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A Computational Model of Mild Traumatic Brain Injury*

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Abstract— **Electrical analysis of brain activity reveals the presence of synchronous oscillations over a range of frequencies. These rhythms are readily observed using electroencephalography (EEG). Clinical EEG data shows that Traumatic Brain Injury (TBI) alters these rhythms. Researchers have developed lumped parameter neural mass models (NMM) that can reproduce these various brain rhythms. This paper proposes an NMM based computational model of mild TBI that recreates the clinical EEG changes observed after injury. Specifically, the focus is on recreating changes observed after TBI in the 8-12 Hz alpha and the 4-8Hz theta frequency ranges. Mild TBI is simulated by increasing membrane reactivity and by decreasing synaptic connectivity in the NMM. These results indicate that clinically observed EEG changes with mild TBI are likely due to traumatic synaptic disruption and that with appropriate data, EEG may be used to quantify the extent of TBI in the future.**

I. INTRODUCTION

Traumatic brain injury (TBI) is defined as an alteration in brain function or other evidence of brain pathology caused by an external force [1]. TBI is the leading cause of death in individuals under the age of 35 years. Nearly 500,000 people a year in the United States are hospitalized with head trauma. Of these, approximately 70,000 suffer from a long-term disability and 2,000 remain in a persistent vegetative state, alive but unconscious [2].

The severity of traumatic brain injury is currently graded based upon a 15 point qualitative clinical assessment called the Glascow Coma Scale. Even a mild injury, with a GCS 13-15, from low energy impacts such as a football tackle or IED blast wave, can result in profound confusion and disorientation [3]. While the GCS provides an objective clinical measure of the conscious state after injury, it is not a quantitative evaluation of the extent of neural injury.

This paper formulates a computational model of TBI. The ultimate goal is to create a model that provides a quantitative biomarker of disease progression, treatment response, and prognosis. This paper advances computational models based on recent research on neural mass models (NMM). Specifically, NMM is used to develop a model of the frequency domain changes observed with EEG that occur after mild TBI.

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The paper is organized as follows. Section II outlines the underlying pathophysiology of TBI and current electrodynamic markers of TBI. Section III introduces the Jansen and Rit NMM, and in section IV provides results of numerical simulations of mild TBI based upon current pathophysiological understanding of TBI. The paper concludes by outlining future investigations into computational models of TBI.

II. PATHOPHYSIOLOGY OF TBI

A. Cellular response to brain trauma

The cellular response to TBI has been investigated in animal models that involve studying brain tissue after a mass has impacted a surgically exposed area of brain [4]. It is hypothesized that high mechanical strain results in mechanical perturbation of the cell membrane and physical disruption of synaptic intercellular connections. A significant release of intracellular contents from damaged cells, including the excitatory neurotransmitter glutamate and intracellular cations potassium and calcium, is the most readily observed change after traumatic injury [1] [4].

Cells that are entirely disrupted undergo necrosis in the minutes after injury and trigger an inflammatory response. In surrounding neurons with mildly damaged membranes, the presence of excessive Ca^{2+} and excitatory transmitters set off intracellular cascades that lead to apoptosis and aberrant increased firing rates. Synaptic disruptions are thought to underly more long term neurological consequnces of injury. However no distinct experimental evidence has identifed the consequences of traumatic synaptic disruptions between neurons without neuronal death [1].

B. Electrodynamic biomarkers of TBI

Since the brain is an electrodynamical system, it creates electric fields indicating internal activity that may be recorded at the scalp by way of EEG [5]. EEG has been used after mild injury to detect electrodynamic changes after TBI [6]. Due the fact that it is a passive sensor, EEG is safe, non-invasive, relatively inexpensive, and can be used continuously. Simulation of the effect of TBI on the alpha band (8-12 Hz) was chosen for this initial investigation due to its high power in the frequency range of the resting human brain. Early investigations of TBI began by obtaining EEG recordings of boxers who had been injured in a fight often minutes after trauma [6-8] The most notable difference was diffuse slowing of cerebral activity with increase in delta (0-4Hz) and theta (4-8Hz) activity. Subsequently, several studies on the frequency domain of patients with mild TBI show an increase in theta activity [9-10] reduction in mean alpha frequency [11-14], and an increased ratio between theta and alpha power [11, 14,15] .

