university of groningen / faculty of science and engineering / mathematics and applied mathematics

Sleep-wake Models

Bachelor's Project Mathematics

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Student: B. Bhikha

First supervisor: Prof.dr. H. Waalkens

Second supervisor: Dr. A.E. Sterk

External supervisor: Dr. I. Hoveijn

Abstract

The research in this paper aims to explore two sleep-wake models, namely the two-process model and an improved version of this model called the Phillips and Robinson (PR) model. The two-process model is comprised of two processes whereas the PR model involves three processes. For both models, we examine and graphically illustrate each of the individual processes. We mathematically analyse the differences between these two models and compare them to highlight their similarities whilst showcasing how they are related. This is demonstrated using the theory of "Slow-Fast Systems" where we study the dynamics of the respective subsystems, specifically the slow manifold and the layer problem.

Contents

1 Introduction

Sleep plays a vital role regarding our overall health and well-being [1] and in this paper we will explore this theme by studying the processes that occur in the brain during sleep and during wake. We can study this concept by analysing various sleep-wake models and we will discuss two of these models, specifically the two-process model and the Phillips and Robinson (PR) model.

The two-process model was introduced by Alexander A. Borbély and had a substantial influence on the research done for other sleep-wake models such as the PR model [2, p. 2]. The two-process model involves the homeostatic process and the circadian process which interact with one another to modulate sleep. The homeostatic process controls the sleep pressure whereas the circadian process guides the sleep pressure on when to transition from sleep to wake and from wake to sleep. However, the two-process model struggles to relate to the processes that occur in the body [3, p. 1], whilst the PR model does not have this problem. Thus, the PR model is an improved model which is made up of three processes. This includes, the neurons in the brain that stimulate wake, the neurons in the hypothalamus part of the brain that stimulate sleep and lastly, the process that allows us to shift from wake to sleep and vice versa [3, p. 2].

In this paper, we will analyse these two models intensively and graph their respective processes against time. Furthermore, we will show how the two-process model and the PR model are related so that we are able to accurately make a comparison between them.

2 Two-Process Model

The two-process model is a one-dimensional map comprised of the interactions between two procedures, namely the homeostatic process and the circadian process, hence the fitting name. Based on [3], it is stated that the homeostatic process is also known as a relaxation oscillator where ”sleep pressure” increases when a person is awake and releases during sleep. On the other hand, when we reach the upper threshold of sleep pressure, we transition from wake to sleep and when we reach the lower threshold of sleep pressure, we shift from sleep to wake. This means that when sleep pressure rises to a certain high level, a person will fall asleep and when it drops to a specific low level, a person will awaken. These threshold levels are regulated by a circadian oscillator and this is recognised as the circadian process.

When analysing the homeostatic process, we consider a homeostatic pressure $H(t)$ which is a function of time t. Sleep pressure cannot increase perpetually, thus we choose an exponential function of t which converges to an upper threshold as t goes to infinity. Therefore, when homeostatic pressure increases during wake, we have that,

$$H(t) = \mu + (H_0 - \mu)e^{(t_0 - t)/\chi_W} \tag{2.1}$$

Similarly, sleep pressure cannot decrease endlessly thus we assume that the homeostatic pressure decreases exponentially. Therefore, we select an exponential function that converges to a lower threshold as time goes to infinity. Hence, when homeostatic pressure decreases during sleep, we have that,

$$H(t) = H_0 e^{(t_0 - t)/\chi_S} \tag{2.2}$$

To fully understand the proposed formulae, we establish what the parameters indicate. The variable H_0 represents the starting sleep pressure and μ represents the 'upper asymptote' which is the bound that the homeostatic pressure reaches when there is no shift to sleep. In addition, there is also a 'lower asymptote' which is simply given as zero. Furthermore, we have that t_0 is the starting time, χ_W determines the increase in speed whilst χ_S determines the decrease in speed [3].

If we look at the graphs of the homeostatic process, we notice how sleep pressure differs during wake versus sleep. It must be noted that μ is indicated with a red dotted line in Figure 1.

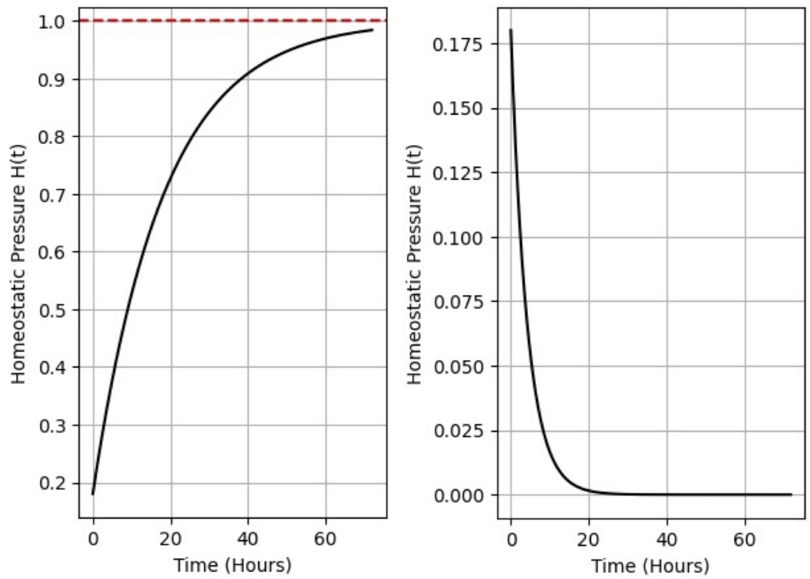


Figure 1: Sleep pressure during wake (left) and sleep pressure during sleep (right)

When studying the circadian process, we explore what happens to the homeostatic pressure $H(t)$ when we shift from wake to sleep and from sleep to wake. When we go from wake to sleep, $H(t)$ will reach the upper threshold $H^+(t)$ and when we go from sleep to wake, $H(t)$ will reach the lower threshold $H^-(t)$. These thresholds are given by the following formula [3, p. 2].

$$H^+(t) = H_0^+ + aC(t) \tag{2.3}$$

$$H^-(t) = H_0^- + aC(t) \tag{2.4}$$

For their respective formulae, H_0^+ and H_0^- represent the mean value and a is a simply a constant representing the amplitude whilst the circadian process itself is denoted by $C(t)$ which is classified as a periodic function of period 24 hours. The circadian process can be given by a simple formula, namely $C(t) = \sin(\omega(t-\alpha))$ where $\omega = (2\pi/24)\ hrs^{-1}$ and α represents the distance from the circadian maximum. The upper and lower thresholds are given by $C(t)$ when it has been shifted and scaled, thus we observe the red lines placed every 24 hours in Figure 2 show that $C(t)$ is indeed periodic.

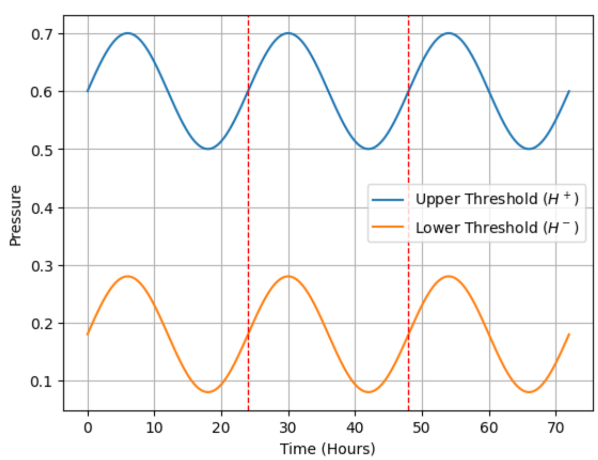


Figure 2: Upper Threshold ($H_0^+ = 0.6$) and Lower Threshold ($H_0^- = 0.17$)

Combining the homeostatic process with the circadian process results in the two-process model. To fully grasp the concept of the two-process model, we can graphically analyse this model for different values of H_0^+ whilst keeping H_0^- constant. By evaluating Figures 3, 4 and 5, the total homeostatic pressure, H, changes direction when it reaches either the upper limit or the lower limit such that there is no activity beyond both thresholds. In these diagrams, we identify where sleep begins and that is when we reach the various peaks of H. When the total pressure drops till the lower limit, this is where sleep is experienced and eventually, H increases again during wake. For a decreased upper threshold, there are more frequent sleep-wake cycles as we reach the sleep threshold more often. For an increased upper threshold, there are less sleep-wake cycles as we reach the sleep threshold fewer times due to a slower increase in the build up of sleep pressure. This can be noticeably seen in Figures 3, 4 and 5 (see Appendix B.1 for parameter values).

