Research Statement

Sleep occupies a large portion of the lives of all mammals - humans sleep for roughly one third of their lifetime. Despite being such a large part of our lives, the mechanisms of sleep are poorly understood. My research focuses on modeling the chemical and electrical mechanisms that govern sleep/wake cycle dynamics. Modeling these dynamics can provide insight into the complex neural mechanisms that control sleep as well as provide a method of noninvasive experimentation. Noninvasive experimentation and predictive modeling are indispensable tools for investigating solutions of all medical problems, not just those related to sleep.

To understand the model I am developing, we need to establish the underlying physiology. We begin with the global dynamics. Human (and most mammalian) sleep-wake cycles are comprised of three states: Wake, Rapid Eye Movement Sleep (REMS), and Non-rapid Eye Movement Sleep (NREMS) [Various [2005]]. These states, characterized by simultaneous readings of brainwave and muscular activity, are initiated and maintained by multiple neuronal regions in the brainstem. The regions responsible for maintaining the states of sleep and wake are mostly located in the hypothalamus and are coupled to each other via electrical and neurochemical signaling. We would like to quantify the chemical and electrical activity generated by neurons that characterize these states.

The electrical signals generated by neurons are called an action potentials. These action potentials make up one step of the neuron to neuron communication process. Upon receiving electrical stimulation, neurons release chemical messengers, known as neurotransmitters, into the space between the delivering and receiving ends of neurons, called a synapse. The neurotransmitter can then take one of three paths [Kandel et al. [2000]] (see Figure 1):

1. It can bind to a receptor, **R**, on the receiving neuron. This then opens an ion channel on the receiving neuron, whether directly or by a messaging mechanism, which changes the chemical gradient and initiates an action potential on the membrane of the receiving neuron. This starts the process over again.
2. It can be degraded and eliminated by a neurotransmitter-specific enzyme, **D**.
3. It can be picked up by transporting enzyme, **T**, that takes it back into the delivering neuron to be recycled.

We can use the laws of mass action and Michaelis-Menten kinetics [Holmes [2009]] to formulate relationships and equations from these basic neurotransmitter dynamics. We look at the case where a particular neurotransmitter has two postsynaptic receptors that it can bind to that affect sleep and wake modulation. This is physically accurate for our particular system of neurotransmitters. We can formulate relations for a general neurotransmitter concentration, [**C**]. The chemical kinetic relationships that arise are as follows:

$$[C] + [R_1] \overset{k_{R_1}}{\longleftrightarrow} [CR_1^*] \underset{\beta_{R_1}}{\overset{\alpha_{R_1}}{\rightleftharpoons}} [CR_1] \tag{1}$$

$$[C] + [R_2] \overset{k_{R_2}}{\longleftrightarrow} [CR_2^*] \underset{\beta_{R_2}}{\overset{\alpha_{R_2}}{\rightleftharpoons}} [CR_2] \tag{2}$$

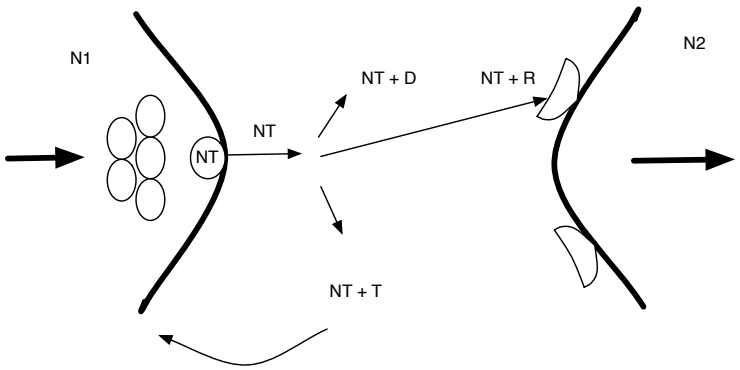

Figure 1: Synaptic neurotransmitter path

$$[C] + [D] \overset{k_D}{\longleftrightarrow} [CD] \xrightarrow{\gamma_D} [D] \tag{3}$$

$$[C] + [T] \overset{k_T}{\longleftrightarrow} [CT] \xrightarrow{\gamma_T} [T] \tag{4}$$

For these relationships, we have the following variable representations:

- $[C]$, the synaptic concentration of neurotransmitter (NT) in a particular region
- $[R_1]$, the concentration of unbound R_1 receptors in the region
- $[R_2]$, the concentration of unbound R_1 receptors in the region
- $[CR_1^*]$, the concentration of the bound neurotransmitter-receptor 1 complex, closed ion channel
- $[CR_1]$, the concentration of the bound neurotransmitter-receptor 1 complex, open ion channel
- $[CR_2^*]$, the concentration of the bound neurotransmitter-receptor 2 complex, closed ion channel
- $[CR_2]$, the concentration of the bound neurotransmitter-receptor 2 complex, open ion channel
- $[D]$, the concentration of the enzyme that degrades neurotransmitter C
- $[CD]$, the concentration of the degrader-neurotransmitter complex
- $[T]$, the concentration of the enzyme that transports neurotransmitter C
- $[CT]$, the concentration of the degrader-neurotransmitter complex

Equations (1) and (2) represent the neurotransmitter concentration $[C]$ binding to open receptors $R_{1,2}$ with rapid equilibrium rate $k_{R_{1,2}}$ to form the closed-ion channel state complex $[CR_{1,2}^*]$, and the subsequent transition to the open ion channel state $[CR_{1,2}]$ with forward and backward transition

rates of α_{R_1} and $\beta_{R_{1,2}}$. It is important to note that the neurotransmitters we are building this system with only have two pertinent sleep and wake effecting receptors apiece, which is why we derive the chemical kinetic relationships for two receptors [Siegel et al. [2006], Cooper et al. [2003]]. We can easily modify the equations to encompass greater or fewer receptors per neurotransmitter affinity. Equation (3) represent the neurotransmitter concentration $[C]$ binding with its degrading enzyme D with rapid equilibrium rate k_D to form the complex $[CD]$, and the subsequent degradation of the neurotransmitter concentration and release of degrader $[D]$ with transition rate γ_D. Equation (4) represents the same process as in Equation (3), but for a transporting enzyme. We have a set of these four relationships for every neurotransmitter in the system. These relationships give rise to a set of differential-algebraic equations formed by the intersection of the rates of change describing each concentration and a set of conserved quantities and equilibrium conditions. We can then reduce these equations to a set of three: the rate of change of the neurotransmitter concentration in a region and the rates of change of the open-ion channel state.

$$\frac{d[C]}{dt} = \frac{r_C - \frac{\gamma_D[C][D^T]}{[C]+k_D} - \frac{\gamma_T[C][T^T]}{[C]+k_T} - (\frac{k_{R1}}{[C]+k_{R1}})\frac{d[CR_1]}{dt} - (\frac{k_{R2}}{[C]+k_{R2}})\frac{d[CR_2]}{dt}}{1 + \frac{k_D[D^T]}{([C]+k_D)^2} + \frac{k_T[T^T]}{([C]+k_T)^2} - \frac{k_{R1}([CR_1]-[R_1^T])}{([C]+k_{R1})^2} - \frac{k_{R2}([CR_2]-[R_2^T])}{([C]+k_{R2})^2}} \tag{5}$$

$$\frac{d[CR_1]}{dt} = \frac{\alpha_{R1}[C]([R_1^T] - [CR_1])}{[C] + k_{R1}} - \beta_{R1}[CR_1] \tag{6}$$

$$\frac{d[CR_2]}{dt} = \frac{\alpha_{R2}[C]([R_2^T] - [CR_2])}{[C] + k_{R2}} - \beta_{R2}[CR_2] \tag{7}$$

The only term left to determine is r_C. This term provides the link to the firing rate dynamics of the neuron groups. Upon every arrival of an action potential, approximately one synaptic vesicle fuses to the neuron membrane and releases its neurotransmitter contents into the synaptic gap [Kandel et al. [2000]]. Since the firing rate of a region is the number of action potentials per unit time, it follows that the rate of release of neurotransmitter from one synapse is equivalent to the quanta of neurotransmitter stored in one synaptic vesicle multiplied by the firing rate of the region. In equivalent terms, $r_C = QF$. To complete the chemical dynamics, we need to determine the firing rate dynamics.

We are interested in the dynamics of the interacting firing rates of entire regions, not of the individual neurons that make up the regions. For this reason, we consider the population of neurons in a region as one neuron producing one local field potential and one firing rate that we can track with a Leaky Integrate and Fire model [Hoppensteadt and Peskin [2002]]. The one dimensional integrate and fire model is derived from conservation of charge, yielding the following equation:

$$\tau\frac{dV}{dt} = -V + \sum I$$

where V is the potential of the neuronal region and $\sum I$ is the sum of the external inputs to the region. We generalize this for the firing rates of the regions generating sleep and wake and represent the external inputs as concentrations weighted by the number of synapses in a region, a ratio of synaptic to regional volume and the strength of connections between regions. For a system of n neurotransmitters and regions, we have the following:

- $\mathbf{F}$ = One-by-n vector of firing rates
- τ = n-by-n diagonal matrix of time constants
- $\mathbf{C}$ = One-by-n vector of regional neurotransmitter concentrations
- $\mathbf{W}$ = n-by-n sparse matrix such that W_{ij} = influence of concentration i on firing rate j

$$\frac{d\mathbf{F}}{dt}\tau = -\mathbf{F} + \mathbf{CW}$$

Weights are also given either positive or negative value based on excitatory or inhibitory influence on a region, respectively. We take synaptic concentrations to regional concentrations by noting that

$$C_R = NC_S\frac{V_S}{V_R}$$

where C_R is the regional concentration of neurotransmitter, C_S is the synaptic concentration of neurotransmitter, N is the number of synapses in a particular region, V_S is the volume of a synapse and V_R is the volume of the region.

