REM Sleep and Thermoregulation

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Abstract

Mammalian body temperature changes in conjunction with circadian rhythm, but the link between body temperature and sleep cycles remains unclear. In the following paper, we investigate the hypothesis that the purpose of the REM/NREM differentiation is thermoregulation. We build a model of the body’s environmental heat loss, metabolic heat gain, and thermoregulatory efforts, coupled with the likelihood of switching between REM and NREM sleep states. By fitting an appropriate probability density function to experimental data and performing simulations in MATLAB, we explore the relative importance of temperature regulation versus other factors in switching sleep states.

1 Introduction

We all sleep. Why is that?

The biological purpose of sleep is one of the greatest remaining mysteries of science. Schmidt recently advanced the hypothesis that sleep is a form of optimal task scheduling. Organisms sleep to perform energy-intensive cellular maintenance and restoration tasks, during periods when it would be suboptimal for the organism to pursue other tasks. A subhypothesis is that Rapid Eye Movement (REM) sleep is a way for the body to increase available energy for central nervous system functions, by temporarily shutting down energy-intensive thermoregulatory tasks.

If true, this would mean that the cycle between REM sleep and non-REM (NREM) sleep is governed, in part, by thermoregulatory needs. We know that when the body enters REM sleep, thermoregulation shuts down, and core body temperature begins to drift away from its optimal point, as determined by the body’s circadian rhythm. When this temperature drifts too far, the body should shift from REM sleep back to NREM, restoring thermoregulation until the temperature is once again close enough to optimum to allow a return to REM sleep, etc., until the organism wakes.

In section 2, we build a crude model relating core body temperature and sleep state, with weighting parameters that indicate the relative dominance of body temperature versus other random effects in determining the shift to and from REM sleep. A discussion of parameter values follows in section 3. We fit this model to available data on average REM/NREM cycle time in rats and humans, respectively, in sections 4 and 5. We numerically fit parameters in MATLAB, and run simulations to illustrate our results in section 6. Section 7 contains a discussion the implications of our results on the importance of temperature regulation in switching between REM/NREM sleep.

2 Model Setup

We will use two primary variables: \( T(t) \), core body temperature, and \( S(t) \), sleep state. \( T(t) \) is a continuous real number, while \( S \) is a boolean, with \( S(t) = 1 \) meaning the body is in REM sleep and \( S(t) = 0 \) meaning it is in NREM sleep.

We begin with the differential equation describing the change in the body’s total heat \( Q \). We can describe changes in the body’s heat as deriving from three sources:

\[
\frac{dQ}{dt} = \left( \frac{dQ}{dt} \right)_{\text{env}} + \left( \frac{dQ}{dt} \right)_{\text{reg}} + \left( \frac{dQ}{dt} \right)_{\text{met}},
\]

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where the subscript “env” denotes heat flow to and from the ambient environment, the subscript “reg” denotes the body’s thermoregulatory efforts, and the subscript “met” denotes the body’s metabolic heat production. We calculate each term above explicitly.

First, let $T_a$ be the ambient environmental temperature, and let $K$ be the heat flow per degree Celsius of temperature difference. Then heat loss to the environment is given by

$$\left(\frac{dQ}{dt}\right)_{env} = -K(T(t) - T_a).$$

Second, assume that $T_a$ lies within the range of temperatures for which the animal (be it rat or human) can thermoregulate. Then we can describe the thermoregulatory effort as a linear function of $T$ and $T_o(t)$, the body’s optimum temperature according to the circadian rhythm. Let $H$ be the rate of heat production per degree Celsius difference between body temperature and optimal temperature; then the thermoregulatory heat production is given by

$$\left(\frac{dQ}{dt}\right)_{reg} = (1 - S)H(T_o(t) - T(t)).$$

Finally, we assume that the metabolic heat production is constant (for rats and humans individually):

$$\left(\frac{dQ}{dt}\right)_{met} = Q_{met}.$$ 

This gives us

$$\frac{dQ}{dt} = -K(T(t) - T_a) + (1 - S)H(T_o(t) - T(t)) + Q_{met}. \quad (1)$$

We then divide equation (1) by the body’s heat capacity, $H_c$, to obtain a differential equation describing the change in body temperature:

$$\frac{dT}{dt} = -k(T(t) - T_a) + (1 - S)h(T_o(t) - T(t)) + P_{met}, \quad (2)$$

where

$$k = \frac{K}{H_c}, \quad h = \frac{H}{H_c}, \quad P_{met} = \frac{Q_{met}}{H_c}.$$ 