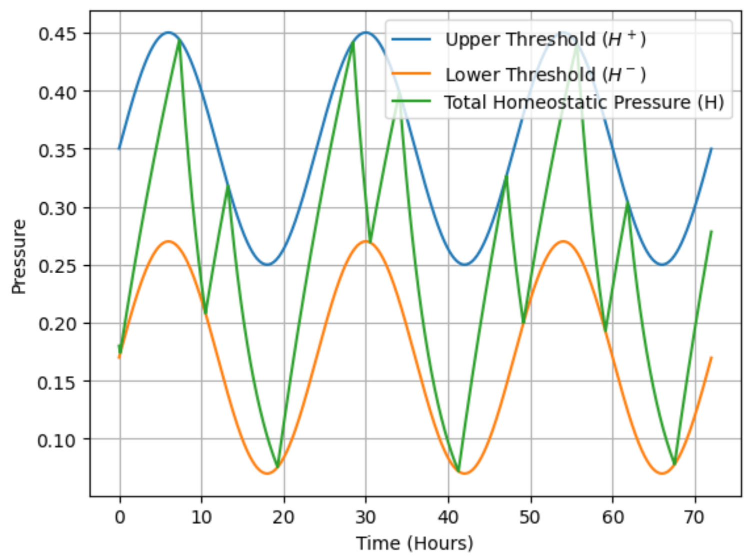


Figure 3: Two-process model with upper threshold $H_0^+ = 0.35$

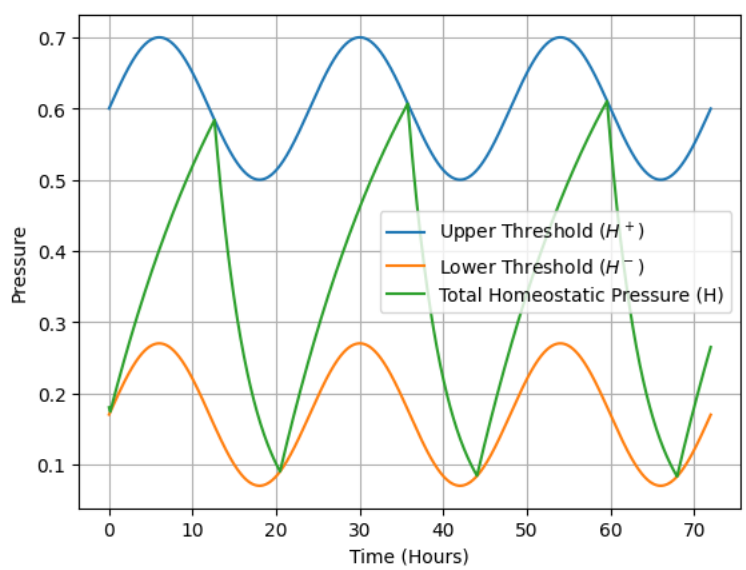


Figure 4: Two-process model with upper threshold $H_0^+ = 0.6$

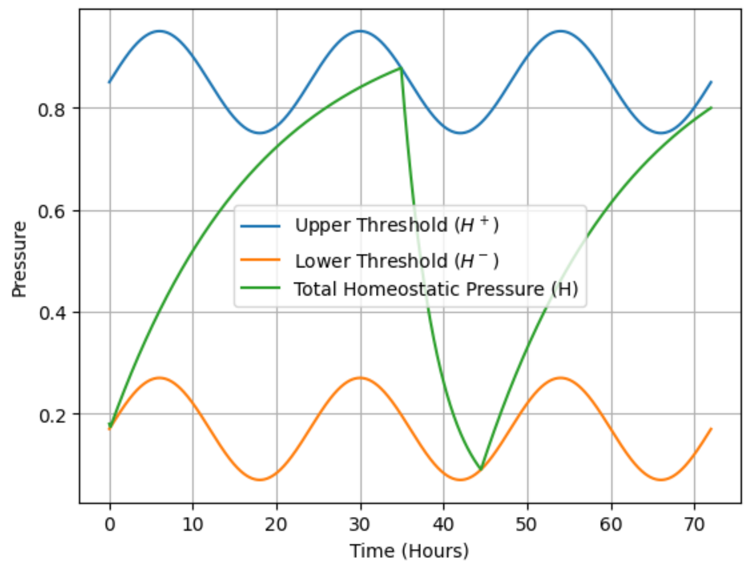


Figure 5: Two-process model with upper threshold $H_0^+ = 0.85$

3 PR Model

The Phillips and Robinson (PR) model is an extension of the two-process model [3] whereby it is composed of three processes. More precisely, the two-process model is exclusively phenomenological, however, the PR model presents us with a physiological foundation. There are two areas of the brain we consider when analysing the PR model which are the monoaminergic (MA) and ventro-lateral pre-optic (VLPO) regions. According to [3] and [4], the neurons in the MA area stimulate wake whilst the neurons in the VLPO area encourage sleep. The last process of the PR model is the shifting between sleep and wake which is comprised of the homeostatic drive $H(t)$ and the circadian drive $C(t)$.

As the MA and the VLPO actively hinder one another from occurring at the same time, this ensures that the model would either be in a wake state or sleep state. We are only able to go between sleep and wake as a result of the model including a drive to the VLPO [3, p. 3]. This drive depends on time and includes the homeostatic and circadian drive as mentioned earlier.

We will begin exploring these concepts by first observing the neurons in the MA and VLPO regions. According to [3, p. 2], the mean cell body potentials relative to rest are depicted by V_m and V_v where the MA group is denoted by m and the VLPO group is denoted by v. The rates at which the neurons are fired are related to these potentials by the firing function, $Q(V_j)$,

$$Q(V_j) = \frac{Q_{max}}{1 + \exp[-(V_j - \theta)/\sigma]} \tag{3.1}$$

We recognise that $Q(V_j)$ is a sigmoid function as seen in Figure 6. Regarding both the formula and the plot of the firing function, Q_{max} is the maximum firing rate. We note that the variable θ is the mean firing threshold that is related to rest which implies that θ decides the moment of switching whereas σ signifies the steepness of the switch. Furthermore, we remark that the "hardness" of the switch is dependent on σ. If we let $p(x) = (1 + \exp[-x/\sigma])^{-1}$, we are able to rewrite the firing function such that $Q(V_j) = Q_{max}p(V_j - \theta)$. When $\sigma \to 0$, we obtain an appropriate step function for the firing rate which is called the hard switch [3, p. 3] where

$$p(x) = \begin{cases} 1 & x \geq 0 \\ 0 & x < 0 \end{cases}$$

When interpreting Figure 6, we establish that when V is negative, then the firing function is close to zero, however, when V is positive, the firing function increases exponentially to Q_{max}.

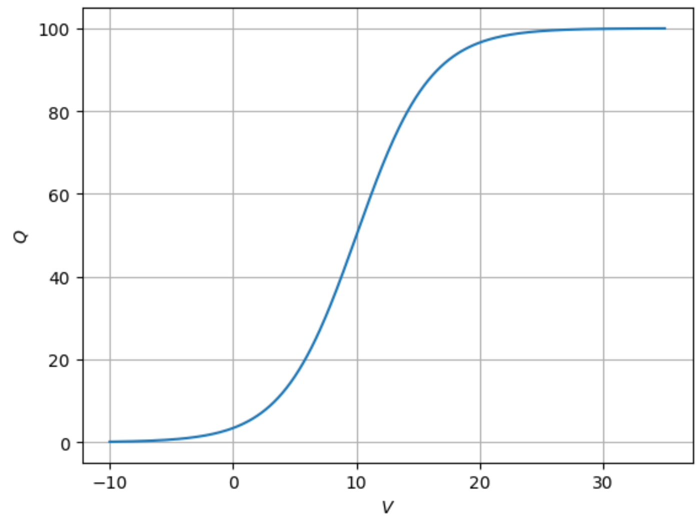


Figure 6: Firing function, $Q(V_j)$, plotted against the potential, V_j

Having defined the firing function allows us to introduce the three processes of the PR model. This is given by the following non-autonomous system of differential equations [4, p. 170],

$$\tau_v \dot{V}_v = v_{vm} Q(V_m) + v_{vc} C + v_{vh} H - V_v \tag{3.2}$$

$$\tau_m \dot{V}_m = v_{mv} Q(V_v) + v_{ma} Q_a - V_m \tag{3.3}$$

$$\chi \dot{H} = \mu Q(V_m) - H \tag{3.4}$$

In the equations presented above, we take the variables to be H, V_v and V_m. Therefore, we observe that χ, τ_v and τ_m portray the speed in which the variables change. The parameters v_{vm}, v_{mv}, v_{vc} and v_{ma} determine the impact that the variables have on each other. In equation (7), Q_a is constant. Additionally, C and H are the circadian drive and homeostatic drive, respectively.

