Modeling Human Sleep Patterns

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ABSTRACT
Human sleep is composed of three main sleep stages, which exhibit fairly regular cycling throughout the night. With sleep-scored polysomnogram recordings from the Sleep Heart Health Study, we examine these patterns found in human sleep, comparing existing models to the trends found in the data. We also consider the structure of REM sleep throughout the night, and study how best to model the reported characteristics and patterns found in actual nights of sleep.

INTRODUCTION
Humans exhibit three main sleep stages: waking, Rapid Eye Movement sleep (REM), and non-REM sleep (NREM). Each stage is characterized by activation or inhibition of different neuron populations in the Ascending Arousal System of the brain. The two populations located in the brainstem both remain active during waking. The locus coeruleus (LC) and dorsal raphe (DR) release excitatory monoamine neurotransmitters serotonin, histamine, and norepinephrine, which promote the waking state. The laterodorsal tegmental nucleus (LDT) and pedunculopontine tegmental nucleus (PPT) also exhibit high firing activity during waking. The neurotransmitter GABA is released by the ventrolateral preoptic nucleus (VLPO) in the hypothalamus, sending inhibitory signals to the LC/DR and LDT/PPT to promote sleep (Phillips and Robinson 2007). During REM sleep, GABA from the VLPO continues inhibiting the wake populations, but the LDT/PPT has reactivated and is firing simultaneously (Diniz Behn and Booth 2010).

The three sleep stages exhibit fairly regular cycling throughout the day and night. The 24-hour circadian oscillation between sleep and wake is regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus. Fluctuation of SCN firing activity corresponds to cycling of light and dark, with higher activity in the light period (Fleshner et al. 2011). It is believed that the sleep homeostat plays a large role in initiating these switches between sleep and wake. The current theory maintains that major metabolic byproduct adenosine accumulates in the brain during waking, increasing sleepiness, which eventually induces sleep at a certain threshold concentration. (Phillips and Robinson 2007). Humans also exhibit an ultradian rhythm of alternating NREM and REM sleep (Carskadon and Dement 2000). While the period of these oscillations is variable among individuals, the mean cycle duration of 90 minutes is fairly accurate, even with a small sample size (Clausen et al. 1974). It has also been found that the proportion of these cycles comprised of NREM decreases over the course of the night, while the amount spent in REM increases throughout sleep (Clausen et al. 1974).

Researchers believe that the “flip-flop” switch, which consists of mutual inhibition between the wake and sleep promoting groups, describes the method of sleep-wake cycling, with transitions initiated by the homeostatic drive. Using a hysteresis loop to model these interactions of the flip-flop switch produces results which accurately represent observed phenomena (Diniz-Behn and Booth 2011). While this theory is widely accepted, it is less clear through what means the REM-NREM cycling occurs. One idea is that the “REM-on” population, which promotes REM sleep, is mutually inhibitory with the “REM-off” neurons that induce the brief wake activation following REM sleep (Lu et al. 2006). In contrast to this idea of a “flip-flop” switch for REM is the theory of “reciprocal-interaction,” which can be modeled by a limit cycle
(McCarley and Massaquoi 1986). In this mechanism, negative feedback from the “REM-off” neurons in the LC/DR when firing is high causes reduction in it’s activity, allowing the inhibition on the “REM-on” group in the LDT/PPT to decrease. As the inhibition from the “REM-off” is decreased, the activity of the “REM-on” increases, stimulating positive feedback to itself. Once LDT/PPT activity has reached a threshold, REM sleep begins. The active “REM-on” population sends excitatory impulses to the “REM-off,” which simultaneously increases in activity level and begins to inhibit the “REM-on” group, ending the REM phase.

