MTH3035 Group Project:
The Circadian Rhythm

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Abstract

The body clock, also known as the circadian clock, refers to the series of internal biological processes within the body that play vital roles in maintaining the health of an individual. Light is found to be the main stimulus that impacts the circadian rhythms, and hence, in this report we explore the effects of light on our body clock. We focus our research on a selection of key areas involving the disturbance of circadian rhythms due to light, including: jet lag, shift work and light pollution. The main aim of this report is to investigate these topics and hence suggest potential treatments to help maintain a healthy body clock, by correcting any disturbances to the circadian rhythms. We conducted our research by analysing various scientific papers and case studies, before modelling our phase shifts using the two models we had selected: the Goodwin model and the Becker Weinmann model. Through modelling our phase shifts using MATLAB, we found that the key points to note are: it takes 5 to 6 days for the body to recover from the impact of jet lag, non-standard shifts cause great disturbance to circadian rhythms, and light pollution results in the suppression of mRNA, hence disrupting the processes involved in the circadian clock. The three most successful treatments that have we decided on are: light therapy, prescribed sleep scheduling and melatonin administration, and through these we believe the circadian rhythm can be re-entrained. However, due to the inability to carry out our own experiments to test the validity of these treatments, we have had to rely on past research, meaning further investigation is required to test the accuracy of these treatments.

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1 Introduction

The Body Clock, also known as the Circadian Clock, refers to a series of biological processes within the body that controls physiology at multiple levels, from gene expression to complex behaviours such as sleep and performance [R1:p430]. The word Circadian comes from the Latin phrase "circa diem" meaning "about a day" [B1:p1] which refers to the approximate 24-hour periodicity of the Circadian rhythms. Our natural body clock follows a cycle that is approximately 24hours and 11 minutes ($\pm$ 16 minutes), according to a study by Czeisler et al. at Havard [S1,p1467]. Circadian rhythms have been known to science for centuries, with the first recorded observation of biological timekeeping in 1729 stemming from French astronomer Jean-Jacques d'Ortous de Mairan, who noted that the leaves of the Mimosa plant moved with a periodicity of 24-hours, even when the plant was moved to a basement without light [W1:p28]. The study of these circadian rhythms investigates the 24-hour oscillations in biological processes at molecular, cellular, and behavioural levels [W1:p28].

Circadian rhythms are sensitive to many different zeitgebers, which are defined as environmental cues that help regulate the cycles of an organism's biological clock [H1]. Light is a key zeitgeber, imposing a large influence on the processes within our body clock, since the exact 24-hour light-dark cycle lines up almost perfectly with the approximate 24-hour circadian clock. An active process called entrainment ensures that the biological clock is stably synchronised to its zeitgebers [R1:p430]. The circadian clock responds differently to a zeitgeber stimulus depending on its phase: at some phases (e.g. late night to early morning), light advances the clock, at others, (e.g. afternoon and evening), light delays [R1:p430]. The physiology and behaviour of most organisms are adapted to these daily predictable oscillations, and the ability given by an internal clock to anticipate the daily cycle is of such importance that internal clocks seem to be ubiquitous [F1:p600].

Disruption of the circadian clock is a pressing issue and can have some extreme side effects on the body. Since circadian rhythms control a variety of biological processes, such as sleep-wake cycles, body temperature, hormone secretion, glucose homeostasis, and cell-cycle regulation, any alteration of these physiologic rhythms will lead to changes in the phase relationship of rhythms to each other, causing internal de-synchronisation [Z1:p132]. This loss of coordination of rhythms may have negative consequences on many physiologic and behavioural functions [Z1:p132], ultimately creating many serious problems within the body. One of the main causes of disruption to the normal circadian rhythms is to do with change to the normal sleep cycle. Chronic disruption of normal circadian rhythms by shift-work and jet lag leads to physiological dysfunction which can manifest as mood disorders, cancer, cardiovascular disease, and metabolic diseases such as diabetes and obesity [W1:p28]. In these cases, many treatments are being developed to help stabilize circadian rhythms and hence prevent serious side effects. Treatments, such as bright light therapy and sleep-wake schedule intervention have been investigated to attempt to stabilize sleep [F1:p605], and hence decrease circadian rhythm disruption. Such interventions are gaining acceptance and are frequently used as treatment options for mood disorders such as unipolar and bipolar depression [F1:p605].

The regulation of the body clock is extremely important in not only the lives of humans, but in those of many other species. For example, the body clock allows organisms to anticipate and cope with events such as migration, hibernation, and the limitation of resources. The synchronization to the external environment, the anticipation of change and the imposition of an internal temporal order provide the basis for an organism's survival [F1:p600].

To begin our project, as a group we decided on a list of aims, which as the project developed became more specific. Since light is the most influential stimuli on the circadian rhythm, we decided to solely focus on modelling this parameter. We aim to be able to create convincing mathematical models to show the influence of light on the circadian rhythm under three different circumstances. Two of these circumstances we have chosen to model are acknowledged circadian rhythm sleep disorders. The third circumstance is the effect of blue light and light pollution on the circadian rhythm, we chose this since we believe it to be a very current and worsening issue in the 21^{st}century.

As of 2020, there are 6 Circadian rhythm sleep disorders that are acknowledged by the international classification of sleep disorders [S1:p1461]. These include; advanced sleep phase type, delayed sleep phase type, jet lag disorder, shift work disorder, irregular sleep-wake phase type, and finally, non-24 hour sleep-wake type [S1:p1461]. These disorders all lead to an established repeated pattern of disturbed sleep because of a misaligned body clock that cannot be explained by primary sleep disorders such as insomnia or narcolepsy [S1:p1461]. We have taken specific interest in jet lag disorder and shift work disorder, since these are the most relatable to us as most members of our group have experienced these at some point.

Jet lag disorder is caused by the crossing of time zones too fast, meaning your body's circadian rhythm cannot keep track of this change in time. Since the intrinsic rhythm cannot keep pace, a misalignment is formed between the homeostatic and circadian process that occur within the body [S3:p102]. This misalignment leads to incorrect circadian 'signalling', which results in the characteristic symptoms of jet lag [S3:p103]. Symptoms of jet lag are very common, especially the more time-zones you jump or the longer your travel time is. Some of the most prominent symptoms are those such as daytime exhaustion, reduced alertness, and reduced cognitive skills [S2:p796], which is a result of your body not being aligned with the local environment and therefore needing to work harder to re-align itself.

Jet lag disorder can be worsened by many factors, such as: the ability to sleep during travel, individual tolerance to body clock misalignment, and the direction of travel [S3:p103]. Numerous studies have shown that symptoms are far worse when travelling eastwards rather than westwards [S1:p1474]. Normally, jet lag symptoms ease each day for every time zone you cross, however a study found that when travelling towards the west, re-synchronisation occurs at a rate of 1.5 hours a day, whereas towards the east it's a rate of 1 hour a day [S2:p797]. These results confirm the idea that travelling eastward results in far worse symptoms of jet lag. However, no matter the direction of travel there will very often be travel fatigue due to the poor air quality aboard planes and uncomfortable seating [S2:p797]. We will be looking into the phase shifts associated with jet lag disorder, and how to potentially lessen or treat the symptoms of jet lag.

An interesting study on jet lag by Samuel Christensen et al [C1:p3] investigated travel data from a traveling app that observes the extent to which 100 people's schedules deviated from their normal. These schedules were created by looking at previous research and mathematical models that portray light schedules that shift the circadian clock to a new time zone. This paper is valuable as it helps in our understanding of jet lag disorder and how it impacts the body clock, and will help further when we are writing up our findings. Another article by Aron Lee and Juan Carlos Galvez [L1:P1] investigates how jet lag affects athletes. From national football league's data, they found that west coast teams consistently beat east coast teams in evening matches. However, there is not enough data to fully support that jet lag can adversely affect athletes' performance. Both of these articles are interesting and useful, but the first source will be a lot more useful in our report as it is looking at data on the average person rather than just athletes, so it is more applicable to our report. Furthermore, the first source is based on gathered information which is fairly reliable, whereas we cannot be sure whether the information in the other article is completely true.

A useful research paper by Azka Hassan et al goes into detail about how jet lag can cause cancer [H5:p1]. The paper concludes that as the circadian rhythm is controlled by genes which are also used to control cell division, a disruption to the clock can cause tumour growth. This article is backed up by another article that looks into shift work and cancer [D1:p5]. This paper similarly concluded that there is an increased risk of breast cancer in individuals who work the night shift. These two sources show that there can be some serious health risks when the circadian rhythm is disrupted, which highlights the importance of our research in helping to improve people's health.

Sharing similarities with jet lag disorder, especially when considering symptoms, shift work disorder is also incredibly prominent in the 21st century. Shift work refers to all the non-standard work schedules such as part-time or permanent night work, and irregular hours or split shifts [S1:p1469]. Examples of shift workers are those working in the delivery or catering industry, and in the health care services. Approximately 15-20% of the workforce in industrialised countries are involved in some form of night or rotational shift work [K1:p91]. However, due to the Coronavirus pandemic, this will have increased due to the increased need for people to work jobs such as couriers and delivery drivers.

An evening shift is defined as a shift between the hours 14:00-00:00, and the night shift overlaps with this, beginning at 21:00 and ending at 8:00 [W2:p42]. Not only can these shifts be incredibly irregular, changing from week to week, but they are also very anti-social hours. The anti-social hours can lead to even shorter sleep duration for workers since many have after work interactions with family and friends or exercise commitments, meaning they still do not catch up on sleep when not at work [W2:p43]. Shift work attempts to override the intrinsic circadian rhythm that leads to misalignments within the local environment and your internal processes. This misalignment causes symptoms such as excessive tiredness, and reduced concentration. It can also lead to an increased chance of illness, both physically and mentally [K1:p91]. The ability to sleep during the day also decreases with age, therefore meaning older people may suffer more with shift work disorder. Overall, the misalignment in circadian rhythm due to shift work has multiple negative impacts, and it can be incredibly hard for shift workers to socialise with those who work a regular 9-5 job. Irregular hours and shift work are simply not compatible with the regular intrinsic circadian rhythm.