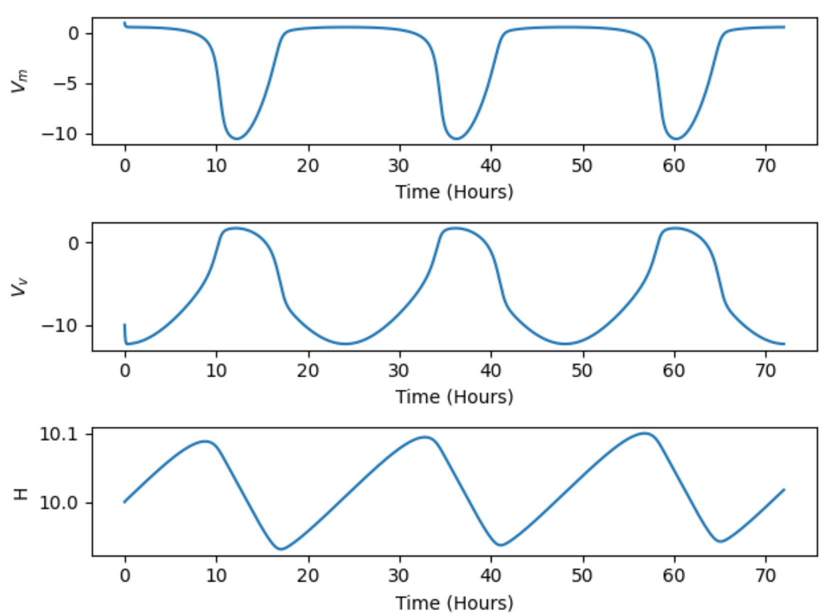


Figure 7: The PR model for the variables V_m, V_v and H

By analysing Figure 7, we will discuss what happens during wake and sleep for the three variables plotted against time. During wake, we can discern that V_m is high whilst V_v and H are comparatively low. This is a result of there being increased activity in the MA region whereas the VLPO area is experiencing decreased activity. As sleep approaches, V_m gradually drops and V_v steadily rises. This is due to an increase in activity in the VLPO area and a decrease in activity in the MA area. When sleep accumulates in the body, we observe that H moderately increases. During sleep, V_m descends reaching its lowest level whilst V_v ascends reaching its highest level. To summarise these concepts [4, p. 175], we alternate between periods of sleep and wake where during wake, we have high V_m, low V_v and rising H. However, during sleep, we have low V_m, high V_v and decreasing H.

4 Slow-Fast Systems

As stated in [3, p. 3], the changes in the homeostatic pressure are significantly slower than the changes that occur in the brain. Thus, the PR model has a clear difference in its timescales. We refer to systems with various time scales or systems that are "singularly perturbed" [5, p. 1] as "Slow-Fast Systems". We begin with the equations that were previously listed in Section 3, namely (6), (7) and (8).

$$\tau_v \dot{V}_v = v_{vm} Q(V_m) + v_{vc} C + v_{vh} H - V_v =: f(V_v, V_m, H) \tag{4.1}$$

$$\tau_m \dot{V}_m = v_{mv} Q(V_v) + v_{ma} Q_a - V_m =: g(V_v, V_m, H) \tag{4.2}$$

$$\chi \dot{H} = \mu Q(V_m) - H =: h(V_v, V_m, H) \tag{4.3}$$

We observe from Appendix B.2 that $\tau_j \ll \chi$ where $j = m, v$. We introduce a dimensionless time $\tilde{t} = \frac{t}{\tau}$, and we differentiate this to obtain

$$\frac{d}{dt} = \frac{d\tilde{t}}{dt} \frac{d}{d\tilde{t}} = \frac{1}{\tau} \frac{d}{d\tilde{t}}$$

Applying the above to equations (9), (10) and (11) and letting $\epsilon = \frac{\tau}{\chi}$ results in

$$\tau_v \frac{d}{dt} V_v = f(V_v, V_m, H) \Rightarrow \frac{d}{d\tilde{t}} V_v = f(V_v, V_m, H)$$

$$\tau_m \frac{d}{dt} V_m = g(V_v, V_m, H) \Rightarrow \frac{d}{d\tilde{t}} V_m = g(V_v, V_m, H)$$

$$\chi \frac{d}{dt} H = h(V_v, V_m, H) \Rightarrow \frac{1}{\tau} \chi \frac{d}{d\tilde{t}} H = h(V_v, V_m, H) \Rightarrow \frac{1}{\epsilon} \frac{d}{d\tilde{t}} H = h(V_v, V_m, H) \Rightarrow \frac{d}{d\tilde{t}} H = \epsilon h(V_v, V_m, H)$$

Therefore, at fast time, we have that the system is given by:

$$\frac{d}{d\tilde{t}} V_v = f(V_v, V_m, H) \tag{4.4}$$

$$\frac{d}{d\tilde{t}} V_m = g(V_v, V_m, H) \tag{4.5}$$

$$\frac{d}{d\tilde{t}} H = \epsilon h(V_v, V_m, H) \tag{4.6}$$

According to [5, p. 1], $\epsilon > 0$ is a small parameter and if we set $\epsilon = 0$, we obtain a "differential algebraic equation" known as the fast subsystem or otherwise called the layer problem. This is given by

$$V_v' = f(V_v, V_m, H)$$
$$V_m' = g(V_v, V_m, H)$$
$$H' = 0$$

where $V_v' = \frac{d}{d\tilde{t}}V_v$. In this case, H is fixed. The fast subsystem allows us to understand what changes occur to both V_v and V_m and how these "fast" variables influence the slow-fast system entirely. We proceed by rescaling the fast subsystem using $\bar{t} = \epsilon\tilde{t}$. By differentiating this, we acquire

$$\frac{d}{d\tilde{t}} = \frac{d\bar{t}}{d\tilde{t}}\frac{d}{d\bar{t}} = \epsilon\frac{d}{d\bar{t}}$$

Applying the above to equations (12), (13) and (14) results in

$$\begin{aligned}
\frac{d}{d\tilde{t}}V_v = f(V_v, V_m, H) &\Rightarrow \epsilon\frac{d}{d\bar{t}}V_v = f(V_v, V_m, H)\\
\frac{d}{d\tilde{t}}V_m = g(V_v, V_m, H) &\Rightarrow \epsilon\frac{d}{d\bar{t}}V_m = g(V_v, V_m, H)\\
\frac{d}{d\tilde{t}}H = \epsilon h(V_v, V_m, H) \Rightarrow \epsilon\frac{d}{d\bar{t}}H = \epsilon h(V_v, V_m, H) &\Rightarrow \frac{d}{d\bar{t}}H = h(V_v, V_m, H)
\end{aligned}$$

Therefore, at slow time, we have that the system is given by

$$\begin{aligned}
\epsilon\dot{V}_v &= f(V_v, V_m, H)\\
\epsilon\dot{V}_m &= g(V_v, V_m, H)\\
\dot{H} &= h(V_v, V_m, H)
\end{aligned}$$

where $\dot{V}_v = \frac{d}{dt}V_v$. For this case, if we set $\epsilon = 0$, we obtain a different system known as the slow subsystem:

$$\begin{aligned}
0 &= f(V_v, V_m, H)\\
0 &= g(V_v, V_m, H)\\
\dot{H} &= h(V_v, V_m, H)
\end{aligned}$$

It can be noted that the equations $0 = f(V_v, V_m, H)$ and $0 = g(V_v, V_m, H)$ represent the fast dynamics of the system which define a manifold on $\mathbb{R}^3$. This is called the slow manifold. However, $\dot{H} = h(V_v, V_m, H)$ represents the slow progression of H on the slow manifold. This can be visualised in Figure 8 where we look at the slow manifold for varying sigma.