**Figure 1:** A) Shows the mutually inhibitory flip-flop model. B) Shows the reciprocal-interaction model for REM-sleep

Many researchers quantify sleep using the REM cycle (REMC), which is defined as the time from the start of one REM period to the beginning of the subsequent one (Feinberg and Floyd 1979). Defining a REM period (REMP) proves a bit trickier. Between 20% and 30% of a sequence of compact REM bouts is comprised of NREM or wake interrupting the REM sleep (Merica and Gaillard 1991), yet most reports state that humans have an average of only 4-6 REM periods per night (Carskadon and Dement 2000). In order to define a REM period, researchers have adopted the fairly arbitrary 15-minute rule, which classifies multiple REM bous as a distinct REM period (also called a REM episode) when followed by 15 minutes of NREM or waking. Through probabilistic analysis, this method has been supported for accurately classifying discrete episodes (Merica and Gaillard 1991) to obtain the 4-6 REM periods per night. Some have also advocated for the use of the NREM cycle (NREMC), defined as the start of stage 2 sleep to the beginning of stage 2 sleep following the subsequent REM period, to quantify sleep. The advantage of the NREMC is that this measure includes the first NREMP for consideration (Feinberg and Floyd 1979). However, many of these studies subtract the intermittent wake during the night when calculating statistics (Feinberg and Floyd 1979, LeBon et al. 2001). New studies are beginning to emphasize the importance of studying the wake bouts for applications as broad as sleep disorder diagnosis and developmental milestones (Arnardottir et al. 2010).

**Figure 2:** Illustration of definitions of REM/NREM cycles and periods (Reproduced from Merica and Gaillard, 1991).

Mathematical models of the patterns in human sleep can help gain insight into the underlying physiology governing the cycling. Phillips and Robinson (2007) developed a model to depict the “flip-flop” between wake and sleep, controlled by the homeostatic and circadian drives. McCarley and Massaquoi (1986) updated the model proposed by McCarley and Hobson of NREM-REM cycling to present the “reciprocal-interaction” through a stable limit cycle, based on the Lotka-Volterra equations for predator-prey interactions. Here, we examine these, as well as a model including both sleep-wake oscillations and the ultradian rhythm, using both the “flip-flop” switch and the “reciprocal-interaction” model (Diniz Behn and Booth 2011). We consider how best to model human sleep, most notably the trends in REM sleep patterning from actual human data.
METHODS

Models:

Mathematical models can help provide insight into the mechanisms and underlying physiology behind human sleep patterns. They also provide suggestions of hypotheses to test experimentally in the lab. Models measure sleep stages by the firing rates, in volts, of the related neuron population. A high firing rate indicates activation of the corresponding population. Because neuron populations exhibit maximum firing rates, as seen from experimentally recorded data, their activity is modeled by logistic equations. Many models are calibrated to represent these physiologically feasible values.

1) Phillips and Robinson (2007):

Phillips and Robinson developed a model for the flip-flop switch between wake and sleep in humans, with parameter values based on experimental sleep data. Three different neurotransmitters are included – the wake-promoting monoaminergic population (MA), the cholinergic population (ACh) of “REM-on” neurons, and the GABAergic signals of the VLPO. Because Phillips and Robinson are primarily modeling sleep and wake transitions instead of the ultradian rhythm, the REM-on/REM-off interactions of the MA and ACh are held as a constant input of ACh to the MA neurons. The flip-flop mutual inhibition between the MA and VLPO means that only one of the two populations is active at a single time, with rapid switches occurring between the two states. Also included in the model are two external forces, both acting on the VLPO, that compose the sleep drive (D). The circadian variable projects from the SCN and the sleep homeostat is measured in somnogenic concentration levels.

The firing rates (Q) of each population (j) are modeled by the following sigmoid:

\[ Q_j(t) = \frac{Q_{\text{max}}}{1 + e^{-\frac{v_j(t)-\theta}{\sigma}}} \]

The equations governing the sleep-wake cycling dynamics are:

\[ \tau_m \frac{dV_m}{dt} + V_m = v_{ma}Q_a + v_{mv}Q_v \]

\[ \tau_v \frac{dV_v}{dt} + V_v = v_{vm}Q_m + D \]

where \( \tau \) is a time constant denoting the response time to switch states and \( v_{jk} \) are the connection parameters describing the effect of population \( k \) on population \( j \).

The sleep drive (D) acting on the VLPO is given by the following:

\[ D = v_{vc}C + v_{vh}H \]

The sleep homeostat (H) is a function of the fairly constant \( Q_m \):

\[ \chi \frac{dH}{dt} + H = \mu Q_m \]

The oscillations of the circadian input are described the sinusoid:

\[ C(t) = \frac{1}{2} \left[ 1 + \cos(\omega t) \right] \]

so that \( \omega \) sets the period of oscillations to a 24-hour day.