With the 21st century came the increased use of mobile phones, leading to the invention of smartphones and tablets. Harmful blue light can come from all sources of artificial light, such as LED lamps [O1:p2]. Blue light wavelengths are more powerful than green wavelengths, and research shows that it suppresses melatonin production for roughly twice as long as the green wavelengths [H3:p26]. Hence, the risk of melatonin suppression increases at night due to people spending increased time on smartphones, laptops, or tablets and these emit such large amounts of blue light [O1:p2]. Exposure to blue light leads to the resetting of the circadian clock [H3:p23], which before bed can lead to people not being able to sleep at the 'normal' time. Blue light is therefore very harmful and disruptive to the internal processes and can lead to irregular sleeping patterns and increased tiredness during the day. Research shows that scheduled blue light exposure could however be used to precisely reset circadian rhythms [H3:p24], and therefore has the potential to cure the disorders previously mentioned, such as jet lag.

An entrained circadian rhythm can aid and promote good restorative sleep allowing you to wake up rested. Although the disruption of the circadian rhythm may only seem to have a small impact on individuals' lives, such as shortened sleep duration for a small period, research and experiments have shown that long-term it can have extremely damaging effects, making this research vital in the prevention of these long-term hazards. From further research, it was made clear to us the extent a damaged circadian rhythm can have on health.

When reading through research papers, we found that the most useful papers where those written by Didier Gonze. Our project leader recommended these papers to us, and they were very helpful in building our initial understanding of the circadian rhythms. The most beneficial paper by Gonze was his paper titled 'The Goodwin Oscillator and its legacy'[G1]. This help us because it introduced our initial model, the Goodwin Model, and this is where our whole project began. We also found the two papers on treatments by Robert Sack titled 'Circadian Rhythm Sleep Disorders:

part I'[S1] and 'Circadian Rhythm Sleep Disorders: part II'[S4] to be very useful when investigating our own findings, since these papers introduced studies which we were able to use to confirm or deny our discoveries.

Hypothesis

When it comes to forecasting the outcomes of our project, we have made a few specified predictions in terms of the three areas we are focusing our report on. We predict that the most treatable of the three will be jet lag, with remedies such as ensuring your body is adjusted to the new time zone, for example through taking planned naps, before the flight being extremely beneficial and easy to carry out. We also predict that the most difficult to find appropriate treatments for will be light pollution, since this is such a common issue in society today and would require a complete lifestyle change in order for any benefits to be seen.

In terms of our findings, we expect to justify the following standard predictions for this project: carrying out non-standard shifts does indeed cause disruptions to our circadian clock, travelling between time zones almost always causes symptoms of jet lag which in turn disturbs our circadian rhythms, and being exposed to light pollution causes disruptions in the protein synthesis processes within the circadian clock.

Table 1: Key Definitions

Term	Definition
Entrainment	It is a series of interactions between brain rhythms. Entrainment refers to the coupling of two independent oscillation systems so that their period of oscillation becomes related by virtue of phase alignment. [B2:pg269-285]
Zeitgebers	Environmental cues that help regulate the cycles of an organism's biological clock. [H1]
Inhibition	Interfering with a process resulting in a reduced outcome.
Circadian Clock	A 24-hour biological process which regulates the body's natural sleep rhythm. [S5]
Oscillations	A repetitive action of two variables between two points.
Homeostasis	A self-regulating biological process to help maintain stability while adjusting to changing conditions.[B3]
Perturbations	An alteration of a function due to an external or internal stimuli, in our case the stimulus we are using is light.[W4:p97].
Advanced Sleep Phase Type	People with an advanced sleep phase cycle will fall asleep hour (or more) earlier than 'normal' and wake up earlier. [K2]
Delayed sleep phase type	A person who falls asleep two or more hours later than 'normal', resulting in them finding it harder to wake up at a desired time.[N1]
Irregular sleep-wake phase type	People with this phase type have no clear circadian rhythm. They can experience wakefulness during 'normal' sleeping hours and tiredness during daytime. [H4]
Non-24-hour sleep-wake type	An Individual who has a sleep-wake cycle of less than 24 hours (normally only slightly less). This can cause their sleep pattern to become irregular.[P1]
Insomnia	A disorder where you have difficulty falling asleep and staying asleep, despite having adequate time to sleep. This difficulty is associated to daytime impairment or distress. [R4,pS7-S10]
Phase Shift	Occurs when a function is moved away from its normal position.
Narcolepsy	A neurological disorder that effects your ability to wake and sleep. Causes uncontrollable daytime sleepiness meaning one may fall asleep at any point. [D2]
Phase response curve (type 1)	Refers to smaller phase shifts (less than 6 hour phase shifts) and involves a continuous transition between delays and advance. [J1]
Phase response curve (type 0)	Refers to a large phase shift. If the phase shifts are plotted as advances and delays, a discontinuity occurs at the transition between delay and advance phase shift. [J1]

2 Methodology

2.1 Project Timeline

Our project began with our first group meeting, in which each member discussed their strengths and weaknesses in relation to the main focus of the project. There was a mix of abilities within the group which we took as a positive, since it enabled us to divide up the roles within the project more easily. We had some members who were very confident with coding, others who were more biologically inclined and others who were research based. However, all members of the group shared the ability of confidently applying our prior mathematical knowledge to this project and of using LaTeX to clearly demonstrate our findings in the final report. We spent the first few days after our initial meeting carrying out independent research into the circadian clock, so that all members felt they had sufficient fundamental knowledge to begin the project. Our project leader, Jamie Walker, initially sent us two research papers by Didier Gonze that provided us with some essential information on circadian rhythms and also introduced a basic system of equations for modelling these rhythms. Upon analysing these papers, and through conducting other intial research, we concluded that light was the zeitgeber imposing the greatest impact on the circadian clock. Hence, we decided to focus almost exclusively on the effect of light on circadian rhythms.

The following stages of our project involved carrying out further in depth research on a range of topics surrounding our main focus of the circadian clock. After a brief group discussion, we decided to investigate the following areas: epilepsy, mental health, shift work, light pollution, blindness, insomnia, and jet lag. Each member of the group was given the responsibility of conducting thorough research into one of these factors and hence providing a summary of how they affect the circadian clock.

Following on from our research, we regrouped and decided to further narrow down our project into three main focuses. The topics we agreed on were jet lag, shift work, and the effects of blue light/light pollution on the circadian rhythm. Once we had decided to centre our research on these areas, two of our group members began working on the initial coding up of our models. The first model we decided to code up was the Goodwin Model, since we deemed it as being one of the more simple models in terms of coding and found it to be a popular system for modelling the circadian rhythm. Once our initial code was written up, we began looking at how we could model the effect of light in different circumstances. Our two main coders were able to produce our first graph to show the effects of jet lag; the code and graph then being checked by two other members of the group who also have a background in coding. It was at this point that three members of the group gave our first presentation, detailing our initial progress on this project.

Our group project leader suggested that we consider other potential models so we could compare these to the models we had already selected, and hence decide whether or not we wanted to make use of these additional models. We researched models such as the Van Der Pol model, Leloup and Goldbeter model, and the Becker-Weinmann model. Upon evaluating this research, we decided against the inclusion of the Van Der Pol and Leloup and Goldbeter models in our project, since we deemed there to be too many parameters within these models, making the coding process too complex and time consuming. However, we did decide to further investigate the Becker-Weinmann model as we felt that coding this model was within our capabilities and would benefit our findings more than solely relying on the Goodwin model to process our results. We continued to produce graphs concerning both shift work and light pollution using the Goodwin Model, whilst also formulating the initial code for the Becker-Weinmann model.

Once we had made progress with generating the first few graphs for each of the three topics, two members of the group began writing up our introduction, whilst the rest of the group worked on formulating the initial stages of the methodology. At this point, we also needed to take some time to create the PowerPoint for our second presentation, which was a task allocated to the two members who would be presenting. Once this presentation had been given and our introduction was completed, the attention of the entire group was turned to finalising our methodology and beginning the write up of our findings. By the ninth week, we were able to finally produce graphs from our Becker-Weinmann code, and therefore we began working on explanations for the graphs produced by this.

With the final presentation approaching, the four members who would be presenting began creating the PowerPoint to sum up our progress. The rest of the group began working on our project conclusion by investigating the different potential treatments available for maintaining a healthy circadian clock. To meet the aims of our project, we had to ensure that we researched into the ways in which we could rectify our circadian rhythm in the case that it became out of sync. Within the last part of our research, we met and discussed all the possible treatments we had found to have potential when considering the maintenance of a healthy circadian clock. We analysed our research and narrowed it down to the treatments that we believed to be the most valid and which were worth researching further. After compiling our final bits of research, we then included the relevant information in the conclusion section of this report. One week before the deadline, we had our final meeting with our project leader, in which we disclosed any remaining queries we had and gained some last minute advice for finalising our report. This then meant that we had the means necessary to complete our final report to the highest possible standard.

2.2 Teamwork

A skill that we utilised and further developed during working on this project was our teamwork skills. Although teamwork is a skill we have made use of in in previous years, it was not to the same extent as was required for this project and this pushed us to improve on our teamwork abilities.

From the beginning, we ensured that tasks were delegated accordingly and fairly to each member of the group, in order to avoid falling behind, since we were already a member down. We made sure to keep on track with the project by being in constant communication with each other on social media and through holding regular weekly meetings with Jamie Walker, our project advisor, to ensure that we were on the right track. During each weekly meeting, we discussed the progress we had made and then improved on certain areas where necessary, and finally set goals for the following week. At our regular meetings, we would also give each other feedback and constructive criticism on the work that had been completed, to ensure that every member of the group was happy with the direction that the project was heading in.

2.3 Introducing our models

The Goodwin Model:

Regulatory mechanisms play an essential role in the survival of organisms, for example, the control of metabolic balance and homeostasis and the response to environmental changes, such as night to day [G1:p1]. These mechanisms begin at a cellular level due to enzyme activity, gene expression, and feedback inhibition [G1:p2]; therefore, as a group the first model we decided on using to model the body clock was 'The Goodwin Model', since it is a basic model that clearly models the gene expression occurring during the circadian cycle. This model was published in the 1965 [G2:p1] by Canadian mathematician Brian Goodwin, and was designed to show how feedback inhibition can lead to regular rhythms and oscillations [G1:p1]. The model is extremely useful in helping one to investigate the properties of circadian oscillators since it responds well to perturbations from outside influences, such as light pulses [W3:p1].