III. NEURAL MASS MODEL OF TBI

A Neural Mass Model (NMM) is used in the present study for describing populations of neurons in the cortex. Since the introduction of the NMMs by Wilson and Cowan [16], these models have been used in a range of disease modeling efforts. In these models, a population of neurons is assumed to have a shared input and output connectivity. Further, spiking activity is modeled for a coalesced population soma rather than for individual neurons. The underlying assumption is that as long as the population of neurons is connected to each other (either directly or via interneurons) the spatial interactions can be neglected in favor of temporal dynamics of the aggregate population. This approach is justified, as there is a high degree of local redundancy in cortical tissues. In other words, many neighboring populations may exhibit similar response to identical stimuli. Thus, a NMM offers a macroscopic view of the temporal dynamics of populations of neurons. While an individual neuron's activity may appear unresolvable, a macroscopic view of the neural population may yield more precise characterization of interactions over larger scales. The NMM representation is mathematically tractable and efficient as only a few variables are needed in the model to capture the dynamics of a population of neurons. They have recently been used to model the electrodynamic changes observed in Alzheimer's disease [17] The present work uses one such model to describe changes in the alpha and theta frequency ranges after TBI.

A. Brief Review of Jansen and Rit Neural Mass Model

A Simulink® (The Mathworks, Inc. 2011) implementation of the Jansen-Rit model [18] for a cortical column is shown in Fig. 1. The model uses three neural sub-populations; an excitatory pyramidal cell population feeds-forward into both an inhibitory and excitatory interneuron population which both feed into the same pyramidal population. Each population includes a post-synaptic potential (PSP) block that converts pulse density into average potential, and a sigmoid block that converts potential into pulse density. The constants C1, C2, C3, and C4 define the synaptic connectivity of the interneurons between different subpopulations. The PSP blocks h_i (inhibitory interneuron) and h_e (excitatory interneurons and pyramidal neurons) represent linear dynamic maps that are defined by the following impulse responses:

$$h_e(t)= A*a*t*e^{-a*t},\ t>0,\ 0 \text{ otherwise} \quad (1)$$

$$h_i(t)= B*b*t*e^{-b*t},\ t>0,\ 0 \text{ otherwise} \quad (2)$$

Here, A and B are the gain, and a and b are the lumped representation of the sum of reciprocals of the time constants of the associated delays. The same values used by Jansen [18] for the occipital cortex are used, in the following simulations. This is an area of the brain vulnerable to TBI caused by linear acceleration/deceleration impacts. The sigmoidal functions in the model are defined as:

$$\text{Sig}(v)= 2*e_0/[1+ e^{r*(v_0-v)}] \quad (3)$$

In equation (3), $2e_0$ is the maximum firing rate, v_0 is the firing threshold and the variable r determines the steepness of the sigmoid. The model also accounts for inputs from other cortical areas. These are modeled as white noise with a uniformly distributed amplification factor.

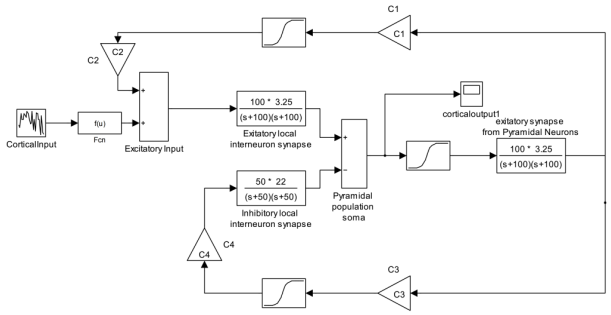

Figure 1. Simulink model for generating alpha rhythm

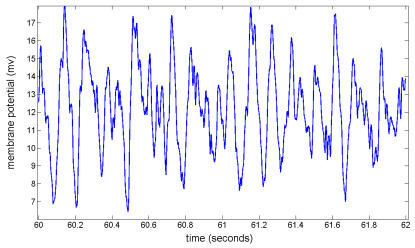

Figure 2. Oscillations in pyramidal population soma

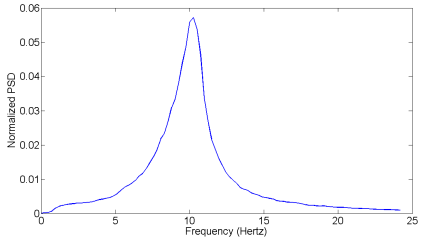

Figure 3. PSD of oscillations in membrane potential showing the alpha rhythm

The membrane potential of the pyramidal population soma is plotted in Fig. 2. The normalized Power Spectral Density (PSD) of the membrane potential is shown in Fig. 3. The PSD plot shows alpha rhythm with peak around and 10 Hz and larger contribution from frequencies in the 8-12 Hz range. Simulation of the changes to the 8-12 Hz alpha rhythm were chosen based on the fact that the alpha rhythm is readily observed in the awake human brain with eyes closed and could be easily obtained after TBI.