Phillips and Robinson constrain their parameters to values that would be physiologically reasonable in humans by considering experimentally recorded values such as maximum neuronal firing rates and thresholds, resting potentials, and
daily sleep lengths in adults. Nominal values were selected from within the realistic ranges. The model with solved using a variable step size Runge-Kutta method.

2) McCarley and Massaquoi (1986):

In their paper, McCarley and Massaquoi present an updated version of their previous model depicting the 90-minute ultradian cycling between REM and NREM sleep. Originally based on the Lotka-Volterra equations modeling predator-prey interactions, the McCarley and Massaquoi model shows the “reciprocal-interaction” between the “REM-on” and “REM-off” neuron populations. The authors name the mPRF neurons as the “REM-on” group, which activates REM sleep. It is now thought that the “REM-on” population is located in the LDT/PPT area, instead. The neurons in the LC and DR are named as the “REM-off” group.

The primary limitation of the first version was the production of different stable solutions for each set of initial conditions. Because biological oscillations tend to remain fairly stable through a variety of initial conditions or external stimuli, the revised model produces a more physiologically realistic limit cycle. To achieve these results, some previously constant coefficients became functions, to more accurately portray phenomena such as a maximum firing rate for neuron populations.

With X representing the “REM-on” population and Y representing the “REM-off” population, the main equations of the McCarley and Massaquoi model are:

\[
X'(t) = a(X) \cdot X \cdot S_1(X) - b(X) \cdot X \cdot Y \\
Y'(t) = -c \cdot Y + d(circ) \cdot X \cdot Y \cdot S_2(Y)
\]

The following sigmoids are used in the main equations. \(a(X)\) represents the positive feedback from the “REM-on” population. \(S_1(X)\) is a sigmoid constraining the firing rate of the “REM-on” population. Using a steep logistic function for \(b(X)\) allows the amount of inhibition on the “REM-on” neurons to be dependent on the activity of the “REM-on” population when \(X\) is very small. Finally, \(S_2(Y)\) constrains the firing rates of the “REM-off” population.

\[
a(X) = a_\text{max} \cdot \frac{1}{1 + e^{-3(X-0.5)}} \\
b(X) = b_\text{max} \cdot \frac{1}{1 + e^{-80(X-0.11)}} \\
S_1(X) = \frac{1}{1 + e^{1.1(X-2.3)}} \\
S_2(Y) = \frac{1}{1 + e^{25(Y-1.9)}}
\]

While the sleep homeostat is not included in this model, the circadian variation over a 24-hour period is represented by \(d(\text{circ})\). \(d_o\) represents the average level of drive input and \(p_o\) determines the phase in the circadian rhythm, so that variations in time of sleep onset can be modeled.

\[
d(\text{circ}) = d_\text{circ} + A \sin[(f \cdot t) + p_\text{circ}]
\]

The model was solved with the Runge-Kutta method of step size 0.05.

3) Diniz Behn and Booth (2011):

The reduced-network model includes populations for wake, NREM, and REM sleep. The model uses the flip-flop switch to produce wake-sleep cycling and the reciprocal interaction to create REM-NREM oscillations. Unlike the McCarley
and Massaquoi model, the autoexcitation of the REM-promoting population and self-inhibition of the wake-promoting LC/DR are ignored. The original model contains five populations: the LC, DR, VLPO, and two subpopulations of the LDT/PPT – REM active and Wake/REM active (Diniz Behn and Booth 2010). The simplified three-population model allows for better analysis of sleep dynamics.

The general form for the firing rate of each population (X=W, N, R) is given by the following equation:

\[
F'_X = \frac{F_{X,\infty}(\sum_i g_{i,X} C_{i,\infty}(F_Y)) - F_X}{\tau_X}
\]

where i represents the neurotransmitters: i=E (noradrenaline), i=G (GABA), or i=A (acetylcholine) and F_Y represents the state promoted by the population that expresses each neurotransmitter, i.