Next, we describe the change in $S$. We assume that the probability of $S$ flipping from one state to another is a time-varying exponential distribution, where $\lambda_0(t)$ is the hazard rate of flipping from NREM to REM and $\lambda_1(t)$ is the rate of flipping from REM to NREM. That is,

$$\lambda_S(t) = \lim_{\Delta t \to 0} \frac{\mathcal{P}(S \text{ switches in } [t, t + \Delta t] | S \text{ has not switched in } [0, t])}{\Delta t}. \quad (3)$$

We can rewrite equation (3) as

$$\lambda_S(t) = \lim_{\Delta t \to 0} \frac{\mathcal{P}(S \text{ switches in } [t, t + \Delta t] \text{ and has not switched in } [0, t])}{\mathcal{P}(S \text{ has not switched in } [0, t])} = \frac{\text{PDF}(t)}{1 - \text{CDF}(t)} = -\frac{d}{dt} \log(1 - \text{CDF}(t)).$$

We will assume that $\lambda_1(t)$ is given by:

$$\lambda_1(t) = \alpha_1(T_o(t) - T(t)) + \gamma_1,$$

where $\alpha_i$ denotes the degree to which the probability of changing state depends on the deviation of the body’s core temperature from optimum, and $\gamma_i$ denotes the degree of independent random chance. We will assume that $\lambda_0(t)$ is given by:

$$\lambda_0(t) = \alpha_0(T_o(t) - T(t))^{-1} + \gamma_0$$

3 Parameters

Rodriguez-Gironés shows that the parameter $k$ is $\frac{1}{R}$, where $C$ is thermal capacitance (or specific heat capacity of an animal times its mass) and $R$ is thermal resistivity. Noting that thermal resistivity is the reciprocal of the the heat-transfer coefficient times surface area, we were able to compute the parameter $k$ by finding values for specific heat capacity, heat-transfer coefficients, body mass, and surface area. We found the following values for those parameters: specific heat capacity of the human body is $3490 \, J/(kg \cdot ^\circ C)$, the heat-transfer coefficient (radiative) is $4.5 \, W/(m^2 \cdot ^\circ C)$, average surface area of a human male is $1.91m^2$ (female $1.71m^2$), and average body mass is $80.7kg$. For rodents, Rodriguez-Gironés gives the values $C = 686.2J/^\circ C$ and $R = 1.14\, CW^{-1}$. The above values imply $k = 4.5 \times 10^{-1}s^{-1} = 3.05 \times 10^{-5}s^{-1}$ for humans and $k = 1.28 \times 10^{-3}$ for rodents.
Experimental data was used to calculate the heat production rate, $h$, for humans and rats. Frank et al. [3] monitored core body temperature in males between ages 20 and 22 after cooling via an intravenous saline solution. From this data, the computed $h$ for humans is $2.98 \times 10^{-4}$ per second. A study by Skidmore et al. [14] provided the data for rats; core body temperature of rats were tested in a cool environment at rest. Here the computed $h$ for rats is $2.0 \times 10^{-4}$ per second. The same study gave numerical data for rats in a heated environment indicating a much more rapid rate of return to optimal body temperature following heat challenge [14]. Due to most thermoregulatory processes being suspended during REM sleep [8], body temperature would naturally decrease to a suboptimal temperature. As a result, our model only takes the cooled case into consideration. A more complete model would include cases where the body temperature is above the optimal temperature suggested by a rat’s circadian cycle.

Parameter $P_{met}$ is the resting metabolic rate. To calculate this parameter for humans and rodents, we used Kleiber’s law, $P_{met} = 70 m^{-2/3}$. We found that for humans, $P_{met} = 6.7305 \times 10^{-3}$ while for rodents $P_{met} = 2.7126 \times 10^{-2}$. Szymusiak and Satinoff [15] describe changes in REM sleep durations in rats as the ambient temperature, $T_a$, which ranges from 23-33°C. We use a broader range of 21-33°C for both humans and rodents.

The circadian modulated body temperature function for humans,

$$T_o(t) = 36.7 + 0.5 \sin t,$$

approximates the experimental data from the following figure:

![Figure 1: Changes in body temperature with respect to time of day, including sleep and wake periods. Adapted from [6].](image)

Although this curve will not accurately describe the overall circadian rhythm for humans, it accurately describes the portion of it occurring during sleep for the average human in a laboratory study.

For rats, optimum temperature lies between 36 and 38 °C [1] and we assume that the rat REM/NREM cycle is short enough that the circadian modulation temperature can be ignored so that $T_o$ is assumed constant.