The Model is as follows [G1:p3]:

$$\frac{dX}{dt} = \alpha_1 \frac{K_n}{K_n + Z_n} - \gamma_1 X \tag{1}$$

$$\frac{dY}{dt} = \alpha_2 X - \gamma_2 Y \tag{2}$$

$$\frac{dZ}{dt} = \alpha_3 Y - \gamma_3 Z \tag{3}$$

The model shows a simple oscillatory negative feedback loop in which a protein is translated and goes on to inhibit its own transcription [R2:p29]. In this model, X can be taken to be the concentration of ('clock') mRNA, Y as the ('clock') protein produced by X, and Z is a second protein known as the transcriptional inhibitor [R2:p29]. The feedback loop is produced as a result of the repression by the inhibitor Z [W3:p2]; the higher the concentration of Z, the lower the concentration of X that will be formed, hence the negative feedback. This inhibition can be seen by the term $\frac{K_n}{K_n+Z_n}$ in equation (1). Without inhibition, X is produced at a steady and constant rate, and the steady production rate of Y and Z rely solely on the production of X and Y respectively [R2:p30]. The α_1 parameter is known as the driver of the model and is the factor that is most sensitive to outside influence. Therefore, α_1 can be used to model the effect of light on the circadian rhythm, where light is taken as a function of time, and we will be using it to mimic pulses of light.

The Goodwin model is a basic model for Circadian rhythm and helps to develop a fundamental understanding of how a single factor, i.e. light, can have a detrimental effect on a healthy circadian clock by causing disturbed rhythms. Another reason we chose to use the Goodwin model is that the system is very popular and widely used in circadian modelling. This meant that we were able to find numerous reports and studies on circadian rhythms that had used the Goodwin model, making it easy for us to compare our results to previous ones.

The Becker-Weinmann Model:

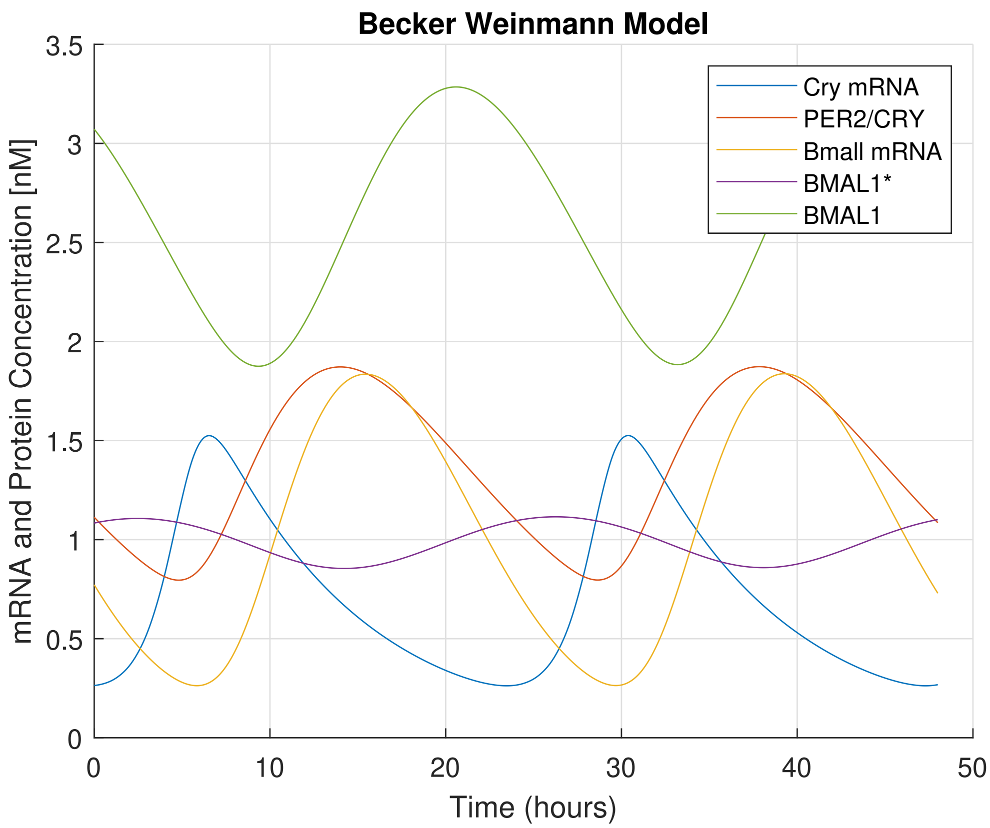

Figure 1: The Becker Weinmann model, in terms of mRNA and Protein Concentration as functions of time.

The second model we have decided to use is the Becker-Weinmann model, as shown in our adaptation in Figure 1. The Becker-Weimann models a mammalian biological clock with a reduced number of variables. We chose this to include alongside the slightly more simple Goodwin model model since it was not as complex as other models, such as Leloup and Goldbeter, and therefore far more efficient as it could be simulated many times within the same code.

The Becker-Weinmann model focuses specifically on the essential parts of the positive and negative feedback loops in our circadian rhythm. There are transcription factors in our circadian rhythm; we will only be using BMAL1 as CLOCK is essentially a fixed parameter. The PER and CRY proteins decrease the rate of their own synthesis by inhibiting BMAL1/CLOCK transactivation activity. CRY genes are vital for the circadian rhythm as it is the inhibitor of the mRNA that causes the negative feedback loop. We only include the PER2 gene out of the PER genes as the null mutation causes arrhythmicity. PER2 is also said to have impact positively on Bmall transcription.

[B5:p3] The Becker-Weimann is described by the following system of differential equations:

$$\frac{dy_1}{dt} = f(trans\frac{PER_2}{CRY}) - k_{1d}y1 \tag{4}$$

$$\frac{dy_2}{dt} = k_{2b}y1^q - k_{2d}y_2 - k_{2t}y_2 + k_{3t}y_3 \tag{5}$$

$$\frac{dy_2}{dt} = k_{2b}y1^q - k_{2d}y_2 - k_{2t}y_2 + k_{3t}y_3 \tag{6}$$

$$\frac{dy_3}{dt} = k_{2t} \cdot y_2 - k_{3t} \cdot y_3 - k_{3d} \cdot y_3 \tag{7}$$

$$\frac{dy_4}{dt} = f(trans_{Bmal1}) - k_{4d}y_4 \tag{8}$$

$$\frac{dy_5}{dt} = k_{5b}y_4 - k_{5d}y_5 - k_{5t}y_5 + k_{6t}y_6 \tag{9}$$

$$\frac{dy_6}{dt} = k_{5t}y_5 - k_{6t}y_6 - k_{6d}y_6 + k_{7a}y_7 - k_{6a}y_6 \tag{10}$$

$$\frac{dy_7}{dt} = k_{6a}y_6 - k_{7a}y_7 - k_7dy_7 \tag{11}$$

The transciption rate of $\frac{PER_2}{CRY}$:

$$f(trans\frac{PER_2}{CRY}) = \frac{v_{1b}(y_7 + c)}{k_{1b}(1 + (\frac{y_3}{k_{1i}})^p + (y_7 + c)}$$

The transciption rate of $trans_{Bmal1}$:

$$f(trans_{Bmal1}) = \frac{v_{4b}y_3^r}{k_{4b}^r + y_3^r}$$

Each yi, $i = 1, 2, 3, 4, 5, 6, 7$, represent different proteins:

$y1 =$ concentration of PER2 or CRY mRNA which are considered to be identical
$y2 =$ concentration of PER2 complex in the nucleus
$y3 =$ concentration of the CRY complex in the nucleus
$y4 =$ concentration of Bmall mRNA
$y5 =$ cytoplasmatic BMAL1 protein
$y6 =$ BMAL1 protein in the nucleus
$y7 =$concentration of a transcriptionally active form BMAL1*, which can be understood as a com-

plex with CLOCK and.or a phosphorylated form of BMAL1

Figure 1 shows the Becker-Weinmann Model we were able to code up using MATLAB and shows the concentration of mRNA and protein concentrations that we have explained above [B5].

2.4 Choosing MATLAB

As a group, we decided to use MATLAB to code up our models for the main reason that we all had some prior experience in this program. Therefore, we would all be able to offer some input in the formulation of our graphs. Python was also suggested as a potential coding platform, however only one member of the group had experience in this program and we therefore decided against this as, in order to work best as a team, we thought it would be best to stick to a coding platform that we all had some former knowledge of. We also believed that MATLAB would enable us to produce graphs at a much faster rate than if we had to learn how to use a completely new computer program in the limited time we were given to complete this project. MATLAB is also meant we were able to add comments on the code as we went along to ensure that all members of the group fully understood each step of the code. The graphs we produced were clear and of a high resolution, whilst also being easy to understand, since MATLAB allowed us to use colours to represent the different lines and perturbations we had introduced.

2.5 Calculating Phase Shifts

We show the effects of jet lag, light pollution, and shift work on the circadian rhythm through phase shifts, which describes the horizontal translation of the function with respect to the regular $sin(x)$ or $cos(x)$. This can be produced mathematically through the phase shift equation:

- $f(x) = A * Sin(Bx - C) + D$

or

- $f(x) = A * Cos(Bx - C) + D$,where $A, B, C, D \in \mathbb{R}$ [M1]

We can then determine the values of B and C before dividing C by B.

- If as a result a positive value is obtained, the graph will be shifted to the right
- If a negative result is obtained, the graph will be shifted to the left [M1]

Our phase shifts have been graphically illustrated by utilising MATLAB and taking the following steps. The first step was to take the Goodwin model without daylight forcing then run it twice – once with perturbation and once without. 24 hours is then estimated in terms of the number of points present in the array before going back 24 hours from the last point, which we label t_1. Following this, an estimate of the differential of the point is taken, however as it oscillates, there can be two points present with the same value but different gradients: one going to the right and one to the left. As soon as a point is found within our tolerance (gradient and concentration), we see whichever one is closer and label this t_2. The difference between these points (t_1 and t_2) is the phase shift.

