MULTISCALE MODELING OF THE SLEEP/WAKE SYSTEMS

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Contents

Abstract. The mathematical modeling of biological processes is a powerful tool for informing both areas of mathematics and biology. Specifically the process of sleep deprivation has benefited from mathematical modeling, where researchers are not sure of many of the biological basis for the data. In our work, we successfully modeled the sleep/ wake system using the flip-flop switch formalism. Our model added on an aspect of the SCN, as the source of communication between the circadian and the neuronal sleep/ wake populations. Additionally, we took on the task of modeling sleep deprivation, both total and chronic. By introducing a constant, we were able to easily model total sleep deprivation so that it matched biological data. We found the process of modeling chronic sleep deprivation to be challenging and were able to contribute to the overall study of the differences between total and chronic sleep deprivation.

1. Introduction

The use of mathematical models for the sleep-wake process helps us better understand the biological process of sleep and the effects of deprivation. Many such have models have been developed[2, 3, 1, 10, 11, 13, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28] and can be categorized by their mathematical formalisms – this paper will focus on the firing rate and neurotransmitter approach. Additionally there will be no distinction between non-REM and REM sleep.

Our approach lies on the biological knowledge of the brain and its control of sleep. It has been well documented that the sleeping and waking cycle is regulated by the circadian rhythm (24.2 hrs); in conjunction, as every human has experienced, the longer one stays awake, the more one longs to sleep. These two ideas led to early theories in mathematically modeling the sleep-wake cycle, called the two process model[7]. Process C is the Circadian rhythm, the biological clock, which is promoted in the brain by the suprachiasmatic nucleus (SCN) — process S, the homeostat, increases the sleepiness while we are awake. Mathematically modeled, they look like the following,

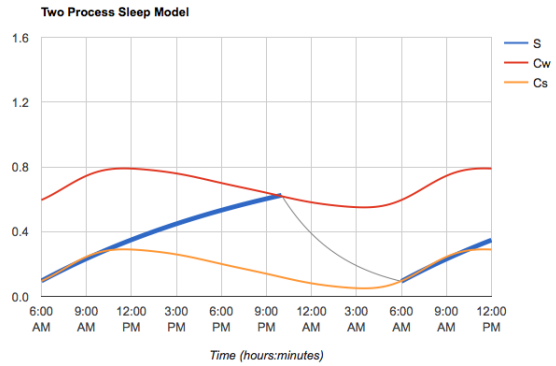

Figure 1: This graph depicts the sleep-wake cycle in which each stage is reached by surpassing the threshold, or intersection of C_w or C_s, named respectively for their stages[6].

Despite early success with the two process model, it fails in many respects because of the lack of biological foundation. For this reason, mathematical modeling of the sleep-wake cycle has shifted towards modeling a "flip-flop switch," which is grounded in a biological process. In the brain specific populations of neurons, like the LC, are responsible for waking—while a different population, the VLPO, is responsible for sleeping. These populations act as a flip-flop switch, where the firing of the wake promoting populations immediately thrusts the body into a wakeful state and the opposite is also true. This interaction can be displayed in the diagram below,

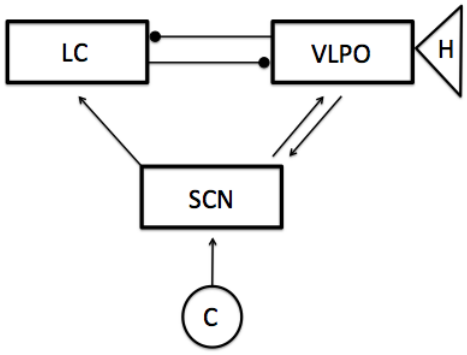

Figure 2: In the diagram above, we use LC to represent the wake promoting population, VLPO to represent the sleep promoting population, C to represent the Circadian rhythm, H to represent the homeostat and SCN to represent the suprachiasmatic nucleus. We can see that the SCN promotes the LC, while we the interaction between the SCN and VLPO was unknown. Additionally, the diagram shows that the VLPO takes input directly from the homeostat. [6].

We can model this interaction mathematically by using differential equations, specifically modified Lotka−Volterra equations. These equations come from the Booth-Behn model while the Kronauer model provides a simply modeled Circadian rhythm[5, 14, 27].

With the power of these previous models, we attempted to model the sleep-wake cycle so that it would replicate biological data. Additionally, we experimented with ways of modeling chronic and total sleep deprivation.

