0.724, 1.08, 1.65, 5.16}

Applying the Taylor-expanded $\mathbf{A}$ model to just B' terms gave:

{A, Train} = {13.6, 1.26, -0.0319, 2.29}
{A, Test-Train} = {0.802, 1.23, 1.49, 5.04}
{A, Test-Train, a, 1} = {0.503, 0.965, 0.405, 1.46}
{A, Test-Train, a, m} = {1.44, 1.57, 0.742, 1.93}
{A, Test-Train, a, n} = {0.653, 0.939, 0.0899, 1.62}
{A, Test-Train, c, 1} = {0.380, 0.761, 0.643, 2.47}
{A, Test-Train, c, m} = {1.44, 1.70, 0.716, 2.03}
{A, Test-Train, c, n} = {0.579, 0.751, 0.377, 2.33}

The results for the no-$\mathbf{A}$ model are the same as immediately above.

A..5. Permitting subtraction as well as addition to efficacies

An argument could be made that the influence of Ca^{2+} waves is to decrease rather than to increase the efficacies. An example with averaging over drifts for the past 10 epochs and permitting the b' coefficient of B' terms to be negative as well as positive barely confirms this. The fitted coefficient indeed is negative in most cases:

{A, Train} = {13.3, 1.16, -0.258, 2.65}
{A, Test-Train} = {1.05, 1.82, 2.63, 11.1}
{A, Test-Train, a, 1} = {0.554, 0.956, 1.07, 3.00}
{A, Test-Train, a, m} = {1.27, 2.18, 1.81, 5.23}
{A, Test-Train, a, n} = {1.07, 1.51, 0.802, 1.91}
{A, Test-Train, c, 1} = {0.489, 0.821, 0.922, 3.51}
{A, Test-Train, c, m} = {0.978, 1.65, 2.44, 9.58}
{A, Test-Train, c, n} = {1.68, 2.48, 1.75, 5.76}

The results for the no-$\mathbf{A}$ model are the same as immediately above.

Averaging over drifts for the past 10 epochs and permitting the a' coefficient of A' terms to be negative as well as positive does not fit as well:

{A, Train} = {14.0, 1.60, -0.0973, 3.63}
{A, Test-Train} = {1.05, 1.42, 1.73, 6.24}
{A, Test-Train, a, 1} = {1.19, 1.35, 0.776, 2.59}
{A, Test-Train, a, m} = {1.77, 2.22, 1.02, 2.74}
{A, Test-Train, a, n} = {0.861, 1.54, 1.51, 4.16}
{A, Test-Train, c, 1} = {0.838, 1.08, 1.38, 4.84}
{A, Test-Train, c, m} = {1.45, 1.73, 1.40, 4.79}
{A, Test-Train, c, n} = {0.871, 1.37, 1.62, 4.77}

The results for the no-$\mathbf{A}$ model are the same as immediately above.

Permitting both the a' coefficient of A' terms and the b' coefficient of B' terms to be negative as well as positive (using $a' = b'$) gives fits between the two:

{A, Train} = {13.6, 1.32, -0.954, 4.51}
{A, Test-Train} = {1.37, 2.61, 3.61, 19.4}
{A, Test-Train, a, 1} = {2.18, 3.10, 0.720, 1.75}
{A, Test-Train, a, m} = {2.58, 5.04, 1.99, 5.68}

{A, Test-Train, a, n} = {0.537, 1.24, 1.68, 4.93}
{A, Test-Train, c, 1} = {1.32, 2.33, 1.70, 4.67}
{A, Test-Train, c, m} = {1.97, 3.60, 3.17, 12.9}
{A, Test-Train, c, n} = {0.831, 1.42, 1.55, 4.62}

The results for the no-**A** model are the same as immediately above.

A..6. More epochs in data

While most runs used 42 epochs with offset at epoch 38, each 3.9 ms, to capture a major part of P300, some runs were done using the the middle segment of all 255 epochs comprising the 1 sec of data/run, i.e., using the middle 87 epochs (the first two epochs do not include some regions due to time delays). These runs took twice as long. Permitting both the a' coefficient of A' terms and the b' coefficient of B' terms to be negative as well as positive give results:

{A, Train} = {14.1, 1.07, -0.276, 2.53}
{A, Test-Train} = {4.04, 15.9, 6.91, 51.5}
{A, Test-Train, a, 1} = {1.36, 2.31, 1.03, 2.61}
{A, Test-Train, a, m} = {15.0, 38.2, 2.20, 6.35}
{A, Test-Train, a, n} = {3.87, 4.81, 0.718, 1.78}
{A, Test-Train, c, 1} = {0.971, 1.79, 1.56, 4.92}
{A, Test-Train, c, m} = {8.30, 27.2, 3.70, 15.6}
{A, Test-Train, c, n} = {2.85, 3.66, 1.46, 3.99}