2.6 Runge-Kutta 4

Whilst coding on MATLAB, we decided to use a Runge-Kutta method. We will now explain why the Runge-Kutta 4 (RK4) was the best option for us when it came to coding up our chosen models. We used the lecture notes from the MTH2005 to explain this method[B6].

We first start from the basics. Taylor Series is an expansion used for deviation h from x. We will only be using $f(x+h)$:

$$f(x+h) = f(x) + hf'(x) + \tfrac{h^2}{2!}f''(x) + \tfrac{h^3}{3!}f'''(x) + \tfrac{h^4}{4!}f^4(x) + \ldots h.o.t.$$

We will now obtain Forward Euler (FE). Using the Taylor Series and rearrange for $f'(x)$:

$$f'(x) = \tfrac{f(x+h)-f(x)}{h} + h.o.t.$$

Now, consider:

$$\text{Discretised } \tfrac{dx}{dt} = F(x) \; x \to x_n$$

Then:

$$\tfrac{dx}{dt} = \tfrac{x_{n+1}-x_n}{\Delta t} + O(\Delta t)$$

This is the Forward Euler Scheme which, as you can see, is 1st order accurate.

Now we will look into the Runge-Kutta scheme. In particular, we will look at Runge-Kutta 4 (RK4). This method improves on the accuracy of the Foward Euler by evaluating the forcing function $F(x,t)$ at several intermediate points within the time-step.

$$\tfrac{dx}{dt} = F(x)$$

Now compute:

$$k_1 = F(x_n, t_n)$$

at the start if the time interval.
Then, evaluate:

$$x_n + a\Delta t k_n \; ; \; t_n + b\Delta t$$

where a and b are to be determined.
Compute k_2, approximately $\Delta x = k_1 \Delta t$;

$$k_2 = F(x_n + a\Delta x, t_n + b\Delta t) = F(x_n + a\Delta k_1, t_n + b\Delta t)$$

Then compute the new point:

$$x_{n+1} = x_n + \Delta t(ck_1 + dk_2)$$

Then for k_3 and k_4:

$$k_3 = F(x_n + \tfrac{\Delta t}{2}k_2, t_n + \tfrac{\Delta t}{2})$$

$$k_4 = F(x_n + \Delta t k_3, t_n \Delta t)$$

Giving the time-step formula:

$$x_{n+1} = x_n + \tfrac{\Delta t}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

The RK4 scheme evaluates F within the time-step.

The Runge-Kutta 4 is fourth order accurate, which is a higher order than Forward Euler. Sometimes, lower order accuracy cannot determine numerical methods, therefore we must use higher order schemes to evaluate the dynamical system. Furthermore, it is evident than the higher the order, the more accurate the method is, therefore the Runge-Kutta 4 is a better method to use than the Forward Euler when using the Goodwin model.

2.7 Limitations

Issues surrounding the Goodwin Model:

The Goodwin Model is a minimal model, which means that it only contains the most essential elements of the circadian clock. This can be a positive, as seen in the following quote: "Minimal models are the remains of Occam's razor; A model should not increase beyond what is necessary; that is, the number of adjustable parameters should not increase beyond what is required to explain something, and no more assumptions should be made than are minimally needed." [R3]. However, minimal models can also potentially cause some issues. As the number of parameters increases in a model, it may suggest some more biological complexity. Since the Goodwin model is a minimal model, we have discovered that it is limited since it only contains one parameter that we can influence, despite our research showing that the circadian clock can be influenced by multiple zeitgeber's at any one time, not just light. These could include; appetite changes, temperature, and social activity. Therefore, through using the Goodwin model, we are potentially preventing ourselves from obtaining more realistic results, which would be obtained through including the impact of more than one zeitgeber at a time.

Another problem we found with the Goodwin Model is that it is often criticized because the Hill function, n, has an "unrealistically" large value. The processes in enzyme kinetics for n and the formation of repressor protein complexes or the cooperative binding repressor to the gene promoter rarely give us Hill coefficients higher than 4. The Hill function is the negative feedback loop exerted by Z on X; equation (1) [G2]. The majority of models tend to use the Hill function to describe the transcriptional repression [K3:p1-2].

Issues surrounding the Becker-Weinmann model:

The Becker-Weinmann model is a mammalian biological clock consisting of a reduced number of variables and does not represent the human circadian rhythm [B5]. This could potentially cause some unreliability in our results since we are using it to model the human body clock. The model consists of 7 differential equations three for each Per2/Cry and Bmal1 (mRNA, complex in the cytoplasm, complex in the nucleus) and one for transcriptionally active Bmal1 [B5]. The model and parameters were based off experimental data from mice, and since it was highly robust to variations in parameters (factor of 2), we are confident that it can be applicable to humans. However, since it is based off experimental data, this could mean some errors may exist within the models parameters and therefore may not be completely reproducible.

The Becker-Weinmann model, with it being more complex that the Goodwin model, took a lot longer for us to code up. Hence, we did not use it extensively due to the duration of time it took to run many of the simulations we wanted to test. With better equipment and a longer period of time, it would have been more feasible to use the Becker Weinmann model more consistently throughout the project. However, since we are only testing the theories and not putting it into practice, the consistent use of the Goodwin model can be justified.

Issues surrounding group work:

Every Friday, we had a scheduled two hour in person meeting with our project leader. However, due to the current COVID-19 circumstances, we came across a few issues, one being that there was a situation where our project leader was awaiting a PCR test result and hence could not attend the meeting. Although this was a concern from the beginning, we were able to have them join our meetings via Microsoft teams so that all members felt they were still involved. Therefore, we managed to overcome this particular limitation.

Deciding to narrow down our project was a difficult decision, since each group member felt strongly about the topics they had researched in the initial stages of the project. After weighing up the pros and cons of to possibilities that came from each topic, we decided to disregard modelling the effects of epilepsy or mental health problems, such as schitzophrenia and bipolar disorder, since we felt these models would be far too complex and time-consuming to code up. This decision was made as a group, and each member felt it was for the best, hence overcoming this limitation.

Another limitation we faced was that we were unable to conduct our own experiments, since we were on a time constraint, but also due to the fact that the experiments we could have carried out may have been considered unethical. Thus it was difficult for us to prove if our recommended treatments would work or not. In the attempt to solve this limitation, we researched a range of experiments and studies and then compared our conclusions to the ones in these studies.

2.8 Entrainment of Circadian Rhythms

We decided that one way to figure out when circadian rhythms can and cannot be entrained is through calculating the bifurcations within the models we are using. To do this, we used the non-dimensionalisation of the equations in the Goodwin model (as shown below), which is carried out to reduce the number of independent parameters [W1:pg3], making the equations a lot easier to analyse and hence obtain the Hopf Bifurcation.

Recall the equations for the Goodwin Model, as seen previously in equations (1)-(3), which take X, Y, and Z to be the concentrations of:

$$X = \text{mRNA}$$
$$Y = \text{Corrosponding Prohibitor}$$
$$Z = \text{Transcription Inhibitor}$$

The following non-dimensionalisation of the Goodwin Model has been adapted from Aurora Woller's paper [W3:p3]. We have simplified the process to show only the key steps, which are as follows:

Taking new variables:

$$x = \frac{\alpha_2\alpha_3}{\gamma_1^2 K_n}X,\ y = \frac{\alpha_3}{\gamma_1 K_n}Y,\ z = \frac{Z}{K_n},\ \text{and } t = \gamma_1 T$$

Our Equations (1) - (3) can now be written as:

$$x' = \frac{\alpha}{1+z^n} - x \tag{12}$$

$$y' = x - y \tag{13}$$

$$z' = y - z \tag{14}$$

Where $\alpha = \frac{\alpha_1 \alpha_2 \alpha_3}{\gamma_1^2 K_i}$ is the only control parameter for n fixed.

We consider α as our bifurcation parameter, and we investigate the Hopf bifurcation of the Goodwin equations (4) - (6) by formulating a third order equation for z only. Steady State solution $z = z^* \alpha$ is given, in implicit form, by:

$$\alpha = z^*(1 + z^{*n}) \tag{15}$$

The characteristic equation is then:

$$\lambda^3 + 3\lambda^2 + 3\lambda + [1 + (1 + z^{*n})^{-1} n z^{*n}] = 0 \tag{16}$$

with the three roots given by:

$$\lambda_1 = -1 - [(1 + z^{*n})^{-1} n z^{*n}] = 0 \tag{17}$$

$$\lambda_{2,3} = -1 + \frac{1}{2}[(1 + z^{*n})^{\frac{1}{3}}(1 \pm i\sqrt{3}) \tag{18}$$

A Hopf Bifurcation offers if $Re(\lambda_{2,3}) = 0$. We find $z* = z_H$ is defined by:

$$z_H \equiv (\frac{8}{n-8})^{\frac{1}{n}}, n > 8 \tag{19}$$

Therefore, bifurcation parameter $\alpha = \alpha_H$ is obtained:

$$\alpha_H = (\frac{8}{n-8})^{\frac{1}{n}} \frac{n}{n-8}, n > 8 \tag{20}$$

(Note that as $n \to 8^+$, $\alpha_H \to \infty$.)

Stable Steady State: $\alpha > \alpha_H$
Unstable Steady State: $\alpha < \alpha_H$

If $n > 8$, the steady state is always a stable or unstable focus for all values of α.

If $n < 8$, the steady state is always a stable focus.

[adapted from W3:p3]

Bifurcation refers to a qualitative change in the dynamics of the system as one or more parameters are varied. The Hopf Bifurcation is a change in stability where two eigenvalues change along the imaginary axis. We will continue to look into this further and what this means in the findings section.