2. Model equations

The equations used to model the sleep wake cycle were based off of the Booth and Behn model[5].

$$S_{VLPO} = \frac{max_{VLPO}(1+tanh(\frac{VLPO_{input}-\beta_{VLPO}}{\alpha_{VLPO}}))}{2} \tag{2.1}$$

$$S_{SCN} = \frac{max_{SCN}(1+tanh(\frac{c-\beta_{SCN}}{\alpha_{SCN}}))}{2} \tag{2.2}$$

$$S_{LC} = \frac{max_{LC}(1+tanh(\frac{LC_{input}-\beta_{LC}}{\alpha_{LC}}))}{2} \tag{2.3}$$

$$fLC' = \frac{S_{LC}-f_{LC}}{\tau_{LC}} \tag{2.4}$$

$$fVLPO' = \frac{S_{VLPO}-f_{VLPO}}{\tau_{VLPO}} \tag{2.5}$$

$$fSCN' = \frac{S_{SCN}-f_{SCN}}{\tau_{SCN}} \tag{2.6}$$

Equations 2.1−2.6 are used to model the $VLPO$, LC and SCN, where $VLPOinput$ and $LCinput$ take into account signals from the SCN. To model the sleep drive, we used the equation below,

$$H' = heaviside\frac{(f_{LC}-\theta W)*(h_{max}-h)}{\tau_{hw}} + heaviside\frac{(\theta W-f_{LC})*(h_{min}-h)}{\tau_{hs}} \tag{2.7}$$

Equation 2.7 was formulated from what we know the action of the sleep drive to do and the simple fact that we want to sleep more after we have been awake for longer. Here, τ_{hw} and τ_{hs} represent constants for the wake and sleep times, respectively. We used the Forger model for the circadian, and the equations will not be included here[14]. thetaW=1.5; tauhw=15.78; tauhs=3.37; hmax=323.88; hmin=-0.05; In all of the equations listed, we had to keep in mind certain biological data[**?**] in order to correctly model the sleep/ wake cycle. For example, our constants for the sleep drive were $\theta W = 1.5$, $\tau_{hw} = 15.78$, $\tau_{hs} = 3.37$, $h_{max} = 323.88$ and $h_{min} = -0.05$, to match recent biological results about the range of the sleep drive.

3. Coupling the sleep-wake cycle

Uncoupled, the sleep/ wake cycle with the equations looks like the figure below,

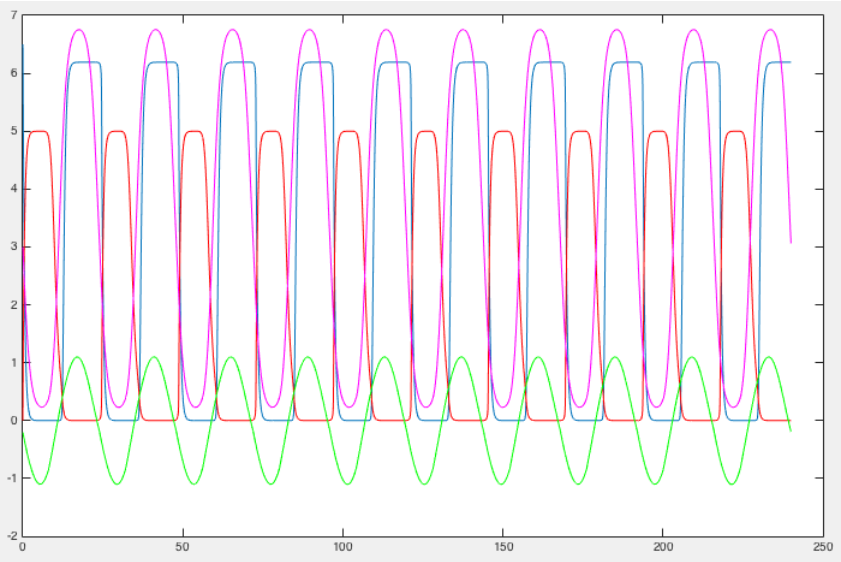

Figure 3: The graph above is of the uncoupled action of the sleep/ wake cycle. In this diagram, the green curve represents the action of the circadian rhythm. The blue curve shows the LC population, while the red curve shows the VLPO firing. The purple is the action of the SCN. On the x-axis, we are measuring time, in hours, and on the y-axis we are measure the firing rates (Hz.).