We use $\mu_r, \mu_n$ to denote the mean and $\sigma_r, \sigma_n$ to denote the standard deviation of the length of a REM or NREM state. We obtain these values in humans from [7], and in rats from [12].
REM/NREM Cycling in Rats

REM/NREM cycles in rats are typically very brief, so we will assume that \( T_o(t) = T_o \) is constant. We will assume that the rat enters REM sleep at \( T(0) = T_o \), and that it enters NREM sleep at the body temperature it has at the end of REM sleep. Then, if we hold \( S(t) \) constant, we can rewrite equation (2) to obtain:

\[
\frac{dT}{dt} = -(k + (1 - S)h)T(t) + kT_a + (1 - S)hT_o + P_m.
\]

This is a standard ODE which can be solved to obtain:

\[
T(t) = a_se^{-bst} - c_S,
\]

where

\[
a_S = T(0) + \frac{kT_a + (1 - S)hT_o + P_m}{k + (1 - S)h},
\]

\[
b_S = k + (1 - S)h,
\]

and

\[
c_S = \frac{kT_a + (1 - S)hT_o + P_m}{k + (1 - S)h}
\]

Note that, since we assume \( T(0) = T_o \) for \( S = 1 \), \( a_1 = c_1 + T_o \). We then obtain the hazard function for switching \( S \) from 1 to 0:

\[
-\frac{d}{dt} \log(1 - \text{CDF}_1(t)) = \lambda_1(t) = \alpha_1T_o - \alpha_1a_1e^{-b_1t} + \alpha_1c_1 + \gamma_1 = \alpha_1a_1(1 - e^{-b_1t}) + \gamma_1
\]

(4)

We integrate equation (4) to obtain log(1 − CDF1(t)):

\[
\log(1 - \text{CDF}_1(t)) = \int_0^t \lambda_1(t')dt' = -\frac{\alpha_1a_1}{b_1}e^{-b_1t} + (-\alpha_1a_1 + \gamma_1)t
\]

(5)

Then, by taking the exponent of both sides of equation (5) we obtain:

\[
\text{CDF}_1(t) = 1 - \exp\left(-\frac{\alpha_1a_1}{b_1}e^{-b_1t} + (-\alpha_1a_1 + \gamma_1)t\right)
\]

(6)

The probability density function can be obtained by differentiating both sides of equation (6):

\[
\text{PDF}_1(t) = (\alpha_1a_1(1 - e^{-b_1t}) - \gamma_1) \exp\left(-\frac{\alpha_1a_1}{b_1}e^{-b_1t} + (-\alpha_1a_1 + \gamma_1)t\right)
\]

(7)

The hazard function for switching \( S \) from 0 to 1:

\[
-\frac{d}{dt} \log(1 - \text{CDF}_0(t)) = \lambda_0(t) = \frac{\alpha_0}{T_o + c_0} (1 - d_0e^{-b_0t})^{-1} + \gamma_0
\]

(8)

\[
d_0 = \frac{\alpha_0}{T_o + c_0}
\]
We integrate equation (12) to obtain:

$$\log(1 - \text{CDF}_0(t)) = -\frac{\alpha_0}{b_0a_0} \log \left( \frac{1 - d_0e^{-bt}}{1 - d_0} \right) - \gamma_0 t$$  \hspace{1cm} (9)

And therefore:

$$\text{CDF}_0(t) = 1 - \exp \left( -\frac{\alpha_0}{b_0a_0} \log \left( \frac{1 - d_0e^{-bt}}{1 - d_0} \right) - \gamma_0 t \right)$$

$$= 1 - \left( \frac{1 - d_0e^{-bt}}{1 - d_0} \right)^{-\alpha_0/b_0a_0} e^{-\gamma_0 t}$$

And derive to obtain the probability density function:

$$\text{PDF}_0(t) = \left( \frac{1 - d_0e^{-bt}}{1 - d_0} \right)^{-\alpha_0/b_0a_0} e^{-\gamma_0 t} \left( \frac{\alpha_0 d_0}{a_0(e^{bt} - d_0)} + \gamma_0 \right)$$

We know the values of the constants other than $\alpha_S$ and $\gamma_S$. We fit $\alpha_S, \gamma_S$ to the observed empirical data by picking arbitrary starting values, calculating the expected value and standard deviation of the state-switching time numerically, and then calculating the error between the theoretical values and the experimental values, and minimizing the error.