3 Findings

3.1 Understanding the effects of forcing

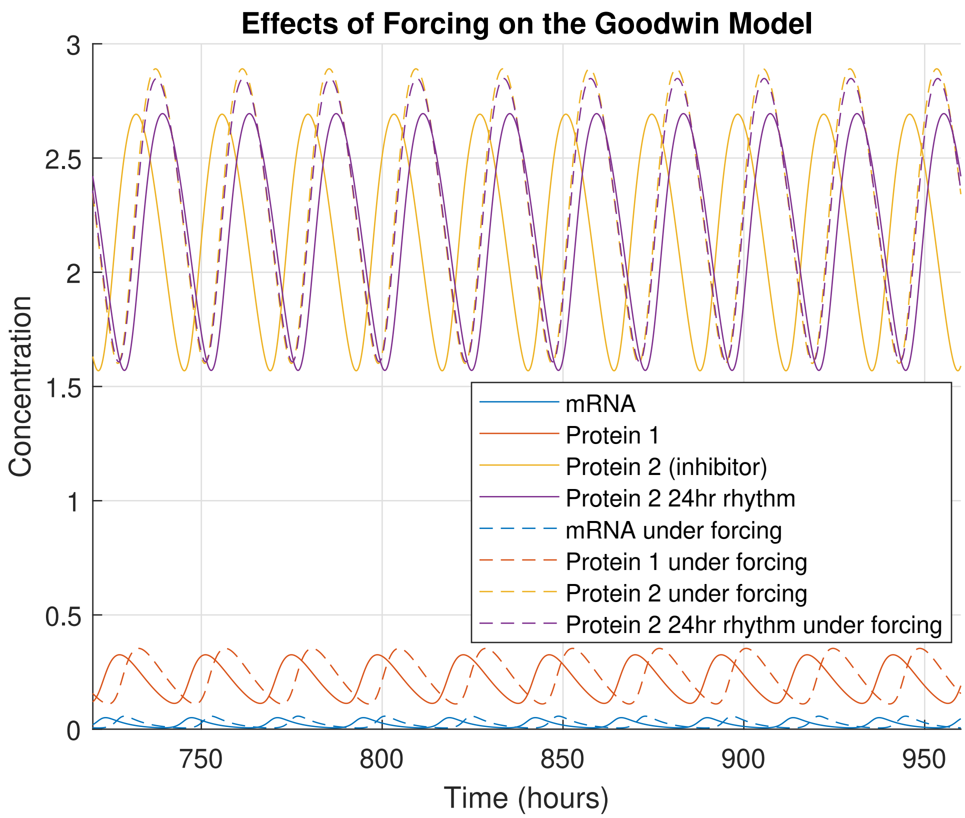

Figure 2: Effects of forcing on the Goodwin Model from the Light/Dark day

As previously mentioned, our circadian rhythm does not naturally follow a strict 24 period. However, with the light-dark cycle, our circadian rhythm adjusts to our 24 hour day. Figure 2 shows the effects of forcing on the Goodwin model. Forcing refers to a force that is applied to our model to depict certain results. When considering our project, forcing refers to the effect of light and dark on the circadian rhythm. Therefore, as previously mentioned, we manipulated the α_1 term in equation (1) of the Goodwin Model to depict pulses of light forced upon the model.

The blue oscillations represent mRNA (X variable in our model), as you can see there is a slight phase shift when under the influence of light. This may be because the mRNA is not strongly effected by the inhibitor (Z variable) and continues production at a steady oscillating rate and concentration, however production is slightly delayed. The red oscillations represent protein 1 (Y variable in our model). When Protein 1 is under forcing it has a very slight increase in amplitude and a slight phase shift. This may be because protein 1 is slightly effected by the inhibition that occurs in equation (1) of the Goodwin Model when under the influence of light.

The orange oscillations represent protein 2 (Z variable in our model), also known as the inhibitor. Protein 2 has a larger amplitude under forcing than with no forcing; it is also slightly shifted to the right. From our previous research, we know that Z is the most altered variable since it is the inhibitor and is triggered by varying zeitgebers, in particular light. Therefore when under forcing, the production of protein 2 is triggered, resulting in a higher concentration of the inhibitor and thus a larger amplitude shown on the graph. Forcing results in increased inhibition meaning the circadian rhythm will be shifted and we will stay awake longer.

The purple solid and dashed lines represent the Z protein (the inhibitor) for when a said person has body clock of exactly 24 hour period. As shown in Figure 2, there seems to be no rightwards shift from the solid line to the dashed line as the blue, red and yellow lines have shown. Nonetheless, there is an increase in production of the protein, seen by the increased amplitude of the dotted line. This is as expected, as we know light is the most influential zeitgeber on the body clock.

3.2 Investigating Jet lag

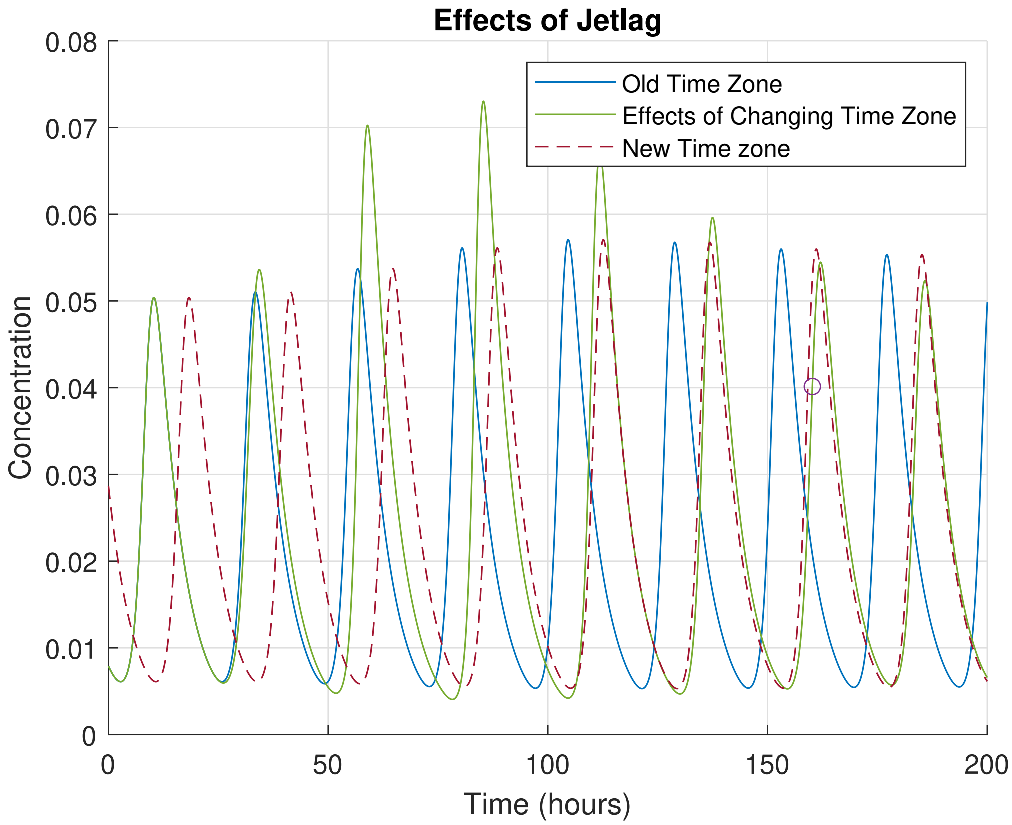

Figure 3: The effects of jet lag on the circadian rhythm, with an 8 hour time difference and an 8 hour flight

We can see our model for jet lag in Figure 3, in which we assume that there is an 8 hour time difference between the two time zones. We also assume that the time taken to get to one time zone to another is 8 hours. We modelled this diagram so that the person who is experiencing the jet lag leaves at time 24 hours and thus arrives at their destination at time 32 hours. The blue line in Figure 3 represents the old time zone and the red dotted line represents the new time zone. The green line indicates the effects of changing time zone on our circadian rhythm. From the model, we can deduce that it takes roughly 5-6 days for our body to adjust to the change in time zone. As shown in the diagram, there is an instant change in our circadian rhythm when leaving the time zone. The mRNA spikes slightly as well as shifting slightly to the right. This implies that the body feels less tired generally and also won't feel tired until later. The amplitude of the oscillation increases for the next 48 hours, however still falls earlier than of the new time zone. This is one of the symptoms of jet lag; fatigue. Although the body may start feeling more awake at certain points of the day (when the concentration of mRNA is high), it still does not fully compensate straight away, thus the body is still adjusting to the new time zone. The amplitude then starts decreasing until it gets to a similar level as the new time zone where the body has started to adjust.

3.3 Light Perturbations

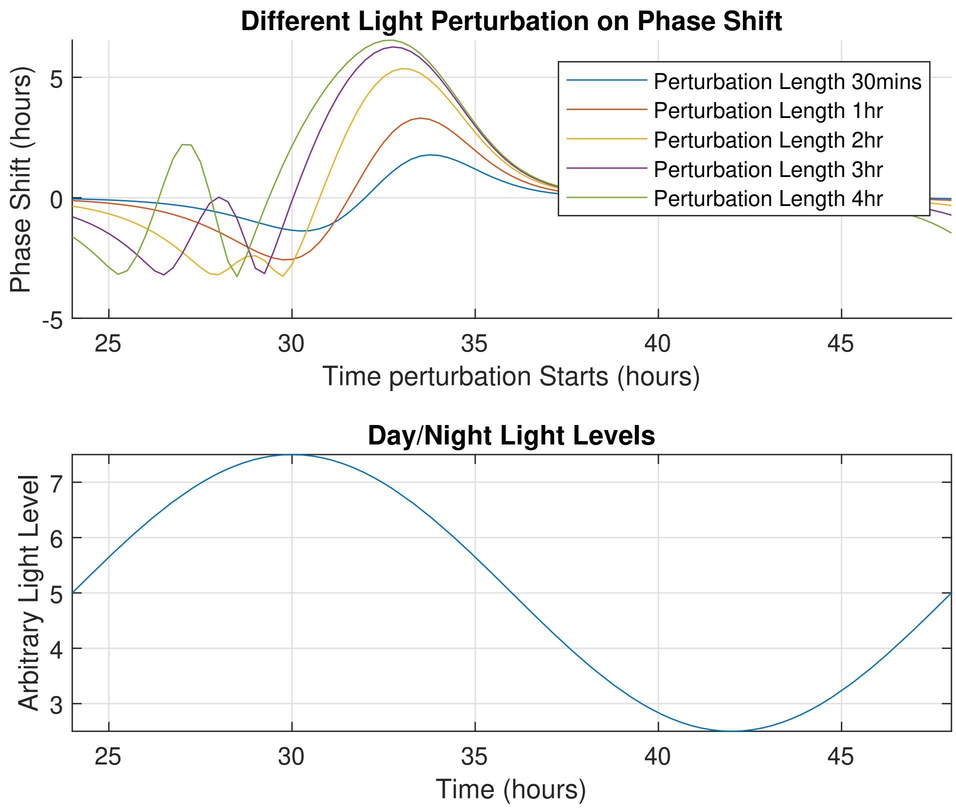

Figure 4: How the length of light perturbations effects phase shifts

In Figure 4, we modelled potential phase shifts for different light perturbations to the circadian clock. We can see that, in general, as the perturbation length increases, the length of the phase shift increases. By comparing the two graphs in Figure 4, we can infer that the greatest phase shift occurs at times of high levels of light. We can use this information to help us to determine the most impactful time to start the light perturbation and length of perturbation when looking at jet lag. This can be used in other theoretical solutions where a phase shift is required. However, this is not so reliable in the case where phase shift has already occurred and is getting re-entrained.