The sleep drive occurs on a different scale, shown below,

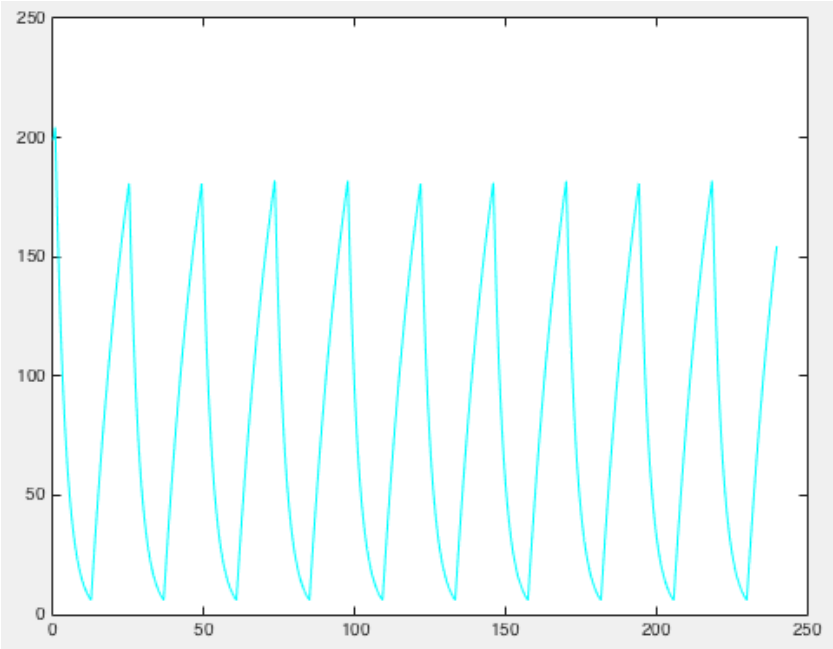

Figure 4: Above we see the action of the sleep drive, which rises during hours of wake and drops exponentially during sleep. The x-axis again shows time (hrs) while the y-axis records the sleep waves.

To see if the light aspect of the circadian rhythm was activating during the correct time, we graphed the action of the light constant against the circadian rhythm. The uncoupled results are shown below,

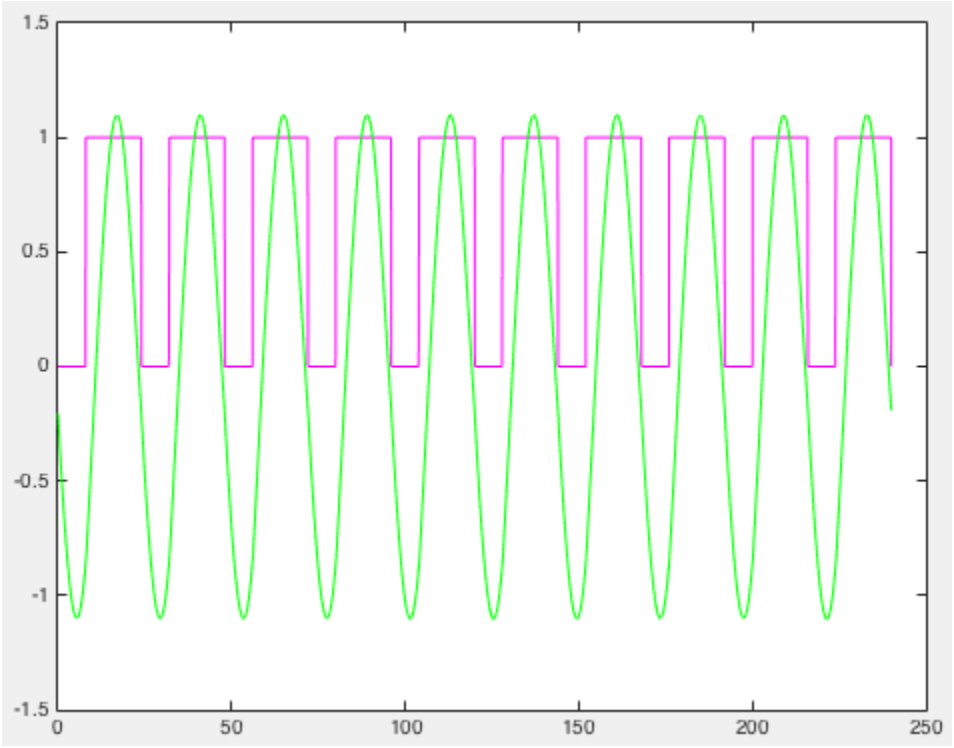

Figure 5: In the graph above, the light constant is shown in purple while the circadian rhythm action is shown in green. The x-axis again measures time.

In all of these graphs we can see that the actions of the VLPO, LC and SCN do not occur at the correct times. We would like our circadian rhythm (and thus, SCN) to be at the highest peak when we are in the middle of our waking day. The fall of our SCN should occur at roughly the same time as falling asleep. Additionally, with these constants we see that the average period of sleeping and waking is 24.1711 hours, which is more hours than is physically feasible. The average sleeping period is 11.8847 hours, much longer than the average human sleep, while the average waking period is only 12.2778 hours.