The new results for the no-**A** model are:

{no-A, Train} = {13.0, 1.14, -0.381, 2.90}
{no-A, Test-Train} = {4.00, 14.1, 4.95, 28.7}
{no-A, Test-Train, a, 1} = {0.977, 1.25, 0.231, 1.48}
{no-A, Test-Train, a, m} = {13.8, 30.3, 1.79, 4.80}
{no-A, Test-Train, a, n} = {1.81, 2.21, 0.860, 2.34}
{no-A, Test-Train, c, 1} = {0.835, 1.19, 0.676, 2.08}
{no-A, Test-Train, c, m} = {7.42, 21.8, 3.13, 12.0}
{no-A, Test-Train, c, n} = {3.74, 10.9, 3.68, 15.5}

The few extremely large Test-Train entries are due to non-typical trials among the set of 10 trials in the data of some of the Test sets, giving non-typically large cost functions using the parameters of the associated Train set; the Train trials were typical relative to other results presented here. For example, while a cost function of 20, averaged over 10 trials, was quite high in this set of runs, Test trials for subject 378, A1_a_m_co2a0000378.ruy, gave several enormous cost functions as high as 135.717, and subject 365, A0_a_m_co2a0000365.ruy, had a Test cost function of 50.920 (rux are Train runs, and ruy are Test runs). This might be due to some subjects during some runs not "paying attention" to the prescribed tasks. This points out the need to use this current testbed on new EEG data.

Except for two cost functions noted below, all other cost functions reported here did not exceed the low 30's. The data is included in graphs in the http://ingber.com/smni14_eeg_ca_supp.pdf file mentioned above (Ingber *et al.*, 2014).

Some runs were performed using the full 255 epochs, requiring a factor of almost 7 per run of running time, gave similar results. Permitting both the a' coefficient of A' terms and the b' coefficient of B' terms to be negative as well as positive give: results:

{A, Train} = {14.9, 1.10, -0.400, 2.91}
{A, Test-Train} = {1.08, 3.28, 5.68, 39.2}
{A, Test-Train, a, 1} = {0.334, 1.05, 0.818, 2.23}
{A, Test-Train, a, m} = {0.717, 1.41, 1.50, 4.14}
{A, Test-Train, a, n} = {3.26, 7.56, 2.00, 5.63}
{A, Test-Train, c, 1} = {0.686, 1.24, 0.323, 1.92}
{A, Test-Train, c, m} = {0.690, 1.22, 1.43, 4.49}
{A, Test-Train, c, n} = {1.88, 5.42, 3.35, 13.6}

The new results for the no-**A** model are:

{no-A, Train} = {13.3, 1.17, -0.341, 2.73}
{no-A, Test-Train} = {1.85, 9.51, 7.22, 54.7}
{no-A, Test-Train, a, 1} = {0.614, 1.23, 0.685, 1.97}
{no-A, Test-Train, a, m} = {7.73, 23.2, 2.26, 6.54}
{no-A, Test-Train, a, n} = {0.851, 1.49, 1.79, 5.14}
{no-A, Test-Train, c, 1} = {0.529, 0.978, 0.808, 2.99}
{no-A, Test-Train, c, m} = {4.27, 16.4, 3.80, 16.1}
{no-A, Test-Train, c, n} = {0.765, 1.31, 1.83, 5.73}

Using more epochs including data in the tails of P300 which may account for the **A** model not faring as well as with data approximately constrained to the rise of the P300 peak. Using the full 1 sec of data in the 255-epoch runs smooths averages out some of the non-typical entries noted in the 87-epoch runs that contain the non-typical spikes in the Test data. For example, Test run A0_a_m_co2a0000378.ruy gave a cost function of 87.814 and A1_a_n_co2a0000369.ruy gave a cost function of 38.307; examination of trials within these runs show some anomalies. However, runs or trials within runs were not cherry-picked for inclusion or exclusion.