3.4 Investigating Shift Work

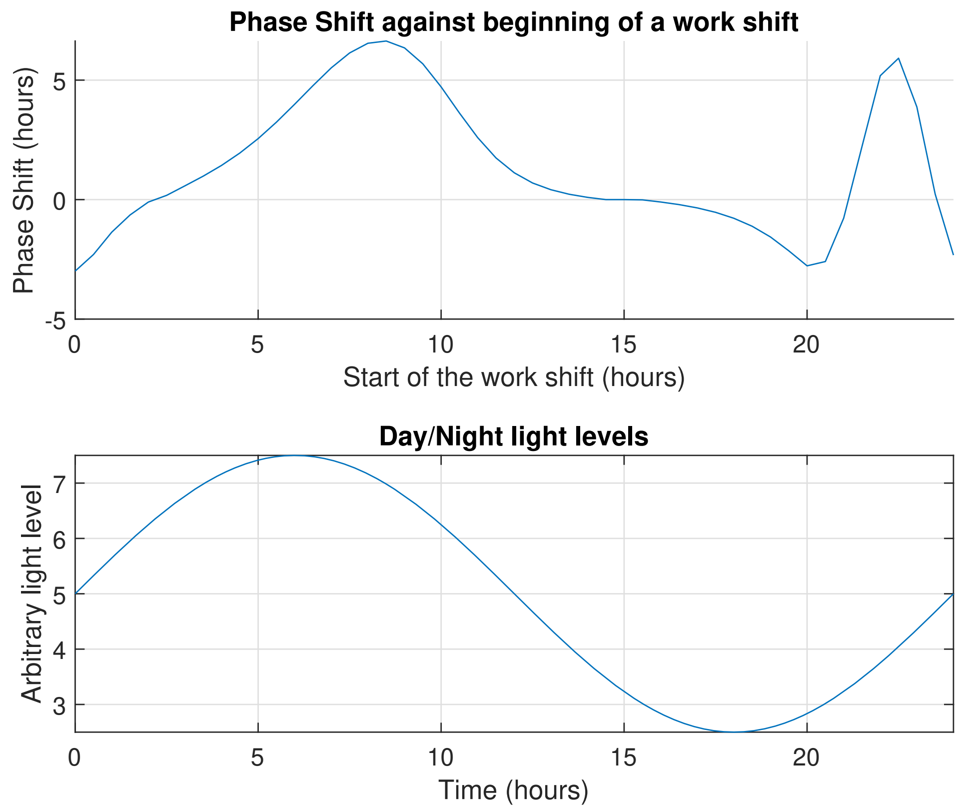

Figure 5: The effects of shift work on phase shifts within circadian rhythms

As stated in our introduction, we have taken shift work to be all the non-standard work schedules, such as part-time or permanent night work, and irregular hours or split shifts [S1:p1469]. After considering this definition, and through further research into shift work, we had to decide on what we believed to be the most prominent areas of shift work that would impact on our circadian rhythms. We concluded that investigating how the start time of the shift effects the phase shifts would be the best way to apply the concept of shift work to our models.

In Figure 5, we can see two separate, though related, graphs. The top graph portrays how the start time of a 9 hour shift shift can cause phase shifts and hence disrupt our circadian rhythms. We have taken 0 on the x-axis to be the time 6am. Knowing this, we can see from the graph that beginning a shift at roughly 8:30am would not cause a phase shift, meaning the circadian clock would be running in a normal, healthy manner. This could be explained by the fact that 8:30am is taken to be a very average and reasonable time to start a working day, as it correlates to an almost 9-5 day which is the most common work hours as it aligns nicely with out natural sleep-wake cycle.

Contrastingly, we can see from the top graph that the greatest phase shift occurs when a 9 hour shift begins at roughly 3pm, hence meaning it would end at midnight. This means that completing a shift between these times would cause great disruption to our circadian rhythms, and hence increase the chance of illness and other complications. This inference lines up nicely with our research, because a 3pm-midnight shift is certainly considered as a non-standard work schedule. Hence, the results from these graphs enable us to come to a conclusion that shift work causes phase shifts and therefore cause a negative impact on our bodies by disturbing our circadian clock.

The second graph in Figure 5 shows the light levels throughout the different hours of the day. In our graph, the greatest level of light is seen at around 12pm and the lowest levels at roughly 12am, which makes complete sense in terms of the 24 hour light-dark cycle. It is interesting to see that there is a very clear correlation between the two graphs in Figure 5, and the trends in both graphs certainly follow the same pattern. This means we can infer that the greatest phase shifts occur at extreme light levels; either very low or very high. This can be understood since light is the main zeitgeber in affect our circadian rhythms, so extreme levels of light will understandably have the greatest impact on our circadian clock.

3.5 Investigating Light Pollution

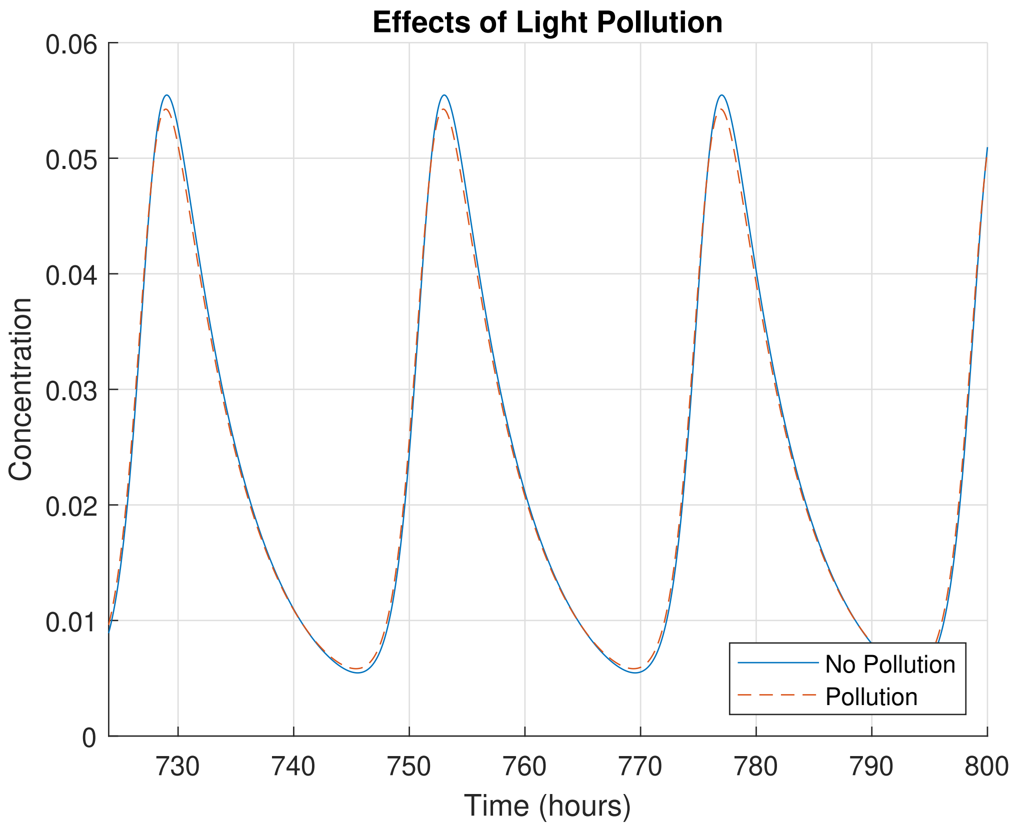

Figure 6: The effects of Light Pollution on concentration of mRNA

The forms of light pollution that we focused our research on were those surrounding unnatural light. Although we tend to only think about our electronic devices, such as phones, tablets and laptops, as the form of light pollution that affects us, other forms of unnatural light like streetlamps and building lights can actually have a significant influence on our circadian rhythm. Figure 6 was produced via our Goodwin Model code and it illustrates the effects of light pollution. The red dotted line represents our circadian rhythm when influenced by light pollution. The blue line represents our natural circadian rhythm without any influence or perturbations. The red line has a slightly smaller amplitude than the blue line, and it is very slightly to the left of the blue line.

From this model, it is clear that light pollution suppresses the mRNA in our circadian rhythm and if it is assumed that no other external stimuli is present, this decrease in mRNA can cause our bodies to feel less tired which as a result makes you stay awake for longer/fall asleep later. The marginal positioning of the red dotted line towards the left of the blue line implies that we remain asleep for a shorter duration as we wake up earlier. As a result, our bodies sleep for a smaller duration of time than what is natural.