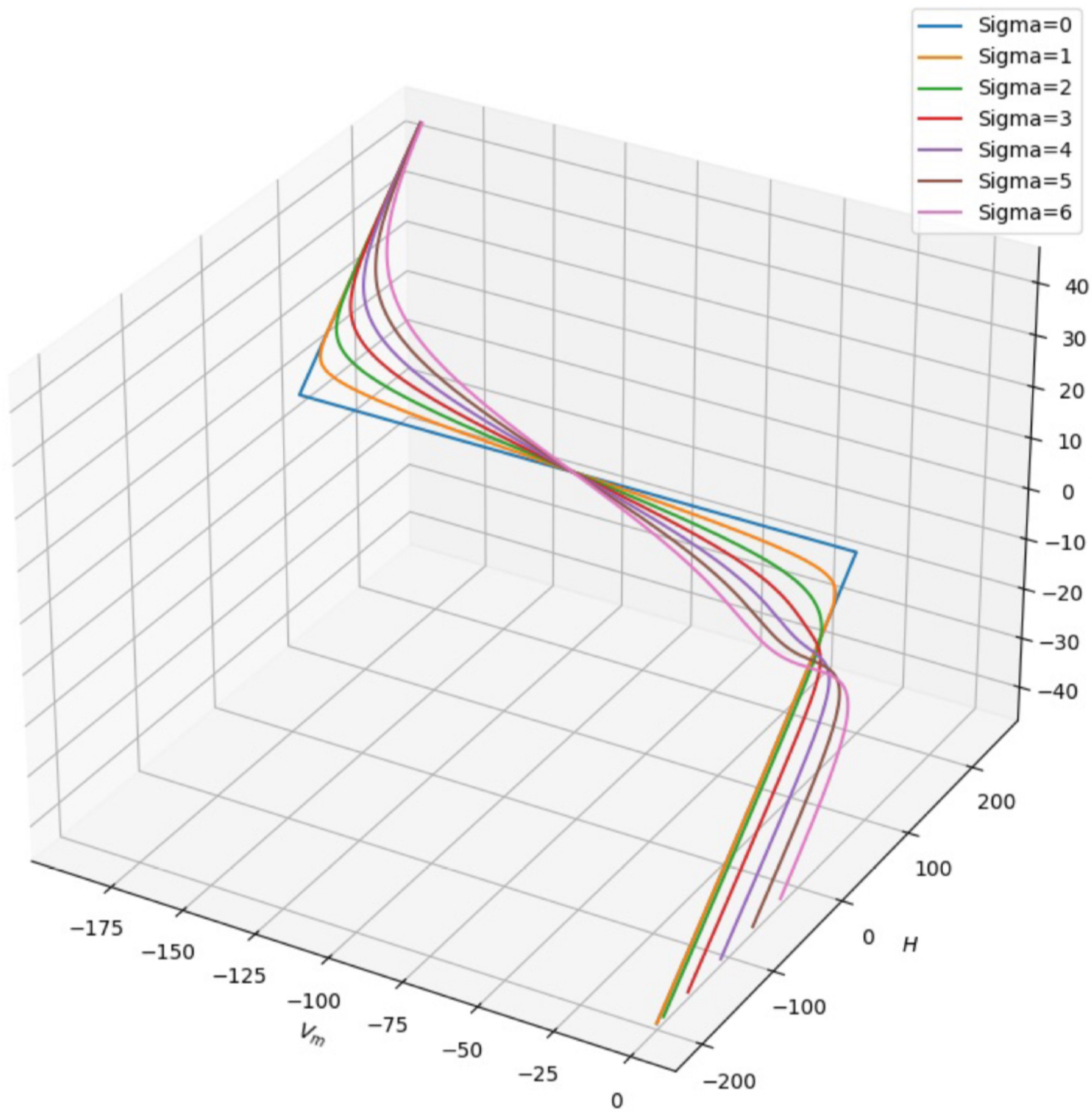


Figure 8: Slow Manifold in $\mathbb{R}^3$

4.1 Comparison of the Two-Process Model and the PR Model

In this section, we will make a comparison between the two-process model and the PR model. In the two-process model, when looking at Figures 3, 4 and 5, the homeostatic pressure shifts from wake to sleep as soon as the upper threshold is reached. When the lower threshold has been reached, there is an instant shift in the homeostatic pressure as well. This immediate shift can be regarded as a hard switch. We know that the changes that occur in the VLPO and MA regions of the brain happen faster than the changes in the homeostatic pressure. Since we are considering the two-process model which heavily involves the homeostatic process, we analyse what transpires at the slow time limit ($\epsilon = 0$). We can explore this by reviewing the PR model when $\epsilon = 0$ which is specified below.

$$\begin{aligned} 0 &= v_{vm}Q(V_m) + v_{vc}C + v_{vh}H - V_v \\ 0 &= v_{mv}Q(V_v) + v_{ma}Q_a - V_m \\ \chi\dot{H} &= \mu Q(V_m) - H \end{aligned}$$

By rewriting the firing function, $Q(V_j)$, with the hard switch, $p(x)$[1], we are left with $Q(V_j) = Q_{max}p(V_j - \theta)$. We can substitute this into the system.

$$0 = v_{vm}Q_{max}p(V_m - \theta) + v_{vc}C + v_{vh}H - V_v \tag{4.7}$$

$$0 = v_{mv}Q_{max}p(V_v - \theta) + v_{ma}Q_a - V_m \tag{4.8}$$

$$\chi\dot{H} = \mu Q_{max}p(V_m - \theta) - H \tag{4.9}$$

If we compare the system of equations in the hard switch limit, we obtain the following cases:

1. $V_m < \theta$ & $V_v < \theta$:
   We recognise that when we make this substitution in equation (16), $p(V_v - \theta) = 0$ since $V_v - \theta < 0$. Thus, we can rewrite the equation to be $0 = 0 \cdot v_{mv}Q_{max} + v_{ma}Q_a - V_m \Rightarrow V_m = v_{ma}Q_a$. However, if we look at the values given in [3, p. 14] (also given in Appendix B.3) of $v_{ma}Q_a$ and θ for the PR model when we have a hard switch, we see that $v_{ma}Q_a = 1.5mV$ and $\theta = 1.45mV$. Thus, $v_{ma}Q_a > \theta \Rightarrow V_m > \theta$ and we reach a contradiction. Consequently, we disregard this case.

2. $V_m < \theta$ & $V_v \geq \theta$:
   When substituting the above criterion into the system of equations, we get that $p(V_m - \theta) = 0$ and $p(V_v - \theta) = 1$. Thus,

$$\begin{aligned} 0 = 0 \cdot v_{vm}Q_{max} + v_{vc}C + v_{vh}H - V_v &\Rightarrow V_v = v_{vc}C + v_{vh}H \\ 0 = 1 \cdot v_{mv}Q_{max} + v_{ma}Q_a - V_m &\Rightarrow V_m = v_{mv}Q_{max} + v_{ma}Q_a \\ \chi\dot{H} = 0 \cdot \mu Q_{max} - H &\Rightarrow \chi\dot{H} = -H \end{aligned}$$

   If we solve the last equation for H, this results in

$$\begin{aligned} \chi\dot{H} &= -H \\ \Rightarrow \chi\frac{dH}{dt} &= -H \\ \Rightarrow \int_{H_0}^{H} \frac{1}{H} dH &= -\int_{t_0}^{t} \frac{1}{\chi} dt \\ \Rightarrow [\ln(H)]_{H_0}^{H} &= -\left[\frac{t}{\chi}\right]_{t_0}^{t} \\ \Rightarrow \ln\left(\frac{H}{H_0}\right) &= -\frac{t - t_0}{\chi} \\ \Rightarrow H(t) &= H_0 e^{(t_0 - t)/\chi} \end{aligned}$$

[1] As stated in Section 3, $p(x) = 1$ when $x \geq 0$ and $p(x) = 0$ when $x < 0$.