The dynamics of the flip-flop switch and reciprocal-interaction are modeled by these specific equations for each population W, N, R:

\[
F'_W = \frac{F_{W,\infty}(g_{G,W} C_{G,W}(F_N) + g_{A,W} C_{A,W}(F_R)) - F_W}{\tau_W}
\]

\[
F'_N = \frac{F_{N,\infty}(g_{E,N} C_{E,N}(F_W)) - F_N}{\tau_N}
\]

\[
F'_R = \frac{F_{R,\infty}(g_{E,R} C_{E,R}(F_N) + g_{A,R} C_{A,R}(F_R)) - F_W}{\tau_W}
\]

While first developed to model rat sleep, the flexibility of the REM behavior in the model (Diniz Behn and Booth 2011) allowed the parameters to be adjusted to fit an average human sleep pattern of 16 hours of wake followed by 8 hours of sleep (Carskadon and Dement 2000). Parameters were also fit to model four REM periods per night, with an approximate length of 20 minutes. Both original and new values for parameters that were changed from the values given in Diniz Behn and Booth (2011) are listed in Table 1.

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<th>New value (human)</th>
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<td>(g_{G,W})</td>
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<td>-1.68</td>
<td>inhibitory effect of GABA on wake</td>
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<td>excitatory effect of ACh on REM</td>
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<td>-1.3</td>
<td>inhibitory effect of GABA on REM</td>
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<td>(g_{G,N})</td>
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<td>-0.1</td>
<td>autoinhibition of GABA on NREM</td>
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<td>2</td>
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<td>-0.9</td>
<td>half-activation threshold of REM</td>
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<td>sensitivity of response of NREM</td>
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<td>(\tau_{hs})</td>
<td>700</td>
<td>510</td>
<td>sleeping timescale of homeostat</td>
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Table 1: Parameters modeling rat and human sleep. \(g_{i,X}\) are the connection parameters between populations. \(\gamma\) is the sensitivity of release. \(\beta\) is the half-activation threshold. \(\alpha\) describes the sensitivity of response, and \(\tau\) are the timescales of the homeostat.
Data:

76 sleep-scored polysomnogram recordings were received from the Sleep Heart Health Study. In order to study healthy adult sleep, all subjects were ages 18-65, with a recorded sleep time greater than or equal to six hours. All subjects also had a sleep efficiency greater than or equal to 80%, total time in REM sleep greater than or equal to 20 minutes, an RDI (respiratory disturbance index) value less than 5, and a minimum oxygen saturation of greater than 85%.

Each night of sleep was scored in 30-second epochs. Data was imported into Matlab, where it was reduced to only the sleeping period, with one minute of wake on either end. Matlab was also used to calculate statistics on, analyze, and characterize the data.

RESULTS
Models:
1) Phillips and Robinson

The Phillips and Robinson model shows a quick flip-flop switch between sleep and wake. This change is activated by the homeostatic sleep drive, H. The homeostat increases during waking, and initiates the switch to sleep at a certain threshold, after which it decreases until wake begins again. Like typical human sleep, the time spent awake is greater than the time spent asleep.

It can be verified that the homeostatic drive is indeed causing the oscillations between sleep and wake by setting the input of the circadian and homeostatic drives to zero, one at a time. When \( v_{vc} \), the connection parameter between the circadian oscillations and the VLPO is set to zero, the model still shows a fairly regular switches between wake and sleep. In contrast, when \( v_{vh} \), describing the homeostat’s influence on the VLPO, is set to zero, the model no longer includes long-term cycling between the two stages. Instead, the model remains in wake, because there is not a sufficient drive input for the VLPO to activate.

2) McCarley and Massaquoi

The McCarley and Massaquoi model shows the stable cycling between REM and NREM sleep. The amount of time in REM sleep is represented by the area of the higher, orange “REM-on” curve above the maximum height of the smaller,
blue “REM-off” curve. The amount of REM sleep varies with the circadian rhythm, with more REM occurring when the circadian input is at a minimum. Low activity of the SCN occurs during the dark period, as do internal temperature minimums, which have been found to correspond with longer REM periods (Zulley 1980).

The phase plane illustrates the stability of the model for any feasible combination of initial conditions. This means that the model represents stable NREM-REM cycling regardless of what time in the 24-hour cycle the simulation is beginning sleep.