### 5 REM/NREM Cycling in Humans

For humans, REM/NREM cycles are relatively long, so that $T_o(t)$ will vary. Based on the figure in [?], we will approximate $T_o(t)$ during sleep by:

$$T_o(t) = 36.7 + 0.5 \sin t$$  \hspace{1cm} (10)

We will normalize so that $t = 0$ corresponds to the time when we enter our current sleep state, so that equation (10) becomes

$$T_o(t) = 36.7 + 0.5 \sin(t + t_0).$$

Then, when we are in a single sleep state, we can rewrite equation (11) to obtain

$$\frac{dT}{dt} = -a_S T(t) + b_S \sin(t + t_0) + c_S.$$  \hspace{1cm} (11)

$$a_S = k + (1 - S)h$$

$$b_S = 0.5(1 - S)h$$

$$c_S = kT_a + P_{\text{met}} + 36.7(1 - S)h$$

We solve equation (11) to obtain

$$T(t) = -d_S (\cos(t + t_0) - a_S \sin(t + t_0)) + e_S e^{-a_s t} + \frac{c_S}{a_S}$$

$$d_S = \frac{0.5(1 - S)h}{1 + (k + (1 - S)h)^2}$$

$$e_S = T(0) + d_S(\cos t_0 - a_S \sin t_0) - \frac{c_S}{a_S}$$

Then our hazard function for $S$ transitioning from 1 to 0 is

$$-\frac{d}{dt} \log(1 - \text{CDF}_1(t)) = \alpha_1 (g_1 + d_1 \cos(t + t_0) + (0.5 - a_1 d_1) \sin(t + t_0)) - e_1 e^{-a_1 t} + \gamma_1$$  \hspace{1cm} (12)

with

$$g_S = 36.7 - \frac{c_S}{a_S}$$

If we integrate equation (12) we obtain

$$\log(1 - \text{CDF}_1(t)) = -\alpha_1 d_1 \sin(t + t_0) + \alpha_1 (0.5 - a_1 d_1) \cos(t + t_0) - \frac{\alpha_1 e_1}{a_1} e^{-a_1 t} - (\gamma_1 + \alpha_1 g_1)t - q_1$$  \hspace{1cm} (13)

$$q_S = -\alpha_S d_S \sin t_0 + \alpha_S (0.5 - a_S d_S) \cos t_0 - \frac{\alpha_S e_S}{a_S}$$
And from equation (13), we obtain the cumulative density function:

\[
\text{CDF}_1(t) = 1 - \exp \left( -\alpha_1 d_1 \sin(t + t_0) + \alpha_1 (0.5 - \alpha_1 d_1) \cos(t + t_0) - \frac{\alpha_1 e_1}{a_1} e^{-\alpha_1 t} - (\gamma_1 + \alpha_1 g_1) t - q_1 \right)
\]  \hspace{1cm} (14)

And then derive this to obtain the probability density function:

\[
\text{PDF}_1(t) = -\exp \left( -\alpha_1 d_1 \sin(t + t_0) + \alpha_1 (0.5 - \alpha_1 d_1) \cos(t + t_0) - \frac{\alpha_1 e_1}{a_1} e^{-\alpha_1 t} - (\gamma_1 + \alpha_1 g_1) t - q_1 \right) \\
\times \left( -\alpha_1 d_1 \cos(t + t_0) - \alpha_1 (0.5 - \alpha_1 d_1) \sin(t + t_0) + \alpha_1 e_1 e^{-\alpha_1 t} - (\gamma_1 + \alpha_1 g_1) \right)
\]  

Then, we repeat the process with the hazard function for \( S \) switching from 0 to 1:

\[
\log(1 - \text{CDF}_0(t)) = \int_0^t \left( \alpha_0 \left( g_0 + (0.5 + a_0) \sin(t' + t_0) + d_0 (\cos(t' + t_0) + e_0 e^{-a_0 t'}) \right)^{-1} + \gamma_0 \right) dt'
\]  \hspace{1cm} (15)

\[
\text{CDF}_0(t) = 1 - \exp \left( \int_0^t \left( \alpha_0 \left( g_0 + (0.5 + a_0) \sin(t' + t_0) + d_0 (\cos(t' + t_0) + e_0 e^{-a_0 t'}) \right)^{-1} + \gamma_0 \right) dt' \right)
\]

\[
\text{PDF}_0(t) = -\exp \left( \int_0^t \left( \alpha_0 \left( g_0 + (0.5 + a_0) \sin(t' + t_0) + d_0 (\cos(t' + t_0) + e_0 e^{-a_0 t'}) \right)^{-1} + \gamma_0 \right) dt' \right) \\
\times \left( \alpha_0 \left( g_0 + (0.5 + a_0) \sin(t' + t_0) + d_0 (\cos(t' + t_0) + e_0 e^{-a_0 t'}) \right)^{-1} + \gamma_0 \right)
\]