As stated in [3, p. 13], we can find the switch from sleep to wake when $V_v = \theta$ so that we are able to derive the lower threshold, H^-.

$$\begin{aligned}
V_v &= v_{vc}C + v_{vh}H \\
\Rightarrow v_{vh}H &= V_v - v_{vc}C \\
\Rightarrow H &= \frac{V_v - v_{vc}C}{v_{vh}} \\
\Rightarrow H^-(t) &= \frac{\theta - v_{vc}C(t)}{v_{vh}}
\end{aligned}$$

3. $V_m > \theta$ & $V_v \leq \theta$:
   It is noted that $p(V_m - \theta) = 1$ and $p(V_v - \theta) = 0$. Hence,

$$\begin{aligned}
0 = 1 \cdot v_{vm}Q_{max} + v_{vc}C + v_{vh}H - V_v &\Rightarrow V_v = v_{vm}Q_{max} + v_{vc}C + v_{vh}H \\
0 = 0 \cdot v_{mv}Q_{max} + v_{ma}Q_a - V_m &\Rightarrow V_m = v_{ma}Q_a \\
\chi\dot{H} = 1 \cdot \mu Q_{max} - H &\Rightarrow \chi\dot{H} = \mu Q_{max} - H
\end{aligned}$$

   We are able to find H by solving the last equation.

$$\begin{aligned}
\chi\dot{H} &= \mu Q_{max} - H \\
\Rightarrow \chi\frac{dH}{dt} &= \mu Q_{max} - H \\
\Rightarrow \frac{1}{\mu Q_{max} - H}dH &= \frac{1}{\chi}dt \\
\Rightarrow \int_{H_0}^{H} \frac{1}{\mu Q_{max} - H}dH &= \int_{t_0}^{t} \frac{1}{\chi}dt \\
\Rightarrow [-\ln(\mu Q_{max} - H)]_{H_0}^{H} &= \left[\frac{t}{\chi}\right]_{t_0}^{t} \\
\Rightarrow -\ln\left(\frac{\mu Q_{max} - H}{\mu Q_{max} - H_0}\right) &= \frac{t - t_0}{\chi} \\
\Rightarrow \ln\left(\frac{\mu Q_{max} - H}{\mu Q_{max} - H_0}\right) &= \frac{t_0 - t}{\chi} \\
\Rightarrow \mu Q_{max} - H &= (\mu Q_{max} - H_0)e^{(t_0 - t)/\chi} \\
\Rightarrow H &= \mu Q_{max} - (\mu Q_{max} - H_0)e^{(t_0 - t)/\chi} \\
\Rightarrow H(t) &= \mu Q_{max} + (H_0 - \mu Q_{max})e^{(t_0 - t)/\chi}
\end{aligned}$$

   According to [3, p. 13], we are able to find the shift from wake to sleep when $V_v = \theta$. This allows us to determine the upper threshold, H^+.

$$\begin{aligned}
V_v &= v_{vm}Q_{max} + v_{vc}C + v_{vh}H \\
\Rightarrow v_{vh}H &= V_v - v_{vm}Q_{max} - v_{vc}C \\
\Rightarrow H &= \frac{V_v - v_{vm}Q_{max} - v_{vc}C}{v_{vh}} \\
\Rightarrow H^+(t) &= \frac{\theta - v_{vm}Q_{max} - v_{vc}C(t)}{v_{vh}}
\end{aligned}$$

4. $V_m > \theta$ & $V_v > \theta$:
   With these specifications, we obtain $p(V_j - \theta) = 1$ for $j = m, v$. Hence, when regarding equation (16), we derive that $0 = 1 \cdot v_{mv}Q_{max} + v_{ma}Q_a - V_m \Rightarrow V_m = v_{mv}Q_{max} + v_{ma}Q_a$. Furthermore, as $v_{mv} < 0$ and $Q_{max} > 0$, then $v_{mv}Q_{max} < 0$ and consequently, we get that $v_{mv}Q_{max} + v_{ma}Q_a < \theta$. However, this would mean that $V_m < \theta$ which is a contradiction. As a result, we disregard this case.

In Figure 8, we observe that for the hard switch limit case, namely when $\sigma = 0$, there are only two shifts where we switch from sleep to wake and vice versa. This is explained due to the fact that we are only concerned with the two cases above which have not been disregarded. We notice that for the cases that we do indeed consider, we get that the equations we have obtained for H from the PR model when $\epsilon = 0$ and with the hard switch are the same as the equations for H in the two-process model.

Furthermore, if we calculate the difference in the threshold levels, $\hat{H}(t) = H^+(t) - H^-(t)$, we find that

$$\hat{H}(t) = -\frac{v_{vm}Q_{max}}{v_{vh}}$$

According to [3, p. 3], $\hat{H}(t)$ can be explained as the degree, during wake, which the MA region hinders the stimulation of the VLPO area.

4.2 Dynamics of the Fast Subsystem

We recall that the layer problem is given by

$$V_v' = f(V_v, V_m, H) \tag{4.10}$$

$$V_m' = g(V_v, V_m, H) \tag{4.11}$$

$$H' = 0 \tag{4.12}$$

where $V_v' = \frac{d}{dt}V_v$ and H is constant. As stated in [5, p. 2], we are able to give definition 4.1.

Definition 4.1 *The points on the critical manifold where the matrix*

$$\begin{pmatrix} \frac{\partial f}{\partial V_v} & \frac{\partial f}{\partial V_m} \\ \frac{\partial g}{\partial V_v} & \frac{\partial g}{\partial V_m} \end{pmatrix}$$

has no eigenvalues on the imaginary axis are called **normally hyperbolic***, as equilibria of the fast subsystem which are hyperbolic in the fast direction.*

We have that for the layer problem,

$$J = \begin{pmatrix} \frac{\partial f}{\partial V_v} & \frac{\partial f}{\partial V_m} \\ \frac{\partial g}{\partial V_v} & \frac{\partial g}{\partial V_m} \end{pmatrix} = \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix}$$

Thus,

$$\det(J - \lambda I) = \det \begin{vmatrix} -1-\lambda & 0 \\ 0 & -1-\lambda \end{vmatrix} = (-1-\lambda)^2 \Rightarrow \lambda_{1,2} = -1$$

The eigenvalues are both real and negative and therefore, the subsystem is stable [6] and also, by definition 4.1, the equilibrium points on the critical manifold are normally hyperbolic. As a result, the slow manifold is normally hyperbolic. Therefore, the equations (4.10) and (4.11) allow us to approach the slow manifold along the plane where H is fixed.

4.3 Dynamics of the Slow Subsystem

Following on from Section 4.1 and 4.2, we have that

$$H^+(t) = \frac{\theta - v_{vm}Q_{max} - v_{vc}C(t)}{v_{vh}} \qquad \& \qquad H^-(t) = \frac{\theta - v_{vc}C(t)}{v_{vh}}$$

where H^+ is where we shift from wake to sleep and H^- is where we shift from sleep to wake. These two switch points can be identified in Figure 8 where $\sigma = 0$. Alongside the switch points, we consider the equilibrium points which occur when $\dot{H} = 0$. When $V_m < \theta$ & $V_v \geq \theta$, we have that $H = 0$ when $\dot{H} = 0$ and when $V_m > \theta$ & $V_v \leq \theta$, we have that $H = \mu Q_{max}$ when $\dot{H} = 0$. Let H^0 represent the equilibrium point $H^0 = 0$ and H^1 represent the other equilibrium point, namely $H^1 = \mu Q_{max}$. Therefore, we have 4! cases where we can observe the dynamics. However, we know that $H^+ > H^-$ (as $v_{vm} < 0$) and additionally, $H^1 > H^0$ (as $\mu Q_{max} > 0$). With these restrictions, we can look at the following possible cases:

1. $H^+ > H^- > H^1 > H^0$

   - For small H in the wake state, namely when $V_m > \theta$ & $V_v \leq \theta$, we have that V_v is simultaneously small since V_v depends on H (as $V_v = v_{vm}Q_{max} + v_{vc}C + v_{vh}H$). Furthermore, H increases as a result of $\chi\dot{H} = \mu Q_{max} - H$ and therefore, will converge to the point $H^1 = \mu Q_{max}$.
   - We can decipher the stability of the equilibrium point H^1 by looking at the equations below:

$$f_1(V_v, V_m, H) = v_{vm}Q_{max} + v_{vc}C + v_{vh}H - V_v$$
$$g_1(V_v, V_m, H) = v_{ma}Q_a - V_m$$
$$h_1(V_v, V_m, H) = \mu Q_{max} - \chi\dot{H} - H$$

     It is only necessary to examine h_1 as the system is non-autonomous and thus, the dynamics only occur on a one-dimensional manifold. Therefore, we find that the derivative of h_1 with respect to H is given by,

$$\frac{\partial h_1}{\partial H} = -1$$

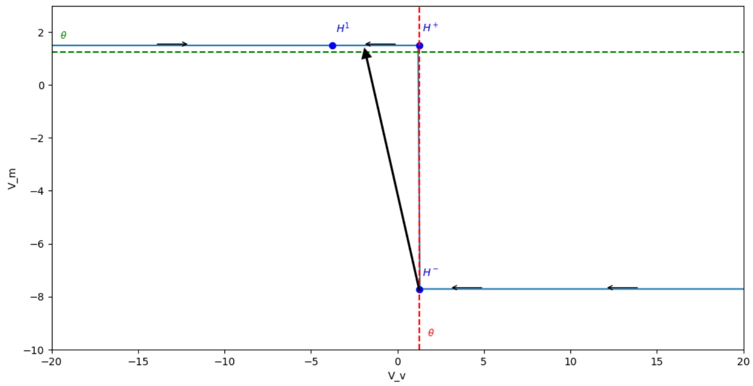
     As $\frac{\partial h_1}{\partial H} < 0$, the equilibrium point H^1 is stable [6].
   - We begin by finding the stability of the equilibrium point H^0 in the same manner. Therefore, we consider the following system of equations:

$$f_2(V_v, V_m, H) = v_{vc}C + v_{vh}H - V_v$$
$$g_2(V_v, V_m, H) = v_{mv}Q_{max} + v_{ma}Q_a - V_m$$
$$h_2(V_v, V_m, H) = -\chi\dot{H} - H$$

     Similarly, we find the derivative of h_2 with respect to H. We get that,

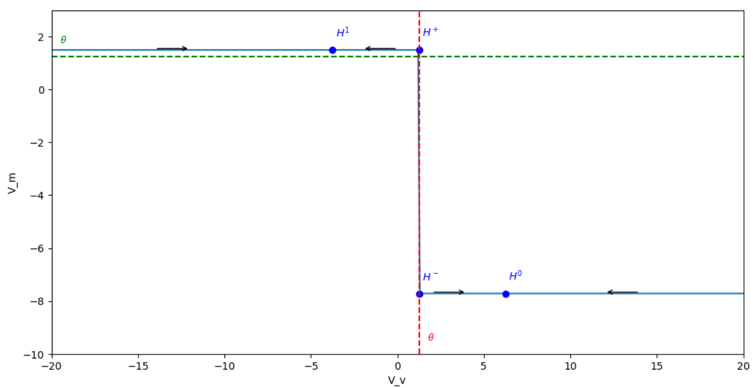
$$\frac{\partial h_2}{\partial H} = -1$$

     Consequently, since $\frac{\partial h_2}{\partial H} < 0$, the equilibrium point H^0 is stable [6]. (The analysis of both equilibrium points applies to all the cases.)
   - For large H in the sleep state, namely when $V_m < \theta$ & $V_v \geq \theta$, we have that V_v will be large. This is due to the equation $V_v = v_{vc}C + v_{vh}H$ where V_v is dependent on H. We know that H is large and that $\chi\dot{H} + H = 0$, and thus, H decreases towards to 0. However, since $H^- > 0$, the system will shift from sleep to wake before H is able to converge to 0. When we shift, we end up back at the point H^1 due to the stability of the equilibrium point and we are therefore unable to shift back to sleep from wake. Hence, we do not have a complete limit cycle.



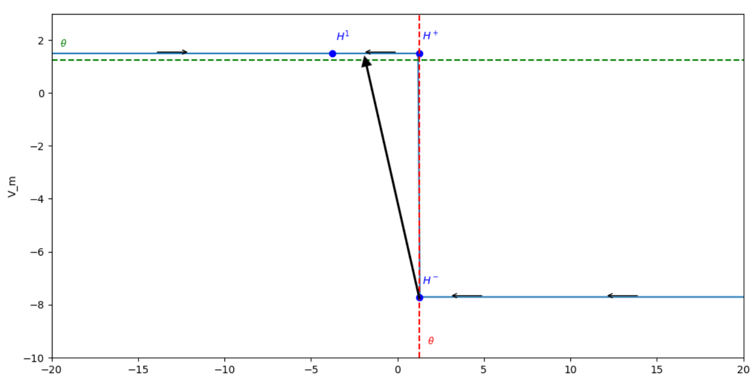
2. $H^+ > H^1 > H^0 > H^-$

- Similarly to the first case, we have that for small H, we will converge to H^1.
- For large H, as $H^0 > H^-$, H^0 appears on the bottom line of the graph. We have shown that H^0 is a stable equilibrium point and thus, we will converge to that point. Therefore, as we converge to both equilibrium points, there will not be a shift from wake to sleep or a shift from sleep to wake. Thus, we do not have a limit cycle.



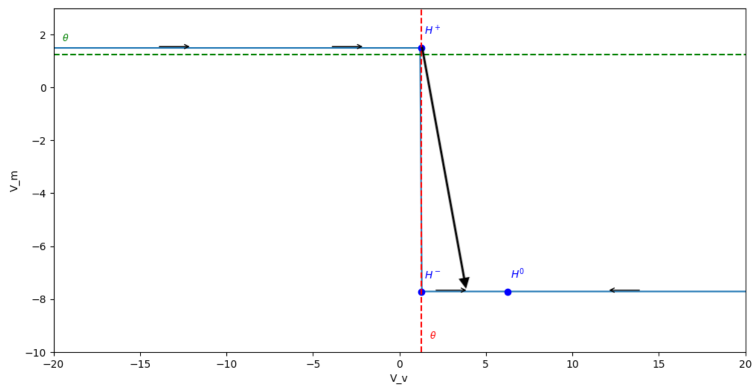
3. $H^+ > H^1 > H^- > H^0$

- We notice that this case behaves the same as the first case we discussed for both small and large H. Thus, we observe that the limit cycle is incomplete.



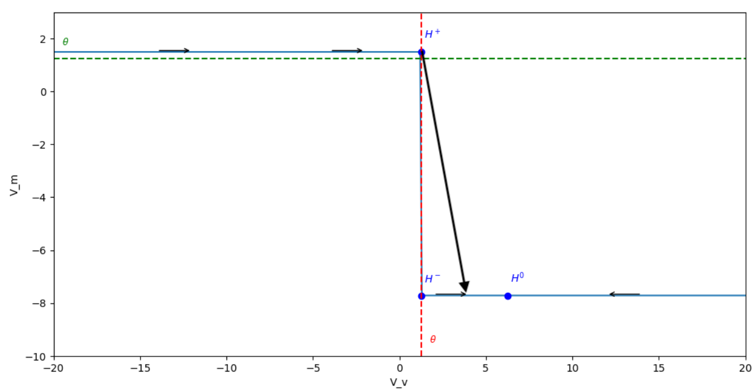
4. $H^1 > H^0 > H^+ > H^-$

- For this case, we have that $H^1 > H^+$ and thus H^1 does not appear in this specific diagram. We establish that since H is small and $\chi\dot{H} = \mu Q_{max} - H$, we will reach H^+ where we will shift from the wake state to the sleep state.
- When we have H large and $\chi\dot{H} + H = 0$, H will decrease towards 0. However, H will converge to the equilibrium point H^1. Therefore, the only switch is from wake to sleep and thus, we have an incomplete limit cycle.