B. Computational simulation of the cortical module

The cortical module circuit shown in Fig 1 is as proposed in Jansen and Rit [18]. A Gaussian white noise is used to simulate extrinsic inputs where the absolute value of the noise signal at each instant is considered as the average firing rate of the afferent neural masses of the respective cell population. The simulation model is implemented using the Simulink environment. The inputs, output and intermediate signals are sampled at 1 kHz. The model output from the 4th second to the end of the simulation is extracted and bandpass filtered using a Butterworth filter of order 10, with lower and upper cut-off frequency of 1Hz and 50Hz respectively. The power spectral density vector is computed in Matlab using a

Welch periodogram with a Hamming window of length 4096 and overlap length of 50%.

TABLE I. VALUES FOR SIMULATION PARAMETERS

Category	Parameter Set	Values
Connectivity	<C1,C2,C3,C4>	<135, 108, 33.75, 33.75>
Post Synaptic Potential	<A, B, a, b>	<3.25 mv, 22 mv, 100/sec, 50/sec>
Sigmoid	<e_0, r,v_0>	<2.5/sec, 0.56/mv, 6 mv>
Cortical Input	<mean, variance>	<2, 2.4>
Amplification	<min, max>	<120 pulses/sec, 320 pulses/sec>

IV. SIMULATING TRAUMATIC BRAIN INJURY

In this section we analyze the impact of TBI on the alpha rhythm observed in Fig 2. We analyze the effect of TBI on the PSD of oscillations in a cortical column and two interconnected neighboring columns.

A. TBI in a Single Cortical Column

Layer V of the cortical mantle contains the highest number of pyramidal cells. In an animal model of mild traumatic brain injury, pyramidal cells were most frequently damaged after low-pressure brain impact [19]. Therefore, the present work models pyramidal cell population damage to analyze the effects of TBI. In mild TBI, only few nerve cells are killed, many are temporarily damaged and do not function properly [1]. The mechanical perturbation of cell membranes results in elevated amounts of extracellular cations and neurotransmitters causing increased depolarization and increase in spiking activity in neighboring neurons. This is modeled in the present work by reducing the firing threshold (v_0) in the sigmoid function eqn (3) of the pyramidal cell mass.

The change in PSD can be observed in Fig. 4. It may be observed that the contribution in the alpha frequency range reduces monotonically with lowering of firing threshold (v_0). Further, as the firing threshold is reduced there is an increase the in contribution from lower frequencies, i.e. increase in PSD of delta and theta bands.

Another component of mild TBI is the physical disruption of synaptic interconnections between neurons that is hypothesized to occur due to shearing forces between dendritic spines and post-synaptic axon terminals [6].

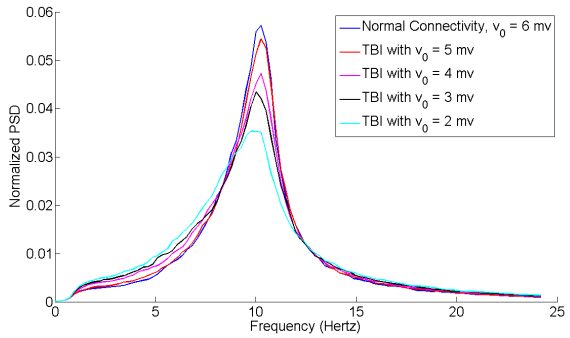

Figure 4. Changes in PSD of membrane oscillations with mild TBI

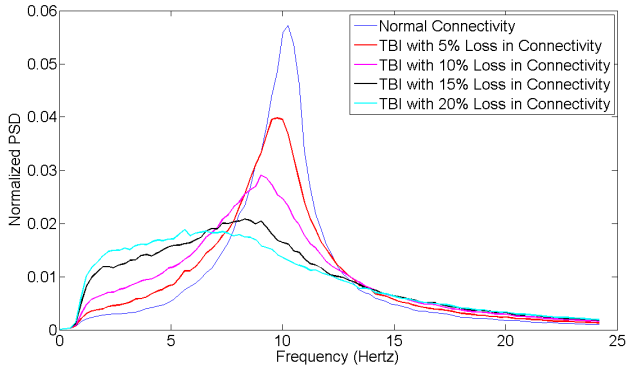

Figure 5. Changes in PSD of membrane oscillations with moderate TBI

The traumatic disruption of synapses between living neurons has not been experimentally verified and should be considered a hypothesis at the present time. To simulate this loss of synaptic connections, the average number of synapses between the pyramidal cell mass and the other excitatory and inhibitory neural masses were decreased in increments in Fig. 5. It is observed that there is a profound decrease in power in the alpha band peak at 10Hz, and a significant increase in theta (4-8Hz) and delta band (0-4Hz). Interestingly, this appears to be the manner which mild TBI affects the human brain [9-15]. The degree of shift in the PSD of the alpha rhythm may be a useful quantitative biomarker for TBI.