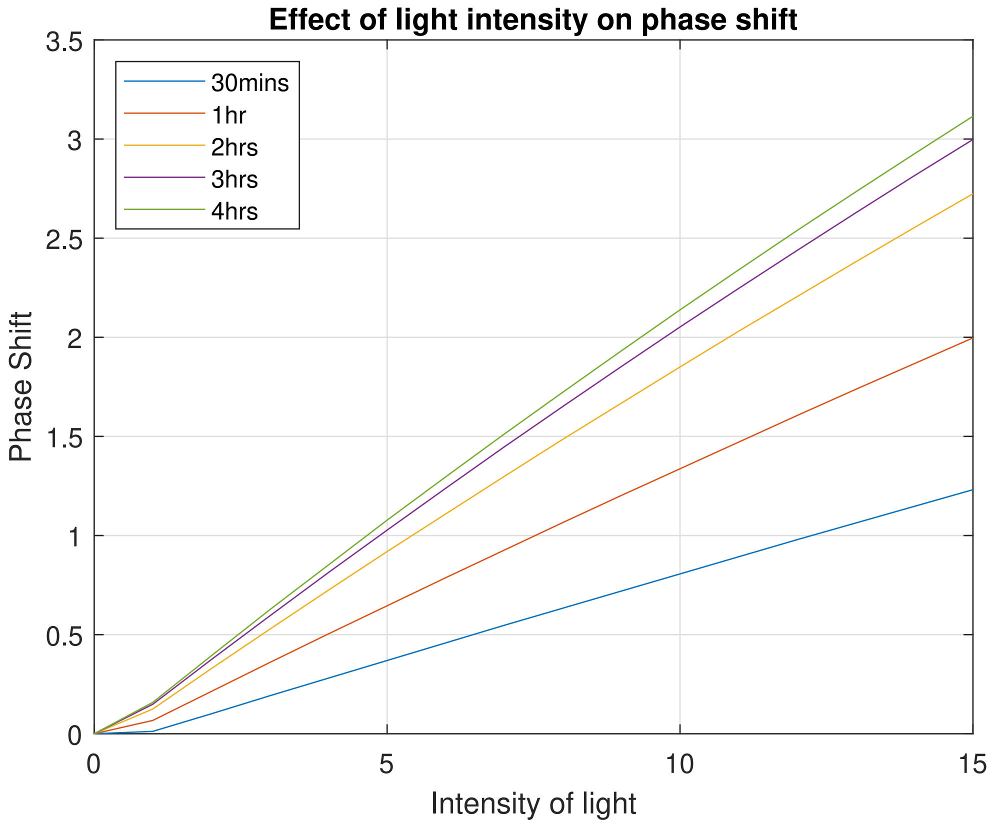

Figure 7: Showing the phase shift for different light intensities for different durations (30minutes to 4 hours)

Figure 7 depicts our phase shift graph, which is remarkably linear. This illustrates that the higher the force of light intensity, the greater the phase shift will be. Since we know light plays a significant role in disrupting the circadian rhythm, it gives us a positive correlation.

Figure 7 shows how being exposed to different light intensities for different amounts of time effects the phase shift of the circadian rhythm. We see a very linear trend with all the different time exposures. From the graph we can deduce that the longer you are exposed to a light source the worst the phase shift is. Looking more in depth, the difference between being exposed for 30 minutes, 1 hour and 2 hours is quite major. This shows us that to avoid a large phase shift which can therefore disrupt the circadian clock more then necessary, it is very important to keep light exposure to a minimum. When looking at times where light has been exposed for a lot longer (3 hours and 4 hours), the different between the slopes are very minimal, which implies that there is little difference between light intensity and phase shift for the two different exposures. This suggests that when you are exposed for longer periods of times, there is a point where the phase shift can't become any bigger.

Furthermore, when looking into how much light intensity effects the phase shift, it can be inferred that each time we see a positive linear relationship between light intensity and phase shift it suggests that regardless of the duration of time you're exposed to light, the higher the intensity you're going to be exposed to results in a greater phase shift.

3.6 Entrainment and the Hopf Bifurcation

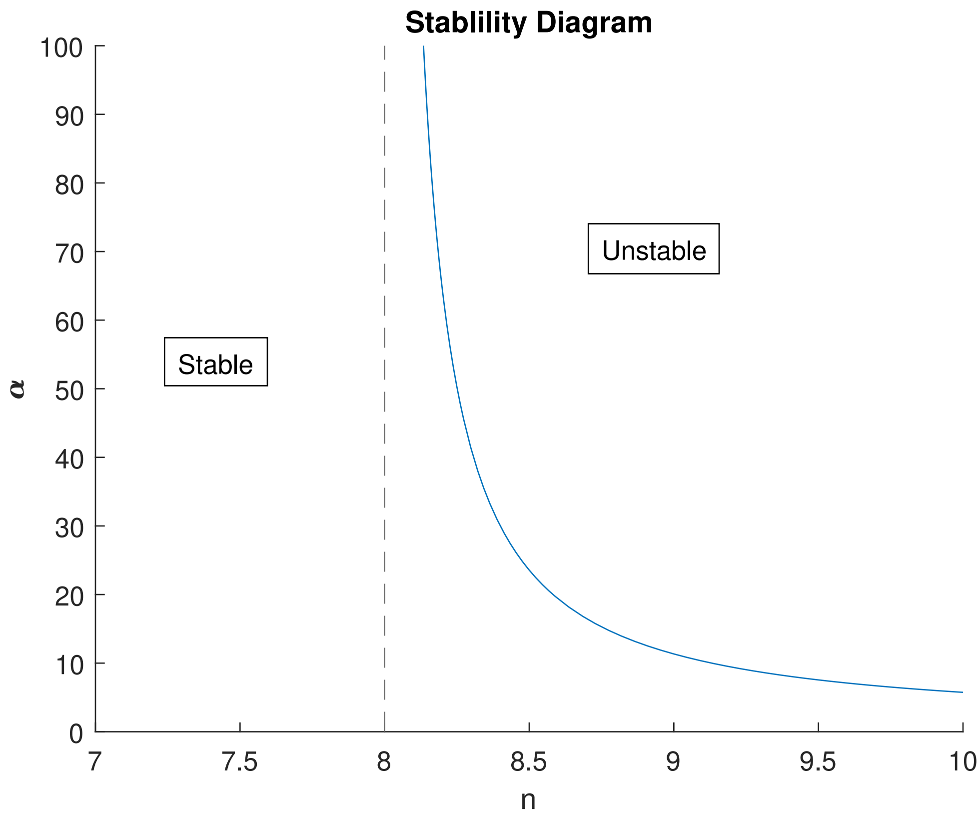

Figure 8: Stability Diagram in terms of α and n [adapted from W3:p3]

We previously mentioned the Hopf Bifurcation in the methodology section. This showed us when n is stable and unstable for values of α, our bifurcation parameter, using $\alpha = \alpha_H n$ from equation (20).[W3:p3] Figure 8 shows this stability diagram. Underneath the blue line is the stable focus, and above the blue line in the unstable focus, as discussed previously. Where the graph is shown to be unstable, the circadian rhythm can no longer be re-entrained. This implies that when left to the natural light-day cycle, the circadian rhythm will move further away from stability and will therefore worsen the body clock. Due to this, it is important that we have treatments for the unstable cases else it will cause serious health issues.

We found a paper from the Exeter online library that influenced our decision in researching about when our bodies can not be re entrained. Creaser used a different model to us and went into very in depth mathematical models that we do not fully understand at our level [C3]. Therefore, we went to further research other papers with similar concepts but for the Goodwin Model. We found that [W3] paper was extremely useful to analyse and hence have adapted it into our report.

4 Conclusions

Our main aims for this project included understanding the circadian rhythm, investigating what circumstances lead to it being disturbed and the impacts of this, and in turn looking at ways of treating the disturbed rhythm and lessening the symptoms of this impact. Although finding treatments for circadian disorders is a relatively new area within biological research, during our research we concluded that there were three main types of therapy repeatedly being investigated and studied by scientists. Therefore, as a group we have decided to focus on these three treatments, apply them to our three topics and hence come up with our own opinions and conclusions to finalise our project.

The three main treatments we will be considering in regards to each area of our study are: Prescribed sleep scheduling, timed light exposure and therapy, and melatonin administration. We will compare our findings and proposed treatments to the real-life studies performed in some of the research papers we have found, since we have been unable to carry out our own case studies.

Prescribed sleep scheduling refers to planned napping or pre-planned sleep times. In trials, it has been shown that planned napping for up to an hour improves alertness and was found to counteract tiredness during the day, or during work [S1:p1471]. However, there have been no real conclusive studies performed to confirm this, since trials are hard to undertake due to a lack of participants and the fact that they are very time consuming [S4,p1495].

Our second form of treatment, timed light exposure and therapy, has been found to be beneficial in correcting some circadian rhythm disorders [G3:p674]. This form of treatment refers to the patient being exposed to timed bright light, preferably enriched blue light [G3:p669], at specific times of the day in order to produce either a phase delay shift or a phase advance shift of the circadian rhythm. Since the Circadian system is the most sensitive to light during what we consider the 'biological night', bright light exposure is most effective when performed shortly before sleep or shortly before waking [G3:p670].

Melatonin administration is a treatment widely considered by scientists, and it involves taking (melatonin) tablets, usually before bed. This can be considered a less natural process than that of prescribed napping or timed light exposure, and could therefore cause some controversy ethically. Additional melatonin has been shown to accelerate the resetting of the circadian rhythm [S1:p1476], hence responding to a disturbed circadian clock. However, overall data does not support the use of melatonin since it doesn't produce a change in circadian rhythm that is significant enough. It also may be expensive, and could be potentially dangerous [S1:p1472]. Therefore, it is not a widely publicised treatment.

We believe that it is important to maintain a healthy circadian rhythm as there are many health risks when this isn't done. An article about lack of sleep in adolescences shows that there is a correlation between sleep and the following: obesity, depression, school performance, quality of life and risk taking behaviours. Although, adolescences are generally easily adaptable to change and they tend be a lot healthier, since they're able to be more active [C2]. There has also been research regarding shift workers with excessive sleepiness, pathological fatigue, anxiety and depression [F]. We will now explain how each of these treatments can lessen the symptoms of the below disorders, and which treatment we would prescribe for each disorder. Depending on the disorder some treatments may be found to be more useful than others, also it may be that for optimal recovery a mixture of many treatments may be required.

4.1 Proposed treatments for jet lag

As previously seen in our model for jet lag (Figure 3), it takes around five to six days to fully adjust to a new time-zone that has an eight hour difference to ones previous time-zone. Therefore, many people will suffer from symptoms of jet lag for a majority of their trip. In a study of non-pharmacological interventions, there was limited evidence to suggest that any treatments for jet lag are sufficient; from a review of 13 studies on various jet lag interventions, 9 of these showed no significant impact, and only 1 reported any benefits to the interventions [B4:p48]. However, we will still explain how the three treatments could hypothetically lessen jet lag symptoms.