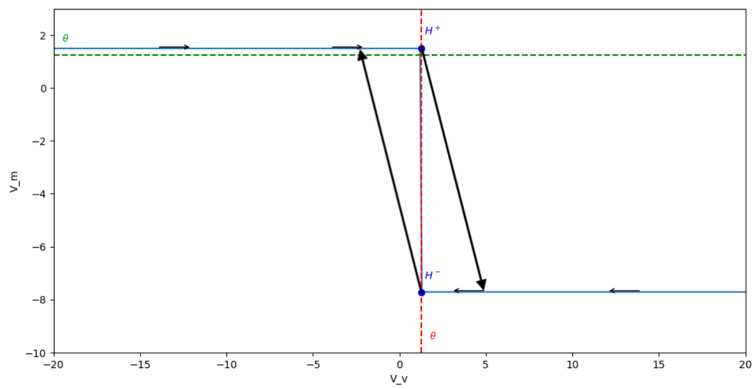
5. $H^1 > H^+ > H^0 > H^-$

- It is observed that this case behaves similarly to the fourth case, whereby, we have an incomplete limit cycle.



6. $H^1 > H^+ > H^- > H^0$

- In the wake state, we have that for a small H with the corresponding equation $\chi\dot{H} = \mu Q_{max} - H$, V_v will increase till it reaches the point H^+. We will then switch from wake to sleep.
- In the sleep state, we have that for a large H, we get that V_v will be large. With this information and $\chi\dot{H} + H = 0$, V_v will decrease till it reaches the point H^- where it will then switch from sleep to wake. We end up back in the wake state and the process repeats itself, hence, we have a complete limit cycle.



By studying these six cases, we discern that only the case $H^1 > H^+ > H^- > H^0$ results in a limit cycle. We claim that this process is the same as the two-process model. This has been shown and proved throughout section 4.

5 Conclusion

In this paper, we have shown that the two-process model is the same as the PR model with a hard switch and when $\epsilon = 0$. We arrived at this conclusion by firstly, describing each of the models in great detail. We recognised that because the PR model includes functions of the body, it is an improved version of the two-process model. Due to the PR model involving the neurons in the brain, we know that the changes that occur in the MA and the VLPO areas of the brain occur at a faster rate compared to the changes that occur in the homeostatic pressure. Therefore, we have different timescales for the PR model, hence, we analysed these two sleep-wake models using the concept of slow-fast systems which results in the slow subsystem and the fast subsystem. We looked at the PR model where $\epsilon = 0$ and when we have a hard switch, we found two equilibrium points for that system which were used when analysing the dynamics of both the subsystems. Furthermore, we found that we do indeed have a limit cycle when studying the dynamics of the slow subsystem. Therefore, we have precisely shown how the two-process model is related to the PR model.

References

[1] M. R. Irwin. Why sleep is important for health: a psychoneuroimmunology perspective. *Annual review of psychology*, 66(1):143–172, 2015.

[2] A. A. Borbély, S. Daan, A. Wirz-Justice, and T. Deboer. The two-process model of sleep regulation: a reappraisal. *Journal of sleep research*, 25(2):131–143, 2016.

[3] A. C. Skeldon, D. Dijk, and G. Derks. Mathematical models for sleep-wake dynamics: comparison of the two-process model and a mutual inhibition neuronal model. *PloS one*, 9(8):1–16, 2014.

[4] A. J. K. Phillips and P. A. Robinson. A quantitative model of sleep-wake dynamics based on the physiology of the brainstem ascending arousal system. *Journal of biological rhythms*, 22(2):167–179, 2007.

[5] R. Haiduc. A fifty minute introduction to slow-fast systems. *Cornell University, Ithaca*, 2004.

[6] E. M. Izhikevich. Equilibrium. *Scholarpedia*, 2(10):2014, 2007.

A Python Code

A.1 Homeostatic Process

```python
import numpy as np
import matplotlib.pyplot as plt

t = np.arange(0, 72, 0.01) #time array
mu = 1 #upper asymptote
t_0 = 0 #starting time
chi_s = 4.2 #decrease in speed
chi_w = 18.2 #increase in speed
H_0 = 0.18 #starting pressure

def H_sleep(H_0, t_0, t, chi_s):
    return H_0 * np.exp((t_0 - t) / chi_s)

def H_wake(mu, H_0, t_0, t, chi_w):
    return mu + (H_0 - mu) * np.exp((t_0 - t) / chi_w)

H_sleep1 = H_sleep(H_0, t_0, t, chi_s)
H_wake1 = H_wake(mu, H_0, t_0, t, chi_w)

plt.figure(figsize=(3, 5))
plt.plot(t, H_sleep1, color='black')
plt.xlabel('Time (Hours)')
plt.ylabel('Homeostatic Pressure H(t)')
plt.grid(True)
plt.show()

plt.figure(figsize=(3, 5))
plt.plot(t, H_wake1, color='black')
plt.axhline(y=1, color='r', linestyle='--')
plt.xlabel('Time (Hours)')
plt.ylabel('Homeostatic Pressure H(t)')
plt.grid(True)
plt.show()
```

A.2 Circadian Process

```python
t = np.arange(0, 72, 0.01)
omega = np.pi / 12

def C(omega, t):
    return np.sin(omega * t)

n = len(t)
H0_plus = np.ones(n) * 0.6
H0_minus = np.ones(n) * 0.17
a = 0.1

H_plus = H0_plus + a * C(omega, t)
H_minus = H0_minus + a * C(omega, t)

plt.plot(t, H_plus, label='Upper Threshold ($H^+$)')
plt.plot(t, H_minus, label='Lower Threshold ($H^-$)')
for i in range(1, 3): #this will add lines for each 24hr period
    plt.axvline(x=i*24, color='red', linestyle='--', linewidth=1)
plt.xlabel('Time (Hours)')
plt.ylabel('Pressure')
plt.legend()
plt.grid(True)
plt.show()
```

A.3 Two-Process Model

```
t = np.arange(0, 72, 0.01)
omega = np.pi / 12

def C(omega, t):
    return np.sin(omega * t)

n = len(t)
H0_plus = np.ones(n) * 0.6
H0_minus = np.ones(n) * 0.17
mu = 1
a = 0.1
t_0 = 0
chi_s = 4.2
chi_w = 18.2
H_0 = 0.18

def twoprocessmodel(n, H0_plus, H0_minus, mu, a, t_0, chi_s, chi_w, H_0):
    H_plus = H0_plus + a * C(omega, t)
    H_minus = H0_minus + a * C(omega, t)

    Hs = np.zeros(n)
    Hw = np.zeros(n)
    i = 0

    for i in range(n):
        Hw[i] = mu + (H_0 - mu) * np.exp((t_0 - t[i]) / chi_w) #sleep pressure during wake
        if Hw[i] <= H_plus[i]: #checking if sleep pressure during wake is lower than the upper threshold
            j = i
            break #we break since we do not have to change direction yet

    k = 0

    for i in range(j, n):
        t_0 = t[j]
        H_0 = Hw[j]
        for i in range(j, n):
            Hs[i] = H_0 * np.exp((t_0 - t[i]) / chi_s) #sleep pressure during sleep
            Hw[i] = 0
            if Hs[i] >= H_minus[i]: #checking if sleep pressure during sleep is more than the lower threshold
                k = i

        t_0 = t[k]
        H_0 = Hs[k]
        for i in range(k, n):
            Hw[i] = mu + (H_0 - mu) * np.exp((t_0 - t[i]) / chi_w)
            Hs[i] = 0
            if Hw[i] <= H_plus[i]:
                j = i
        i = j + 1

    H = Hw + Hs #total homeostatic pressure = wake + sleep
    return H_plus, H_minus, H

H_plus, H_minus, H = twoprocessmodel(n, H0_plus, H0_minus, mu, a, t_0, chi_s, chi_w, H_0)


plt.plot(t, H_plus, label='Upper Threshold ($H^+$)')
plt.plot(t, H_minus, label='Lower Threshold ($H^-$)')
```

```
plt.plot(t, H, label='Total Homeostatic Pressure (H)')
plt.xlabel('Time (Hours)')
plt.ylabel('Pressure')
plt.legend()
plt.grid(True)
plt.show()
```