![Phase plane](image)

**Figure 6:** A) The phase plane for the model shows a stable limit cycle. B) The model output depicts the large increase in REM episode duration from the first episode to the second that has been reported (Zulley).

3) **Diniz Behn and Booth**

The original output models rat sleep over the course of 7200 seconds (2 hours), while the human model depicts sleep patterns over 7200 minutes (120 hours or 5 days). Nocturnal rats spend a higher percentage of time in sleep during the light period and spend more time awake while it is dark. In contrast to this polyphasic sleep, humans have, on average, 16 hours of solid waking time, followed by 8 hours spent mostly in sleep (Carskadon and Dement 2000). The rat model shows two REM episodes per cycle of wake, NREM, and REM. The revised human model shows 16 hours of sleep, followed by 8 hours of sleep with 4 REM episodes per night. Graphs of both model outputs are shown below.

![Graphs](image)

**Figure 7:** A) Shows output of reduced model with parameters set to depict polyphasic rat sleep for 7200 seconds (2 hours). B) Output for reduced model on a human timescale. Depicts five 24-hour days of human sleep-wake cycling.

When just the sleep portion of the human model is examined, it can be seen that the firing rates of the VLPO remain high throughout the entire night of sleep. REM sleep is characterized by an activation of the LDT/PPT neurons in addition to an active VLPO. The wake population shows brief activation following each REM period, which is consistent with
the reciprocal-interaction mechanism being modeled, as the “REM-on” population excites the wake-promoting group. The 8-hour sleep period ends in REM sleep, followed by activation of the LC/DR populations.

The durations of the REM bouts in the model are around 20 minutes. This is close to the reported means of 24.8 minutes (Clausen et al. 1974) and 23.2 minutes (Aserinsky 1971). The graph below shows the lengths of the REM durations in the human model throughout the night with the mean durations of successive REM periods in subjects with four REMPs listed in Clausen et al. (1974) and the SHHS data analyzed in this report. While the durations of the REM bouts in the model are roughly the length of reported REM bouts throughout the night, the model fails to show the large increase in duration from the first REM period to the second.

**Figure 8:** Close-up of sleep period in reduced human model. Sleep is characterized by activation of the VLPO, with intermittent activations of the LDT/PPT to produce 4 REM periods.

**Figure 9:** Graph comparing durations of successive REM periods in the model and in the data. Data points were the reported values in Clausen et al. for subjects with 4 REMPs in the night and the mean durations of the first 4 REMPs in the SHHS data.

**Data:**

The mean total sleep time for the 76 recordings was 7.82 hours. The minimum sleep time was 6.35 hours and the maximum was 9.96 hours. Hypnograms depicting the sleep over the course of the night for two different subjects are displayed below. The data shows varying degrees of fragmentation in the REM and NREM sleep, with brief awakenings throughout the night.

**Figure 10:** A) Hypnogram showing one night of sleep. The top represents wake, the middle is NREM, and the bottom is REM sleep. B) Hypnogram for the subject with the most fragmented night of sleep, as calculated by total number of REM bouts.
Three classic measures were used to quantify the human sleep. The mean bout durations, number of bouts, and percent time in each state were calculated. As in LeBon et al. (2001), no minimum length or specific structure was used to restrict what defined a bout. The mean bout durations for wake throughout the night are short (around 2 minutes), as expected. However, the mean duration of NREM bouts ends up being near 12 minutes, much less than the reported values of 50-100 minutes (Clausen et al. 1974), 72-132.5 minutes (LeBon et al. 2001), and 95.2-102.1 minute (Merica and Gaillard 1986). Similarly, the mean REM bout duration is around 11 minutes, still significantly lower than the reported 24.8 minutes (Clausen et al. 1974) or 23.2 minute (Aserinsky 1971). In addition, the mean number of bouts calculations differ from other reported values. Most strikingly, the mean number of REM bouts is near 10, while it is generally reported that there are 4-6 per night (Carskadon and Dement 2000). There are also a very large number of wake bouts during sleep. These differences are a result of high levels of fragmentation in the sleep of some subjects. Most of the characteristics of these fragmentations are not analyzed in papers (Merica et al. 1993). As a result, data was later studied in search of patterns of fragmentation throughout the night, following methods suggested by Merica and Gaillard (1991). While the mean duration and number of bouts show apparent differences when no limitation on bout duration is in place, the percent time spent in each state resembles reported values. Most of the night is spent in NREM sleep, with Carskadon and Dement (2000) reporting 75-80%, comparable with our near 70% calculation. Carskadon and Dement also report that 20-25% of the night is spent in REM sleep, and we calculate near 20%.