6 Results

In order to find appropriate values of \( \alpha \) and \( \gamma \) for both humans and rats in both REM and NREM we used the known parameter pairs \((\mu_r, \sigma_r)\) and \((\mu_n, \sigma_n)\). We formulated a MatLab code using the optimization package, fmincon, which give proposed values of \( \alpha \) and \( \gamma \) the output was the corresponding \( \mu \) and \( \gamma \) which we could compare to the parameter values described in the section 3 paper. Unfortunately due to the complexity of the NREM Human PDF we were unable to ascertain any data on this part of the formulation. Meanwhile, we were able to find values of \( \alpha \) and \( \gamma \) for the other cases, along with corresponding error percentages display the following table. We can note that in each case the \( \alpha \) is larger than the \( \gamma \) by at least a few order of magnitude. Hence, using also the fact that the most temperature can reasonably deviate from optimal temperature is 10°C before death, we can ascertain that the \( \alpha \) carries a higher weight within the model.

<table>
<thead>
<tr>
<th>Type</th>
<th>Parameter</th>
<th>REM (sec)</th>
<th>NREM (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodents</td>
<td>( \alpha )</td>
<td>0.001236052279503</td>
<td>0.013508551511742</td>
</tr>
<tr>
<td></td>
<td>( \gamma )</td>
<td>4.97005×10^{-7}</td>
<td>0.000379986258318</td>
</tr>
<tr>
<td></td>
<td>( \mu )</td>
<td>111.23 (5.8% error)</td>
<td>4.91027×10^{4} (0.44056% error)</td>
</tr>
<tr>
<td></td>
<td>( \sigma )</td>
<td>59.6 (40% error)</td>
<td>1.59363×10^{3} (0.99073% error)</td>
</tr>
<tr>
<td>Humans</td>
<td>( \alpha )</td>
<td>2.46×10^{-6}</td>
<td>in progress</td>
</tr>
<tr>
<td></td>
<td>( \gamma )</td>
<td>0</td>
<td>in progress</td>
</tr>
<tr>
<td></td>
<td>( \mu )</td>
<td>953.08 (15% error)</td>
<td>in progress</td>
</tr>
<tr>
<td></td>
<td>( \sigma )</td>
<td>500.59 (7% error)</td>
<td>in progress</td>
</tr>
</tbody>
</table>

Simulations were performed using MATLAB. For any given set of parameters we can simulate the length of REM and NREM periods for any amount of time (typically for rodent simulations we used 30 minutes or 1 hour). For the found rodent \( \alpha \) and \( \gamma \) values, the simulations gave an average length of REM and NREM cycles that were consistent with the observed data (see figure above for an example).
7 Discussion

Our results show a tentative correlation between REM/NREM cycle time and thermoregulatory needs. However, there is much more work to be done before the results can be considered conclusive.

First, we need of a full distribution of REM/NREM cycle times, rather then just mean and standard deviation. This would allow us to fit many more parameters than we have so far.

Additionally, our parameter values, specifically NREM mean and standard deviation for rats should be updated to reflect a more realistic situation.

Upon reflection we need to reconsider the formulation of our $\lambda$ values, and determine a specific method to verify if we have found realistic $\alpha$ and $\gamma$.

In particular, it is possible that REM/NREM cycle times are controlled by an internal clock set to some “default time”, and the apparent link to thermoregulation is illusory, with the change in $T_o(t) - T(t)$ serving as a proxy for this effect. In a future, enhanced version, we would replace our $\lambda_i(t)$ with functions of the form:

$$\lambda_i(t) = a_i |T_o(t) - T(t)|^\delta_i + \beta_i(t - t_0) + \gamma_i$$

In addition, our code at present compares the first cycle time, with temperature starting at the Circadian optimum, to the average cycle time. In a future enhanced version, we would iterate sleep cycles multiple times and take the average, using multiple starting temperatures and multiple ambient temperatures.

Finally, to fully implement the model for human REM/NREM cycles, we need to build a better optimizing function, that is able to handle integrals of non-elementary functions.

Nonetheless, we think that our current results are promising, and indicate the value of further work in this area.
References