First we investigated how prescribed sleep scheduling could benefit those suffering from jet lag. Studies from our research papers suggested that the person who will travel could dedicate two or three days within arrival to the new time-zone to swiftly re-aligning their circadian rhythm [S1:p1475]. This re-alignment may occur faster under this circumstance rather than if you were attempting to continue life as normal which would lead to eventual fatigue.

From our own experiences of jet lag, members of the group were able to suggest potential other options. One option, falling under the category of prescribed sleep scheduling, was the idea that one could begin to re-align their circadian to the new time-zone before travel. This would mean adjusting the body a day at a time prior to the flight; this would not just include a change to the sleep schedule but would also require the person to do things like start eating and exercising at times that line up with the new time-zone to feel the full benefits of this treatment.

As a group, we feel this form of treatment would be beneficial to people or families who are travelling for a holiday, since it will mean people can enjoy their holiday to the full extent without the negative symptoms of jet lag causing difficulties. However, this requires dedication and may be unrealistic; it also may not completely work since you will inevitably experience travel fatigue [S1:p1475] no matter what precautions are taken. For people travelling on business trips that only last a couple of days, it would be an unnecessary and unrealistic treatment, since adjusting to the new time zone before travel may mean they are unable to attend work or continue with their day to day life.

The second proposed treatment for jet lag is timed light exposure. For those travelling eastwards, for example travelling from the USA to the UK, they will typically experience difficulty waking in the morning, and daytime fatigue [G3:p670]. Proposed bright light therapy for eastwards travel would include early morning bright light exposure and dim light in the evening hours; this would result in a phase-advance shift.

For those travelling westwards, for example from the UK to the USA, typical jet lag symptoms involve daytime fatigue and waking too early. Therefore, bright light exposure in the evening before sleep and dim light in the morning will help reduce these symptoms, since this results in a phase-delay shift [G3:p670]. As a group we consider this to be another good treatment, however it would be time consuming and would require dedication much like the prescribed sleep scheduling. Also, we are unsure if there are medical implications to being exposed to too much bright light or if it is dangerous for your eyes.

The third treatment, albeit similar to the previous one, is shown from Figure 4 where timing exactly how long to stay in bright light and when to do this is done to adjust the circadian rhythm. The top diagram [Figure 4] demonstrates that it is possible with jet lag to naturally adjust your circadian rhythm by determining the length of light perturbation and, therefore, when to start this light perturbation in order to adjust the circadian rhythm to the new time zone. Although this may be difficult to implement, it may be very useful for frequent travellers. Furthermore, this may be helpful for when the natural circadian rhythm may be disturbed due to short term circumstances that can not be helped, i.e. late night work or study. With this knowledge, people can readjust their circadian rhythm in order to regulate and maintain their day to day lives. This is one way of naturally entraining the body clock. Nonetheless, being able to strictly manage this is very difficult, especially in the busy lives that most people tend to have.

Our final treatment in relation to jet lag is melatonin administration. Melatonin improves quality of sleep by increasing amplitude, instead of creating a phase shift of sleep/wake cycles [S4:p1496]. In a study we found in our research papers, it was shown that compared to a placebo, melatonin accelerated entrainment four days faster; it was six days for entrainment via melatonin, and ten days via the placebo [S1:p1476]. Therefore, suggesting that for our model the adjustment time would now only be about three and a half days, rather than five or six days. Melatonin administration would require the person that is travelling to take tablets before they start travelling in order to acclimatise their body prior to travel. This could be a complicated process and, in order for the best outcome, the melatonin would need to be taken at very specific times which may be hard to calculate when taking into consideration travel times and time-zones.

As a group, we decided the best course of treatment for those suffering with jet lag is prescribed sleep scheduling, since it is the most natural course of treatment. Prescribed sleep scheduling is also the easiest for people to follow, especially when taking into consideration young families that travel. Not only is this an effective treatment, but is also a natural one. There are no ethical issues regarding this form of treatment and is has no potential side effects. Therefore, of the three treatments we are considering, prescribed sleep scheduling is certainly the most appropriate in terms of treating the symptoms of jet lag.

4.2 Proposed treatments for shift work

Our findings on shift work show that the later you begin the shift, the more disrupted the circadian rhythm becomes (assuming a typical 09:00-18:00 shift is a 'normal' shift). Shift work plays an essential part in keeping the world in motion, (as we have seen with the healthcare system during the COVID-19 pandemic), and so many industries involve shift work. Therefore, we have looked into treatments for these workers in order to find ways for them to try and maintain a healthy circadian rhythm.

In some studies carried out it was shown that workers, in particular police officers, benefited from a nap before their night time shift, since it resulted in fewer accidents on shift [S1:p1471]. In relation to our model, having a nap before a night shift may help to stabilise the circadian rhythm and will definitely result in less fatigue during working hours.

When considering prescribed sleep scheduling to lessen the symptoms from shift work, we realised this may be tricky for many workers to achieve, since it requires planned napping [S1:p1471] and shifts tend to be very irregular. One of the main problems with shift work is that it is very irregular and there is never a set pattern, which is why the circadian rhythm can never settle, and hence attempting to plan a nap may be a difficult task.

Therefore, timed light exposure may be a better form of treatment for those suffering with shift work disorder. In a study by Budnick et al., 13 rotating shift workers were exposed to bright light, rather than ordinary light, for at least 50% of their shift for a time span of 3 months. The workers reported an improved alertness and better work ethic under this circumstance [S1:p1472]. This study is in line with our discoveries, since we found that bright light exposure triggers a circadian response, meaning we are able to stay awake longer.

For workers that have multiple night shifts, we would recommend dim lighting in the early morning (after they have finished their shift) in order to promote the need for sleep. Whereas, in the evening we recommend bright light exposure to promote wakefulness. We believe that timed light exposure may in fact help to introduce some sort of structure into workers' lives that are normally fairly irregular. We understand however, that many workers are very stimulated once they have finished their shift, and therefore will struggle to sleep for up to 3 or 4 hours after shift; this in turn only creates an even larger phase-advance shift. Therefore, shift work disorder can be considered a very difficult circadian disorder to treat.

A paper found by Charmane I. Eastern et al studies how giving bright light in night shifts help circadian rhythm, but also how using dark goggles during a day shift helps you adjust to the two different shifts [E1:p535-543]. Another article written a few years later by Charmane [E2:p87-98] backs up the findings of their first paper of using dark goggles during the day as well. Therefore, this would be a very useful treatment to use in terms of a shifted circadian rhythm due to shift work.

Our final potential treatment is melatonin administration. We found that this does improve daytime sleeping but fails to increase alertness, which is an essential part of shift work [S1:p1471]. There is very little evidence to prove or disprove the usefulness of melatonin administration for shift work. We believe, by looking at our models, that potential melatonin administration could mean workers are able to stay up longer resulting in them being able to work longer hours.

However, there are many drawbacks to this form of treatment. Firstly, shift workers tend to be very busy and potentially very tired, therefore remembering to take the tablets and deciding when to take them, may be an unrealistic ask. Also, with such irregular shifts, it would be hard to work out correct dosage and timings. Melatonin administration also may be a fairly expensive treatment, and is something that not everyone can afford. Furthermore, it may not be worth spending any money for this treatment, for some, as it does not increase alertness.

Therefore, we believe timed light exposure to be the best form of treatment for shift workers, since it can be performed whenever with no concerns of 'overdosing', which there would be with melatonin administration. It also doesn't matter when the light exposure takes place, as long as it is at the beginning and end of the shift, meaning this should be easy for shift workers to achieve.

4.3 Proposed treatments for light pollution

The effects light pollution is an issue that now impacts most people in their everyday life, and therefore since it is becoming such a common problem it is important to find ways of lessening the impact. However, it is difficult to relate any of our three treatments to this issue, since a lot of the time it is the individuals choice to expose themselves to blue light in turn leading to a disruption of the circadian rhythm.

As a group we considered potentially having a blue light ban for up to 2 hours before bed, in order to stop the promotion of melatonin which triggers the circadian rhythm; this would allow the circadian system to settle. However, we believe it is mainly up to the individual and whether they choose to use blue light or not.

4.4 Overall Discussion

From the outcome of our results, it is clear to see the significant impact certain factors have on the circadian rhythm. Although these may be of small importance to people who are travelling for holiday purposes or to those that stay up later than usual every now and then, it is important knowledge for individuals that travel across time zones regularly for work, those that do a mix of day and night shifts or students who regularly stay up late completing assignments with the affect of blue light from their electronic devices. Through our findings, the duration of time taken for the circadian rhythm to return to normal after being impacted has been illustrated, which will prove useful to the above mentioned individuals.

Since there is still so much uncertainty regarding the treatments of circadian disorders, it is hard promote any one treatment above another. However, as a group we believe that the best possible treatments are natural ones, rather than treatments such as melatonin administration. We believe natural treatments to be the best course of action since the circadian rhythm is essentially a natural internal process and therefore will most likely respond better to natural treatments.

Reviewing our Hypothesis

At the beginning of this project, we set out a few fundamental predictions, which we will now review. We believe that we have successfully justified the standard predictions we made. We were able to confirm that shift work causes disruptions to the circadian rhythms by comparing the phase shifts created when completing shifts at different times. We were also able to show that travelling to a different time zone affects the concentration of mRNA, and in turn alters the processes within the circadian clock. Finally, we were able to again justify that light pollution disturbs the body clock through finding that light pollution suppresses mRNA production, clearly imposing a fundamental negative impact on the natural state of the processes within the circadian clock.

In terms of our initial predictions regarding treatments, it is fair to see that we were correct in our thinking. We did indeed conclude that light pollution is the most difficult to treat out of the three, with the other two being shift work and jet lag, since using blue light daily is extremely common in today's society and would hence require great intervention to treat successfully. Jet lag will be easy to treat for those going on long trips, and those who have spare time before their trip to prepare themselves for the potential side effects of jet lag, since they have more time to adjust to the changes.

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6 Our MATLAB Codes

For those who are interested, we include a file with all of our MATLAB codes here:
https://docs.google.com/document/d/e/2PACX-1vR3iuuSFcpJd2pvxFGt6X7iMYvaw-ABBB4HFRFlyNoZbr0VzU