Survivor plots for the durations of wake, NREM, and REM bouts throughout the night were also created with data from all 76 subjects. As expected, the wake bout durations for this middle-aged population exhibit a power-law distribution, with mostly very short durations. Similarly, the NREM and REM survivor plots fit an exponential distribution, as is consistent with previous findings in humans and rodents. (Arnadottir et al. 2010). These fits can be seen when the wake bouts are plotted on a log-log plot as a straight line, and as a straight line on semi-log plots for the NREM and REM bouts.

Figure 11: Classic statistics for all 76 subjects. A) Mean bout durations B) Number of bouts C) Percent time in state

Figure 12: Survivor graphs for all 76 subjects. A) Wake plotted on log-log graph B) NREM on semi-log plot C) REM on semi-log plot
In an attempt to develop a standard rule to characterize the fragmented REM bouts into consolidated REM episodes to locate the reported 90-minute ultradian rhythm, the cumulative total time in REM was plotted. Even for the most fragmented data, these stepped graphs showed around 4-6 segments with non-zero slope, indicating a REM episode. By smoothing the curves and setting a threshold for the slope, it would be possible to classify many short, consolidated REM bouts as a full REM episode. After averaging each 30-second epoch with the data three minutes before and following and using a slope cutoff of 0.2, a smooth curve of the slope showed that the subject with 36 individual REM bouts had only 4 full REM episodes.

Another method in which to study the fragmented data is to adopt the 15-minute rule (Feinberg and Floyd 1974), which was verified by Merica and Gaillard (1991). Using the definitions presented in the introduction, the data was divided into NREMCs, REMCs, and REMP S in order to calculate the average number of each and study the nature of the interruptions. The number of complete REMC ranges from one to five, with a mean of 2.91. 94.74% (n=72) of subjects had a second REM cycle, 68.42% (n=52) a third, 22.37% (n=17) a fourth, and only 5.26% (n=4) had a fifth REM cycle. The trend is for the durations of these cycles to decrease with each subsequent cycle. The mean duration of all REM cycles is 90.974, almost exactly the reported 90-minute ultradian rhythm. Using ANOVA, the significance levels of the subsequent REMC durations were calculated and listed in Table 2.
With the 15-minute rule, it was found that the number of REMP s ranges from two to six, with a mean of 3.91. The durations for each successive REMP increase for episodes one through four and decrease for numbers five and six. 17 of the 76 subjects had a fifth REMP, and only 4 had a sixth. The histogram for the durations of REMP s is much broader than the histogram for the duration of REMCs. Like the REMC durations, the significance levels for subsequent REMP durations were calculated using ANOVA and are listed in Table 2.

The three classic statistics for analyzing sleep were also computed on each individual REM period. Because of the varying number of REMP s each data set included, the mean bout duration, number of bouts, and percent in state throughout the REMP were also computed for each subject’s first and last REMP. Significance levels from ANOVA are listed in Table 2.
When the total number of inter-REM bouts was calculated (wake and NREM combined) for all cycles, the number of interruptions in REM sleep increases from cycles 1-4, with a trend towards decreasing for cycles 5 and 6. When the total number of bouts was found for each subject’s first and last REM episode, however, there is a large increase in the amount of fragmentation between the first and last REM periods. Significance values from ANOVA are listed in Table 2.