To correct for these mistakes we looked into a few constants that were critical for specifically the action between the LC and the VLPO: the interactions between the SCN-LC, SCN-VLPO and LC-VLPO/ VLPO-LC. We had many questions when first setting out to couple the entire network, for example, was the interaction between the SCN and VLPO positive or negative? To get a sense of where our parameter search should begin, we created a program to return the sleep/ wake period when given a certain range of parameters. This program effectively told us that the interaction between the SCN and VLPO should be negative, and eventually after rounds of experimentation we found that giving constants of 1.25, so an increased coupling between the SCN and LC and -1.15 coupling value between the SCN and VLPO gave us the coupled results in Figure 6. However, even with these changes the coupling was not exact, we could not perfect getting a sleep period of 8 hours and having the SCN act when the LC was at its midpoint. To do this, we had to look into more constant values.

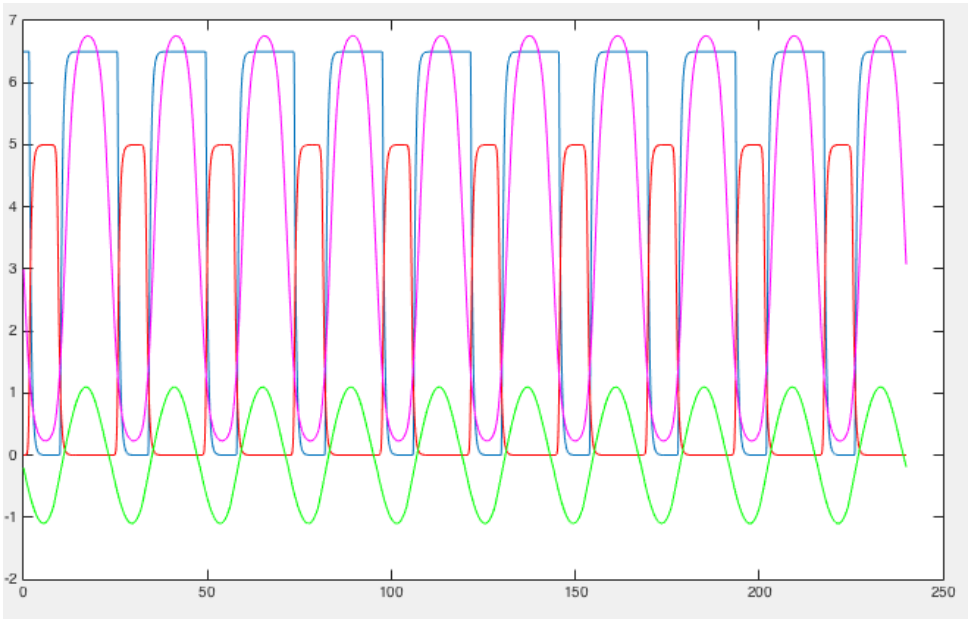

Figure 6: In the graph above, the light constant is shown in purple while the circadian rhythm action is shown in green. The x-axis again measures time.

Our next step was to look into the action of the LC and VLPO equations themselves. These equations rely on many constants but the ones that were of particular interest to us were the β_{VLPO} and α_{VLPO}, two constants that change the threshold of sleep onset.

$$\beta_{VLPO} = k_2 * h + k_1 \tag{3.1}$$

Where k_2, k_1 are constants and h is the input from the sleep drive. If we were to graph β_{VLPO} against h, we would get a linear relationship, shown below,

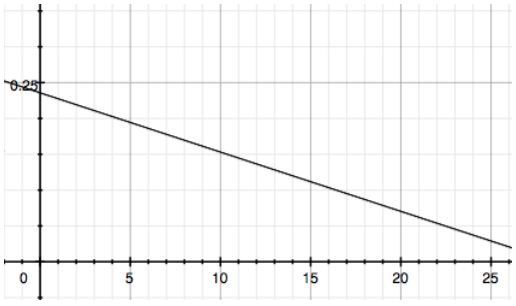

Figure 7: In the graph above, we wanted to see the relationship between the β_{VLPO} and h. h is on the $y-$axis while β_{VLPO} is on the x-axis.

Because of the biological data, we knew when we wanted the sleep and wake to occur, so it was just a matter of a simple calculation to find that we should set k_1 to 0.23537 and k_2 to -0.00827. The change in β_{VLPO} can be described in the graph below,

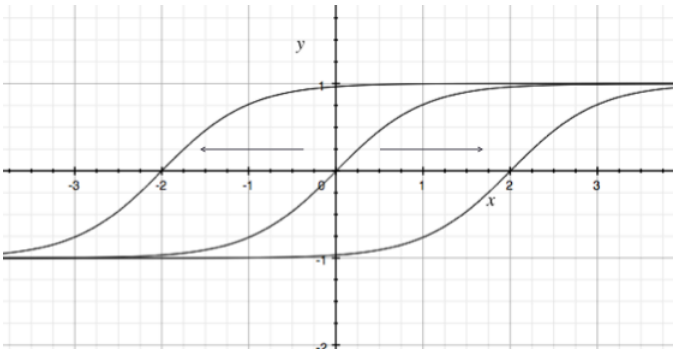

Figure 8: This graph shows the change in the threshold of sleep and wake , as modeled by the $tanhx$ function.