B. TBI in Two Interconnected Cortical Columns

This section will analyze the impact of cortico-cortical connectivity on the PSD. Since a future goal is to localize injuries in a multi-column model, a model of two connected cortical columns is examined presently. The connectivity model developed by Jansen and Rit for an occipital cortex is shown in Fig 6. In this model, pyramidal output from the cortical columns C1 and C2 provides an excitatory input to the other column. The attenuation factor value of 10 (i.e. K=10) is used in the Jansen- Rit model [18].

Fig. 7 shows the effect of an equal amount of injury on two interconnected cortical columns, simulated with v_0 = 2 mv. The PSD of both cortical columns is similar due to the symmetry of the columns. Furthermore, in comparison to PSD of the single column scenario illustrated in Fig 4, the same magnitude of injury does not cause the same absolute decrease power in the normalized PSD at 10Hz.

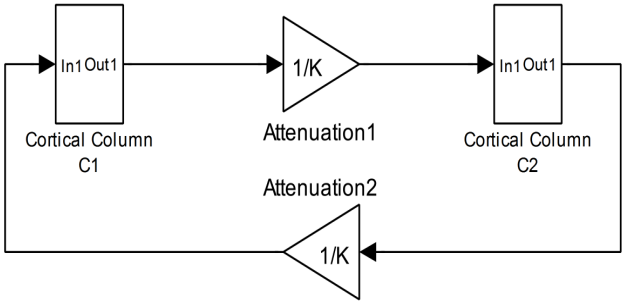

Figure 6. Connecting cortical columns

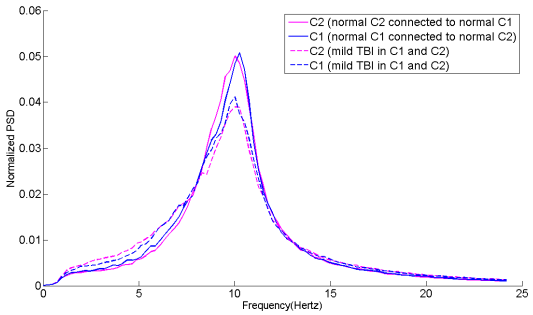

Figure 7. TBI in two columns

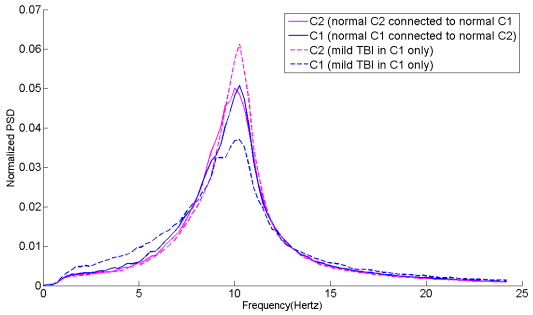

Figure 8. TBI in column C1 only

Figure 8, presents the PSD of the two interconnected cortical columns after injuring only one of the columns (C1) with v_0 = 2 mv. The injured C1 alpha power decreases and the uninjured C2 alpha power increases. These results indicate that a network of multiple neural masses interconnected in a biologically realistic manner can result in complex PSD behavior with and without TBI.

C. Summary and Future Research Directions

The present paper simulated two well-described consequences of mild TBI. Firstly, elevated levels of extracellular cations and excitatory neurotransmitters causing increased firing rate of neural masses result in a monotonic decrease in power in the alpha frequency band. Secondly, traumatic synaptic disruption, decreases the connection strength between neural masses and result in the shifting of power from the alpha frequency range to the theta frequency range. This second result is well supported by clinical literature [9-15]. It provides a novel explanation of clinical electrophysiological findings: the EEG changes after mild TBI can be caused by synaptic disruption between living neural populations. The degree of shift in the PSD of the alpha rhythm may be a useful quantitative biomarker for TBI, and merits further investigation.

The present two cortical column model simulations reveal the difficulties in analysis associated with the use of multiple NMM to simulate multiple interconnected areas of the brain. Future studies will incorporate simulation of traumatic synaptic disruption and simulation of injury using larger numbers of interconnected neural masses such as those described in Pons et al [20]. Application of other analytical approaches will be explored in future research including multi-column models of TBI.

CONCLUSION

An overview of the pathophysiology of traumatic brain injury was presented and a neural mass model was utilized to implement well-described aspects of traumatic injury. The result was an accurate simulation of the frequency domain changes observed after human mild traumatic brain injury.

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