![Figure 18: A) Mean total number of bouts (wake and NREM) inside each successive REM episode B) Mean total number of bouts (wake and NREM) for each subject’s first and last REM episodes](image)

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<td>Total interruptions REMP 4</td>
<td>Total interruptions REMP 5</td>
<td>0.6204</td>
</tr>
<tr>
<td>Total interruptions REMP 5</td>
<td>Total interruptions REMP 6</td>
<td>0.1455</td>
</tr>
<tr>
<td>Total interruptions first REMP</td>
<td>Total interruptions last REMP</td>
<td>8.116x10^{-5}**</td>
</tr>
</tbody>
</table>

*significant at p=0.05 level
**significant at p=0.01 level

**DISCUSSION**

**Models:**

All three models serve some advantages in recreating the patterns of human sleep. Both the Phillips and Robinson and Diniz Behn and Booth models have been calibrated to represent physiological feasible values. The McCarley and Massaquoi model shows specific outcomes for beginning in any phase of the 24-hour circadian rhythm. Yet still, there are drawbacks to each of the three models.
The Phillips and Robinson equations do not include REM sleep, and is thus unable to model the ultradian rhythm, and the changes in REM sleep throughout the night. This model also fails to allow for any change in outcome depending on the time of sleep onset during the 24-hour day or account for any external stimuli. The McCarley and Massaqoui model only shows dynamics during sleep, and does not depict any interactions with the wake-promoting population. While a stable limit cycle of REM and NREM oscillations is approached, the model continues to switch between these two states, and does not show the switches into and out of sleep.

While the reduced Diniz Behn and Booth model shows the interactions between all three types of populations and includes wake, NREM, and REM, and the sleep homeostat, the circadian drive is absent in the model. Thus, this model fails to portray the effect of the 24-hour circadian rhythm on sleep patterns. One outcome of this is the patterning of the REM sleep. While the durations of the REM episodes in the model remain fairly constant, the trend in the data is for REM episode duration to increase throughout the night, likely as a result of internal temperature governed by the circadian rhythm. Including a sinusoid with a 24-hour period to represent the circadian variation throughout a day could allow the REM episodes in the model output to increase in duration throughout the night. On the other hand, the data does not show four consolidated REM periods as the model suggests. Further work to improve the model could depict the fragmentations of REM sleep that occur throughout the night. These interruptions in the REM sleep could be fit to patterns of frequency and character found in the data.

Data:

The sleep of 76 healthy participants from the SHHS study is fairly representative of trends reported in the literature. The survivor plots for NREM and REM bout durations fit an exponential distribution, as was found in Arnadottir et al. (2010). This same study reported that for a population of healthy adults ages 34 to 56, the wake bout distributions resembled a power-law distribution, but at older ages, the survivor plot was more exponential in character. The wake bouts were not significant for either distribution in the younger populations (Arnadottir et al. 2010). Because our age range (18-65) is much larger than the range reported to exhibit a power-law distribution, yet is centered near this interval, we might hypothesize that the transition into and out of a power-law type distribution is gradual, meaning that most different patterns of waking will occur in the extremities of age range – newborns and the elderly, neither of which are represented in the data set.

Our reported mean number of REM cycles is 2.91. The mean number of NREM cycles is 3.91. Since the REM cycle as a measure always omits the first NREM episode and last REM episode, the number of NREMCs is always less than the number of REMCs. This value is slightly lower than reported values of 4.1, 4.3, and 4.6 NREMCs for healthy populations (Merica et al. 1993). However, many of these same papers acknowledge the large variations in sleep patterns among individuals (Feinberg and Floyd 1979, Clausen et al. 1974, Le Bon et al. 2001). With a sample size of only 76, it is possible that a higher proportion of these subjects had fewer REM cycles than average. Clausen et al. (1974) also reports, however, that even with a small sample size, the mean cycle lengths are fairly consistent. The mean duration across all REMCs is 90.974, very close to the 90-minute ultradian rhythm. Although Feinberg and Floyd (1979) reported a significant umbrella-shaped curve for REMC durations throughout the night, Clausen et al. (1974) reported insignificant changes in subsequent REMC durations and Le Bon et al. (2001) showed a monotonic decrease in cycle durations throughout the night. The SHHS
data showed that only the decrease in duration from REMC 1 to REMC 2 was significant. Subsequent comparisons, as well as the first and last REMC durations were not significant at the 0.05 confidence level.