While the α_{VLPO} constant would change the following graph,

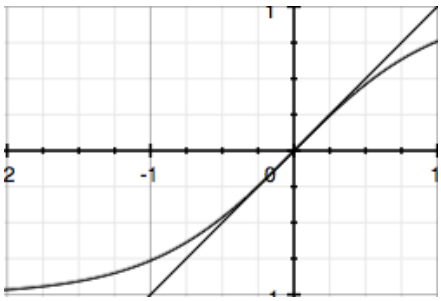

Figure 8: α_{VLPO} changes the slope of the function.

Meaning increasing α_{VLPO} increases the rate at which we get to sleep or wake, but not the value at which the state changes. Keeping all of these constants in mind, after many trial runs we decided on the constant value: $\alpha_{VLPO} = 0.1$.

Our results centered around an average period of 24.0087 hours, an average sleep period of 8.1271 hours and an average sleep of 15.9747 hours.

4. Modeling total sleep deprivation

After correctly modeling the sleep/ wake cycle, we set upon the question of sleep deprivation. First, we attempted to model total sleep deprivation, or one long period of sleep restriction. There have been many biological studies that guided our model showing the effects of total sleep restriction. We used a simple and effective method of affecting sleep deprivation on our model,

$$VLPO_{input} = -g_{NEVLPO} * c_{NE_{LC}} + g_{SCNVLPO} * c_{GSCN} - S \tag{4.1}$$

Where S is a sleep deprivation constant that restricts the VLPO from activating, thereby creating more waking hours. This equation was put into a loop in MATLAB so that we could control at what hour waking and sleeping would occur. We experimented with this constant until we settled on the value of 2, although this constant would have to be changed for shorter periods of sleep deprivation. Below is the result of modeling total sleep deprivation.

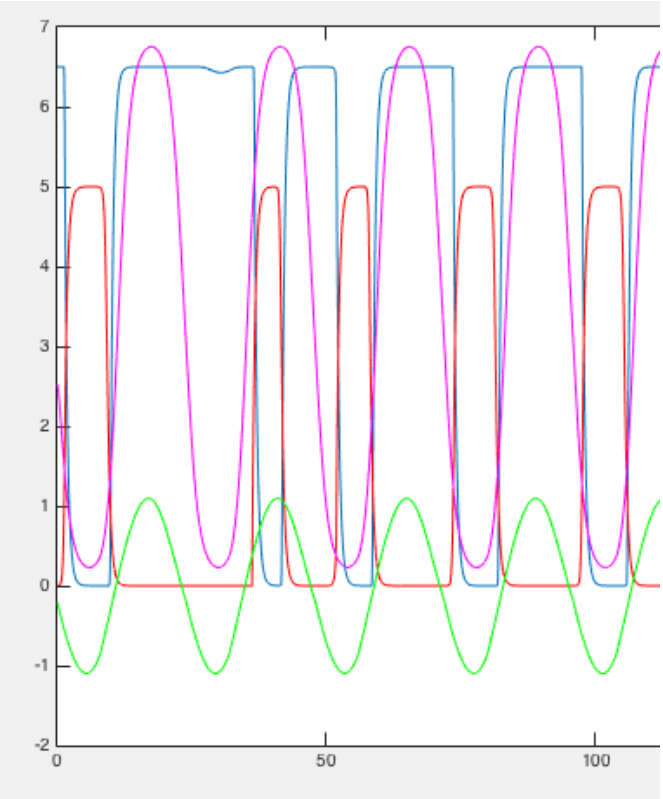

Figure 9: Above is a model of total sleep deprivation and its effects on the sleep/ wake cycle in recovery.