The neurotransmitter contributing to the maintenance of sleep and wake are GABA (gamma-aminobutyric acid), glutamate, orexin (hypocretin), histamine, acetylcholine, noradrenaline (norepinephrine), serotonin and dopamine. Each of these transmitters are located throughout the following neuronal groups: basal forebrain (BF), raphe nuclei (RN), laterodorsal tegmentum (LDT), pedunculopontine tegmentum (PPT), parabrachial nucleus (PB), locus coeruleus (LC), lateral hypothalamus (LH), tuberomammillary nucleus (TMN), ventral periaqueductal gray region (vPAG), and ventrolateral preoptic nucleus (VLPO). During my research at the CLS Neurology Lab at Beth Israel Deaconess Medical Center, I identified the major inhibitory and excitatory connections formed by these neurotransmitters, as well as electrophysiology and microdialysis levels (when available) associated during each stage of activity (wake, REMS, NREMS) of the sleep-wake system Espana and Scammell [2004].

We would like to determine what is the minimal system of neuron regions needed to maintain human sleep/wake cycles. I have so far implemented the following regions and neurotransmitters:

1. The VLPO, containing GABA, the major inhibitory neurotransmitter of the central nervous system. The VLPO exhibits the highest GABAergic firing rates during REMS and NREMS.
2. The PB, which generates glutamate, the major excitatory neurotransmitter in the central nervous system. The Glutamatergic neurons of the PB exhibit the highest firing rates during waking and REMS.
3. The BF, which generates adenosine and acetylcholine. Adenosine acts as a **somnogen** - it builds up in the BF during waking and begins decrease upon sleep initiation, exhibiting one's propensity for sleep.
4. Acetylcholine, generated by the cholinergic cells of the BF. The cholinergic cells of the BF have the highest firing rates during Wake and REMS [Siegel et al. [2006], Espana and Scammell [2004]].

Due to the differences in scaling from the synaptic concentrations to the regional concentrations as well as the range of unbounded parameters, there is room for a great degree of error when implementing this model numerically. For this reason I implement the model with a Backward Euler method of solving. The asymptotic stability provided by this method assures the stability of the algorithm regardless of the stability of the problem, which is largely in question. The four-region model is built and solving without error.

We need to add at least two more regions to make a system capable of maintaining physically realistic human sleep-cycles. Both the monoamines (mostly serotonin) and orexin are essential to control the REMS-NREMS state transitions. Though the system is large and complex, we might be able to gain insight from a theoretical analysis of the equations. I am currently investigating the existence of periodic orbits in the firing rate phase space dynamics, which will help to determine if a realistic self-sustained oscillation is achievable. I also plan to introduce stochastic noise to certain neuronal regions to represent input from neuronal regions that are not described by the model. Circadian regulation is another important aspect of the sleep/wake system. This type of regulation is governed by cellular clocks and keeps sleep-wake cycles synchronized with the 24 hour period that defines the earth's movement around the sun. The introduction of this element with enforce periodicity. I am also interested in the local dynamics of adenosine and it's action as a somnogen. I have worked on a model for Adenosine-Triphosphate metabolism that could be incorporated into this sleep-wake cycle model to reveal more insight into adenosine's actions. I would also like to investigate how neuron activity in sleep enhances learning and memory.

One of my many goals in the development of my career as a research scientist is to bridge the gap between applied mathematics and biology through collaborative efforts. Making models of physical processes based on first principles can help provide insight into the inner workings of these physical processes and provide us with methods of quantifying and simulating phenomena for predictive and preventative use. I have recently begun collaboration with David Rapoport's Sleep Lab at Bellevue Hospital, NYU. The Rapoport lab has kindly shared some of their normal human EEG studies so I may fit the many parameters that arise in the model. It is my hope that with continued work with this lab, I can create a more medically accessible graphic user interface that can be used to perform noninvasive experimentation of pharmacological effects on sleep and wake regulating neuron groups. An interface such as this can also be used for the more simple task of determining one's ideal or perturbed sleep schedule.

I look forward to the continuing challenges and educational opportunities that mathematical and biological sleep research provides.

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