A..7. No CM or DCM

When CM is turned off for the no-**A** model and DCM is turned off for the **A** model, the results for the case corresponding to permitting both the a' coefficient of A' terms and the b' coefficient of B' terms to be negative as well as positive (using $a' = b'$), are much worse than the previous results. The new results for the no-**A** model are:

{no-A, Train} = {20.3, 1.06, -0.0305, 2.35}
{no-A, Test-Train} = {1.09, 1.76, 3.80, 22.9}
{no-A, Test-Train, a, 1} = {1.24, 1.57, 0.941, 2.40}
{no-A, Test-Train, a, m} = {2.03, 3.51, 2.07, 5.97}
{no-A, Test-Train, a, n} = {1.05, 1.20, 0.591, 2.61}
{no-A, Test-Train, c, 1} = {0.856, 1.32, 1.13, 3.96}
{no-A, Test-Train, c, m} = {1.53, 2.59, 3.01, 12.2}
{no-A, Test-Train, c, n} = {0.898, 0.943, 0.889, 4.15}

For the **A** model, with drift contributions from B' only from excitatory postsynaptic connections added to terms $B^{\ddagger E}_{E'}$ as well as to $B^{E}_{G'}$, the results are:

{A, Train} = {20.8, 0.815, 0.0597, 2.75}
{A, Test-Train} = {0.758, 1.40, 4.02, 24.2}

{A, Test-Train, a, 1} = {0.888, 1.12, 0.820, 2.14}
{A, Test-Train, a, m} = {1.45, 2.84, 2.09, 6.01}
{A, Test-Train, a, n} = {0.613, 0.804, 0.126, 1.63}
{A, Test-Train, c, 1} = {0.529, 0.938, 1.39, 4.05}
{A, Test-Train, c, m} = {1.16, 2.07, 3.05, 12.1}
{A, Test-Train, c, n} = {0.579, 0.784, 0.589, 2.49}

The much smaller cost functions of CM and DCM models, which includes the negative argument of exponential functions of conditional probability distributions, is partially due to smaller Lagrangians with multiple local minima (corresponding to states of STM) centered about $M^G = M^{\ddagger E} = 0$ firing states. The linear trough relation, $A^E_E M^E - A^E_I M^I \approx 0$, is kept to retain the proportionality of both M^E and M^I to the Φ EEG, but when the CM or DCM is not active the Lagrangian is large and uniform in M^G space anyway (Ingber, 1984). That this Lagrangian is consistent with these fits gives a fairly conclusive result that the CM and DCM are important to model this EEG data.

B. STM FEEDBACK VIA NANOSYSTEM PHARMACEUTICAL INTERVENTION

Biological systems often present complex multivariable processes, such as those underlying production of Ca^{2+} waves (Ross, 2012). There are opportunities for interactive human inclusion of additional processes as well.

The context of using large-scale noninvasive records to study molecular processes that interact with the large-scale activity, suggests possible engineering tools that might be used for real-time clinical testing and feedback, e.g., during pharmaceutical intervention.

For example, to highlight the importance of such research, there is the potential of carrying pharmaceutical products in nanosystems that could affect unbuffered Ca^{2+} waves in neocortex, e.g., by sensing momentum in that media. A Ca^{2+}-wave momentum-sensor could act like a piezoelectric crystal (Alivisatos *et al.*, 2013; Wang, 2012). At the onset of a Ca^{2+} wave (which afterwards may persist for 100's of ms), there is sudden change of momentum in the environment, giving rise to a force on any object in its path, equal to this change in momentum divided by this onset time. Consider a momentum on the order of 10^{-30} kg-m/s for a typical Ca^{2+} ion. For a Ca^{2+} wave packet of 1000 ions with an onset time of 1 ms, this is estimated to be on the order of 10^{-24} N (1 N $\equiv$ 1 Newton = 1 kg-m/s^2). The nanosystem could be attracted to this site, depositing chemicals/drugs that interact with the regenerative Ca^{2+}-wave process. Even if the receptor area of the nanosystem could be as small as 1 nm^2 (close to the resolution of scanning confocal electron microscopy (SCEM)), this would require it to have an extreme pressure sensitivity of 10^{-6} Pa (1 Pa = 1 pascal = 1 N/m^2).

The nanosystem could be switched on/off at a regional/columnar level by having sensitivity to local electric/magnetic fields. Such piezoelectric nanosystems can affect the background/noise efficacies (Chance, 2007) at synaptic gaps via control of Ca^{2+} waves, which affects the nonlinear states of highly synchronous firings which carry many STM processes, which in turn affect the influence of of Ca^{2+} waves via the vector potential $\mathbf{A}$, etc.

This project thereby offers a noninvasive real-time approach to control feedback at multiple scales among piezoelectric nanosystems, Ca^{2+} waves, and higher information-processing levels of STM.

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