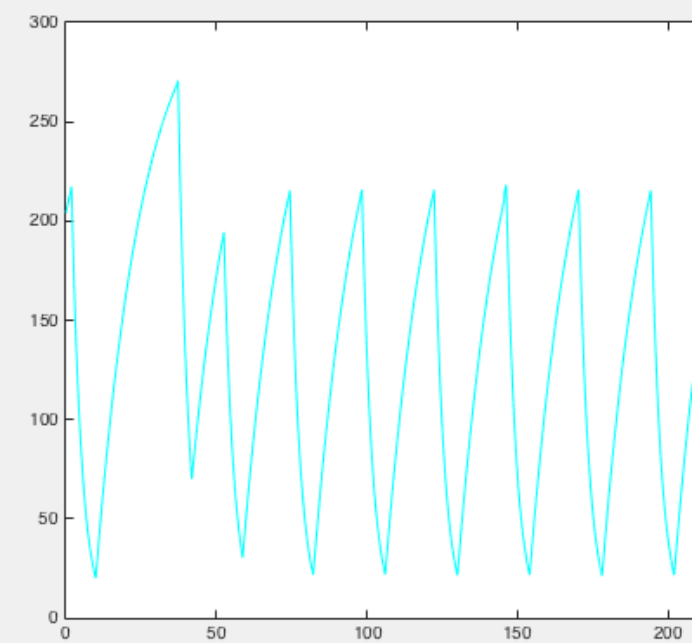

Figure 10: We see the sleep drive rise steeply during the hours of sleep deprivation, shown above.

We could then calculate the amount of sleep the model ran each night: 5.1653 hours on the night of sleep deprivation and 6.4372 hours on the night of recovery. After the third night, the model went back to sleeping 8 hours a night. We compared these results, over a number of trials to clinical data on the hours of recovery after a night of sleep deprivation. In a 1984 study [8], researchers found that the recovery sleep of humans looked like the graph below, (our results are shown below the study)

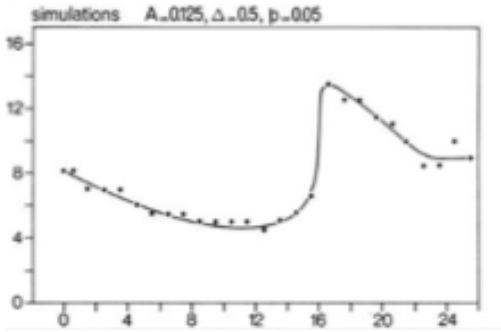

Figure 11: The x-axis on this graph represents the number of hours of sleep restriction and the y-axis represents the number of hours of recovery sleep.

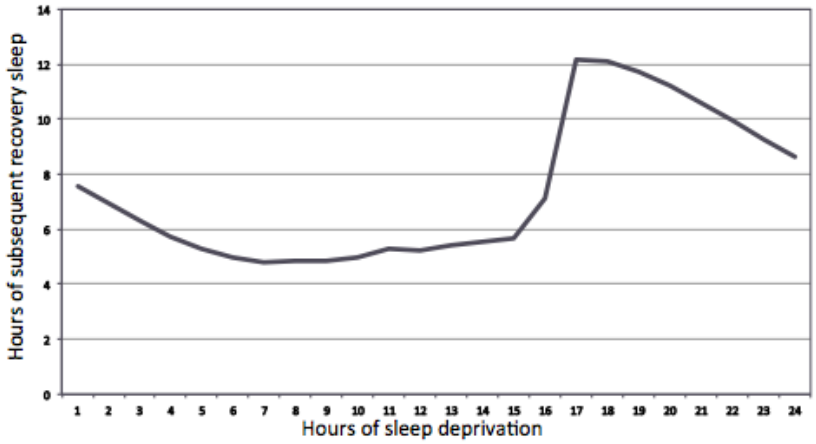

Figure 12: Our results from total sleep deprivation almost perfectly measured the clinical work in this area. This can be seen by the comparison of figures 11 and 12, even the spikes in recovery sleep happened at around the same times.

5. Modeling chronic sleep deprivation

After our success with total sleep deprivation, the next step was to look at chronic sleep deprivation. What does sleeping 5 hours a night do to our sleep recovery? Can we model the effects of chronic sleep deprivation on attention? These are ideas that we are still thinking about.

We first attempted to model chronic sleep deprivation in the same manner as chronic sleep deprivation. This result is shown below,