A.4 Firing Function

```
Qmax = 100
theta = 10
sigma = 3

def Q_j(V, Qmax, theta, sigma):
    return Qmax / (1 + np.exp(-(V - theta) / sigma))

V_vals = np.linspace(-10, 35, 400) #interval on the x-axis from -10 to 35
Q_vals = Q_j(V_vals, Qmax, theta, sigma)

plt.plot(V_vals, Q_vals)
plt.xlabel('$V$')
plt.ylabel('$Q$')
plt.grid(True)
plt.show()
```

A.5 PR Model

```
t = np.arange(0, 72, 0.01)
n = len(t)
omega = np.pi / 12

def C_PR(omega, t): #circadian drive for the PR model
    return 0.5 * (1 + np.cos(omega * t)) #not the same one as the two-process model

C = C_PR(omega, t)

x = np.array([-10, 1, 10])
Qmax = 100
theta = 10
sigma = 3
v_maQ_a = 0.7
v_vm = -1.9
v_mv = -1.9
v_vc = -6.3
v_vh = 0.19
chi = 10.8 * 3600
mu = 3600 * 10 ** -3
tau_v = 10
tau_m = 10

def PRmodel(n, x, Qmax, theta, sigma, v_maQ_a, v_vm, v_mv, v_vc, v_vh, chi, mu, tau_v,
    tau_m):
    xArray = np.zeros((n, 3)) #matrix with n rows and 3 columns for the three variables
        Vm, Vv and H

    for i in range(n): #Euler method
        xArray[i, :] = x
        dx = np.array([
            1/tau_v * (v_vm * Qmax / (1 + np.exp(-(x[1] - theta) / sigma)) + v_vc * C[i]
                + v_vh * x[2] - x[0]),
```

```
            1/tau_m * (v_mv * Qmax / (1 + np.exp(-(x[0] - theta) / sigma)) + v_maQ_a - x
                [1]),
            1/chi * (mu * Qmax / (1 + np.exp(-(x[1] - theta) / sigma)) - x[2])
        ])
        x = x + dx #add till we get one value in each column which is the integrated Vv,
            Vm and H

    return xArray

xArray = PRmodel(n, x, Qmax, theta, sigma, v_maQ_a, v_vm, v_mv, v_vc, v_vh, chi, mu,
    tau_v, tau_m)
plt.subplot(3, 1, 1)
plt.plot(t, xArray[:, 1])
plt.xlabel('Time (Hours)')
plt.ylabel('$V_m$')

plt.subplot(3, 1, 2)
plt.plot(t, xArray[:, 0])
plt.xlabel('Time (Hours)')
plt.ylabel('$V_v$')

plt.subplot(3, 1, 3)
plt.plot(t, xArray[:, 2])
plt.xlabel('Time (Hours)')
plt.ylabel('H')

plt.tight_layout()
plt.show()
```

A.6 Slow Manifold

```
from mpl_toolkits.mplot3d import Axes3D

Qmax = 100
theta = 10
v_maQ_a = 0.7
v_vm = -1.9
v_mv = -1.9
v_vc = -6.3
v_vh = 0.19
tau_v = 10
tau_m = 10

Vv = np.arange(-45, 45, 0.1) #interval
t = np.arange(0, 72, 0.01)
omega = np.pi / 12

def C_PR(omega, t):
    return 0.5 * (1 + np.cos(omega * t))

C = C_PR(omega, t)

Sigma = np.arange(0, 7)
n = len(Vv)

Vm = np.zeros((n, n))
H = np.zeros((n, n))
Qv = np.zeros((n, n))
Qm = np.zeros((n, n))

def Q(V, theta, sigma): #firing function
    return Qmax / ( 1 + np.exp(-(V - theta) / sigma ))

for j in range(7):
```

```
    sigma = Sigma[j]

    for i in range(n):
        Qv[i, j] = Q(Vv[i], theta, sigma)
        Vm[i, j] = v_mv * Qv[i, j] + v_maQ_a
        Qm[i, j] = Q(Vm[i, j], theta, sigma)
        H[i, j] = (Vv[i] - v_vc * C[i] - v_vm * Qm[i, j])/v_vh

fig = plt.figure(figsize=(10, 10))
ax = fig.add_subplot(111, projection='3d')

for j in range(7):
    ax.plot(Vm[:, j], H[:, j], Vv, label=f'Sigma={Sigma[j]}')

ax.set_xlabel('$V_m$')
ax.set_ylabel('$H$')
ax.set_zlabel('$V_v$')
ax.legend()

plt.show()
```

A.7 Dynamics of the Slow Subsystem

```
Vv = np.arange(-40, 40, 0.1)

def C_PR(omega, t):
    return 0.5 * (1 + np.cos(omega * t))

C = C_PR(omega, t)

Qmax = 4.85
theta = 1.45
tau_v = 10
tau_m = 10
chi = 10.8 * 3600
mu = 3600 * 10 ** -3
v_vm = -1.9
v_vc = -6.3
v_vh = 0.30
v_mv = -1.9
v_maQ_a = 1.5
Sigma = np.arange(1, 7) #sigma ranges from 0 to 6


n = len(Vv)
Vm = np.zeros((n, n))
H = np.zeros((n, n))
Qv = np.zeros((n, n))
Qm = np.zeros((n, n))
Hdot = np.zeros((n, n))

a = np.zeros(n)
b = np.zeros(n)

def Q(V, theta, sigma):
    return Qmax / ( 1 + np.exp(-(V - theta) / sigma ))

for j in range(6):
    sigma = Sigma[j]

    for i in range(n):
        Qv[i, j] = Q(Vv[i], theta, sigma)
        Vm[i, j] = v_mv * Qv[i, j] + v_maQ_a
        Qm[i, j] = Q(Vm[i, j], theta, sigma)
```

```
        H[i, j] = 1 / v_vh * (Vv[i] - v_vc * C - v_vm * Qm[i, j])
        Hdot[i, j] = (mu * Qm[i, j] - H[i, j]) / chi

for i in range(n):
    if Vv[i] >= theta:
        a[i] = 1
    Qv[i, 6] = Qmax * a[i]
    Vm[i, 6] = v_mv * Qv[i, 6] + v_maQ_a
    if Vm[i, 6] >= theta:
        b[i] = 1
    Qm[i, 6] = Qmax * b[i]
    H[i, 6] = 1 / v_vh * (Vv[i] - v_vc * C - v_vm * Qm[i, 6])
    Hdot[i, 6] = 1 / chi * (mu * Qm[i, 6] - H[i, 6])

fig = plt.figure(figsize=(12, 6))
ax = fig.add_subplot(111)

ax.plot(Vv, Vm[:, 6])
ax.plot([theta], [v_maQ_a], 'bo') #H+
ax.plot([theta], [v_maQ_a + v_mv * Qmax], 'bo') #H-
ax.plot([theta - 5], [v_maQ_a], 'bo') #H1
ax.plot([theta + 5], [v_maQ_a + v_mv * Qmax], 'bo') #H0
ax.set_xlabel('V_v')
ax.set_ylabel('V_m')

ax.axis([-20, 20, -10, 3])

plt.show()
```

B Parameters

B.1 Two-Process Model

Parameter	Two-Process Model
μ	1
ω	$2\pi/24$ hrs^{-1}
χ_S	4.2 hrs
χ_W	18.2 hrs
H_0	0.18
a	0.10

B.2 PR Model

Parameter	PR Model
Q_{max}	100 sec^{-1}
χ	10.8 hrs
θ	10 mV
σ	3 mV
v_{vm}	-1.9 mV sec
v_{mv}	-1.9 mV sec
v_{vc}	-6.3 mV
v_{vh}	0.19 mV nM^{-1}
$v_{ma}Q_a$	1.0 mV
τ_m	10 sec
τ_v	10 sec

B.3 PR Model with a Hard Switch

Parameter	PR Model with a Hard Switch
Q_{max}	4.85 sec^{-1}
χ	10.8 hrs
θ	1.45 mV
σ	3 mV
v_{vm}	-1.9 mV sec
v_{mv}	-1.9 mV sec
v_{vc}	-6.3 mV
v_{vh}	0.19 mV nM^{-1}
$v_{ma}Q_a$	1.5 mV
τ_m	10 sec
τ_v	10 sec