Similarly, the mean number of REM periods of 3.91 is slightly less than the average of 4-6 (Carskadon and Dement 2000), which could also be attributed to variation among individuals. However, the mode of the data is 4 REMP, and many others report that the most subjects had a fourth REMP (Claussen et al. 1974, Feinberg and Floyd 1979). Although the histogram for REMP durations shows a large variation in REMP length, the trends across the day for successive REMPs clearly show an umbrella-shaped curve. The most widely reported pattern in REMP durations is the large increase in length from REMP 1 to REMP 2 (Claussen et al. 1974, Zulley 1980, Carskadon and Dement 2000, Terzano et al. 2005). The difference in duration from REMP 1 to REMP 2 was significant at the 0.01 confidence level. The further increases from REMP 2 to REMP 3 and REMP 3 to REMP 4 were insignificant. The decreases in duration to REMP 5 and REMP 6 were both significant at the 0.05 level. Because many subjects have a fourth REM cycle, but much fewer include a fifth, some researchers only study the first four REMCs, and thus only look at the first four REMPs (Merica and Gaillard 1991). The increase in durations for the first four REMPs, including the significant increase from REMP 1 to REMP 4 is consistent with results presented in these studies. Although the subsequent decrease in REMP durations for episodes five and six were significant, no assumptions about general behavior can be made due to the small sample size of subjects with five and six REMPs. Even within published results including these later episodes, results vary. Claussen et al. (1974) reports insignificant changes in REMP durations after the second episode, while Aserinsky (1969) found a decrease in durations during the second half of the night and Terzano et al. (2005) found an increase in length from REMP 1 to REMP 4, followed by a shorter REMP 5.

Perhaps including a larger number of data sets with five and six REMPs could confirm or contradict these findings.

While computing the mean bout durations, number of bouts, percent in each state, and creating survivor curves gives some insight into the characteristics of a night of sleep, it doesn’t paint the complete picture. In all actuality, the reported 90-minute ultradian rhythm (Carskadon and Dement 2000) is hidden beneath many consolidated, fragmented REM bouts. As our data shows, with a mean value of 10.61 REM bouts per night, even a healthy human’s night of sleep in interrupted by many brief awakenings or entrances into NREM. Not frequently studied, perhaps these interruptions into the smooth cycling patterns depicted in the models could provide more insight into the mechanisms governing sleep state. Simply using the 15-minute rule alone to analyze patterns in human sleep throughout the night does not allow for this more in-depth analysis.

Calculating the basic quantifying statistics on each REMP helps to characterize the patterns of the fragmentation over the course of the night. These measures were calculated as the means of each subject’s first and last REMP, since a fourth REMP may be the last episode for some subjects, but may be in the middle of the night for others, and thus may have different characteristics. The mean bout durations shows that wake interruptions are shorter than the NREM interruptions. The mean duration of REM bouts increases throughout the night, indicating either fewer fragmentations or longer REM episodes. The number of bouts shows a very significant increase in the number of intermittent wake bouts between the first and last REM episode. The increase in number of NREM interruptions is also significant. While the percent of each REM episode spent in NREM does not change significantly, the percent spent in wake increases at a 0.01 confidence level from the first to the last episode. This increase in the amount of wake is hypothesized to be due to the increasing pressure to wake near the end of the night as a result of the circadian rhythm (Merica and Gaillard 1991). By analyzing the
total number of interruptions (wake and NREM) throughout the night, it can be seen that sleep becomes more fragmented from the first to the last REM episode. This could also be due to the increased propensity for the wake population to activate, as the increased durations of REM sleep provide increased stimulation to the wake population, according to the reciprocal interaction theory (McCarley and Massaquoi 1986).

Because not much work has been done to study the characteristics of the fragmentation of human sleep throughout the night, future work should include modeling these rarely represented ideas. A model of wake, NREM, and REM sleep in humans could be modified to include fragmentation of the REM sleep. This patterning would aim to depict the increased proportion of wake as the night progresses, as well as the increase in total number of interruptions. By more accurately modeling a night of human sleep, new hypothesis can be created to test experimentally. Most significantly, by creating a more accurate representation of typical REM sleep, the mechanisms of REM sleep generation and cessation can be better investigated, perhaps leading to more information on topics such as the role of REM sleep in memory, mental health disorders, and development.

REFERENCES