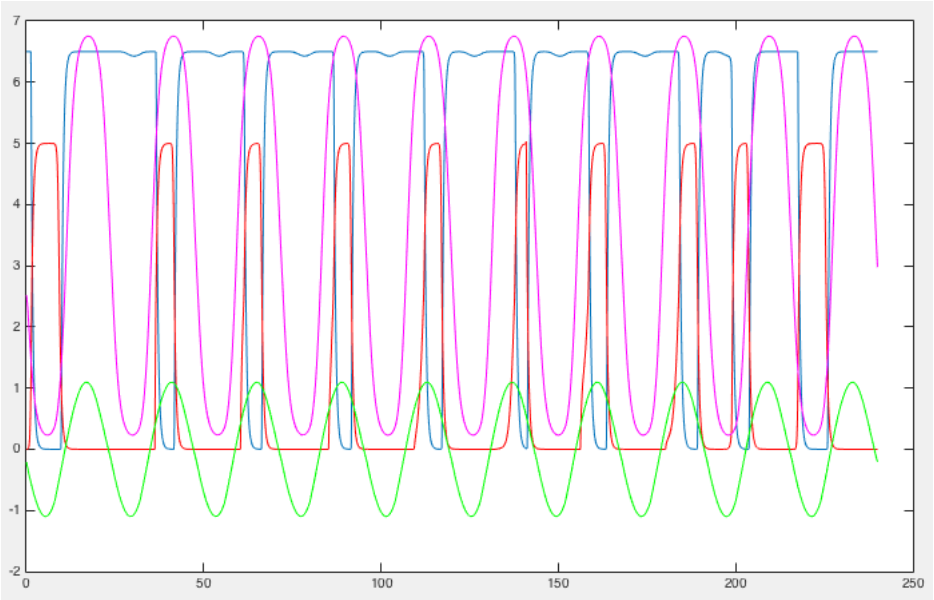

Figure 13

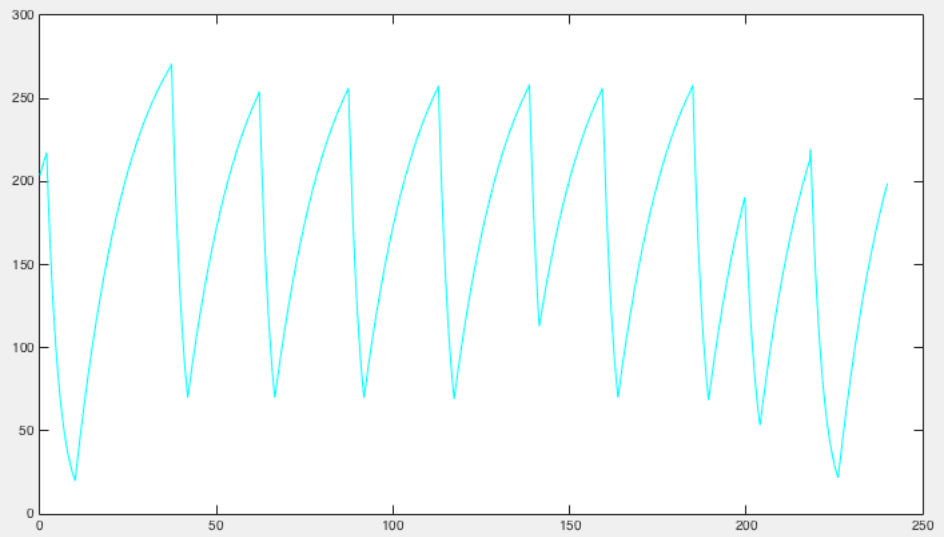

Figure 14

Although we were able to model chronic sleep deprivation, Figures 13 and 14 highlight some of the difficulties we have had with it. We were not able to focus the sleep deprivation for specific time period and had trouble getting the sleep deprivation down to exactly 3 hours a night. This model works more easily with total sleep deprivation since we can restrict sleep and then let the model recover by itself.

Chronic sleep deprivation was a very interesting, and easily applicable topic. For example, we can no longer use the sleep drive to predict sleep deprivation when considering chronic sleep loss. The formalisms used in this project for chronic and total sleep deprivation will hopefully be applied to the app Entrain, an iPhone application that projects the amount of light one needs to adjust to a new area.

6. Future experiments

Although we were not able to research in all of the directions we wanted to, this project left us with a lot of ideas and new questions. For example, one of our main questions at the end of the project was: could we accurately predict attentiveness from chronic sleep deprivation? There are many studies that look at the lapses in a PVT test attentiveness in sleep deprivation[4, 9, 12, 29, 30] and we were interested in the conjunction of this test with our model formalism. From these results we started thinking about the various ideas that they posed essentially answering the question, how is chronic sleep deprivation different from total sleep deprivation? There were two different ideas proposed: an adaptation to sleep deprivation and the idea of calculating wakefulness rather than sleep deprivation.

In a study at University of Pennsylvania[30] measured PVT lapses, or psychomotor vigilance tests, against extended wakefulness. They compared this to total sleep deprivation to find the graph below,

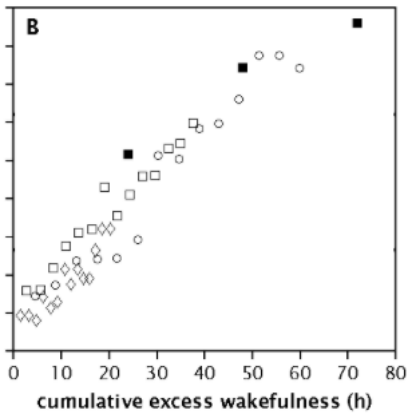

Figure 14: In this graph, the y-axis is PVT lapses[30].

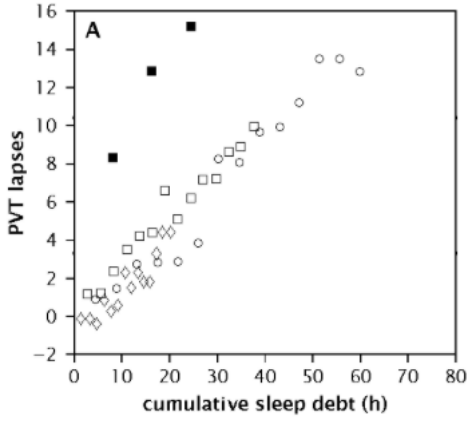

Figure 15 [30]

Upon first glance, it looks like the Figure 14 is a more effective way of thinking about chronic sleep deprivation. However, it is important to note that if we think about extended wakefulness, this will not change the calculation of chronic sleep deprivation, only how we think about total sleep deprivation. We need only to look

at the two graphs above to know that this is true−only the points (black) that represented total sleep deprivation were shifted.

Because of this, we were more inclined to believe that an adaptation to sleep deprivation was a more likely player in chronic sleep deprivation. For example, the experiment below best supports the idea,

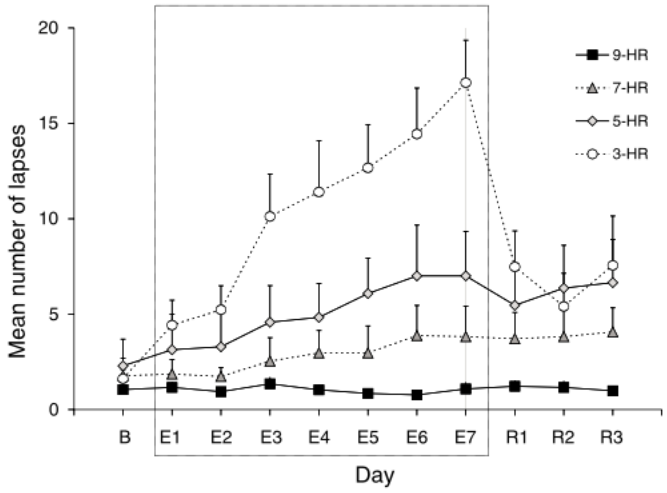

Figure 16 [4]

We can see that there is a period of adaptation, one that is not present in Van Dogen's results [29, 30]. Perhaps it is an adaptation to chronic sleep deprivation, which is why the sleep drive does not increase after repeated days of sleep deprivation.

The best clue we have as to how to model chronic sleep deprivation with our model formalism comes from a recent study[17] that marks PVT lapses along with the circadian rhythm, shown below,

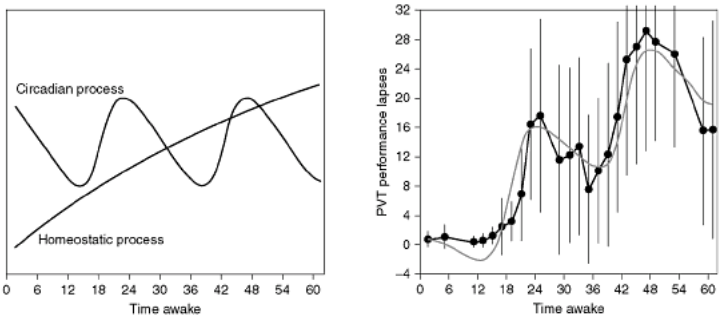

Figure 17 [17]

These papers give us a good clue to as to how to model chronic sleep deprivation. We believe there is a reason why chronic sleep deprivation is so difficult to model using the same methods as total sleep deprivation. We could easily calculate what we needed for total sleep deprivation to induce a specific number of hours lost and regained. We needed only one variable, inhibiting sleep.

However, we saw that it was really hard to model chronic sleep deprivation using the same process. Despite adding specific amounts of inhibition to the LC, we could

not easily produce 3 HR of sleep every night for a week. If we consider the biological basis for the flip-flop switch and the correctness of the overall model, I think this points more to a completely different mechanism, at least in the model, for chronic sleep deprivation. For example, inducing an equation that not only affects the LC but also the VLPO.

There are other things that could be implemented using this model, for example studying morningness and eveningness (are you a morning or night person?). Additionally, our model's light variable could be implemented so that it was in conjunction with wakefulness. Overall, we came a long way, but there is a lot of exciting work left!

7. Acknowledgements

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