# Modelling the Effects of Exogenous Melatonin on the Circadian Rhythm

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***Abstract***— The proposed project is to mathematically model the phase-shifting effects that exogenous melatonin has upon facilitation of the circadian sleep-wake cycle. The already-established mathematical model regards the stimulation of endogenous melatonin production as a regulatory mechanism of circadian phase in conjunction with light-induced entrainment. This model can be improved upon through pharmacokinetics via administration of oral exogenous melatonin to promote supplementary activation of melatonin receptors within the suprachiasmatic nucleus of the mammalian hypothalamus. The outcome of this model shows that the concentration of melatonin plasma is higher with the presence of exogenous melatonin. This result can prove that exogenous melatonin can affect the circadian pacemaker, which then will cause a phase-shifting effect in the circadian rhythm.

***Clinical Relevance*** — This establishes the efficacy in the consumption of the melatonin to positively influence the circadian rhythms accordingly.

## I. Introduction

Melatonin is a hormone that plays the role of the wake-sleep cycle of an individual. This endogenous hormone is released from the pineal gland in response to the darkness and affects the circadian rhythms. Circadian rhythm is the 24-hour internal body clock that helps to regulate sleep and other body functionality such as menstrual cycle, core body temperature and other homeostasis functions [1]. There are studies that prove melatonin has phase-shifting effects on other functions of the body as well, other than sleep cycle.

In the presence of light, the production of melatonin will be suppressed in the pineal gland. On the other hand, pineal gland will continue releasing melatonin during the darkness and causing sleepiness. This is one of the ways how the light affects the circadian rhythm by regulating the production of melatonin in the system. When the exogenous melatonin is introduced to the system, it will regulate the site of the melatonin production and has been shown to synchronize the circadian rhythms and improve the duration and quality of sleep [2].

The exogenous melatonin can be more effective if timing the dose intake correctly. For example, consuming the melatonin in the morning can cause a phase delay and vice versa, consuming the melatonin during the early part of the night can advance the clock [3].

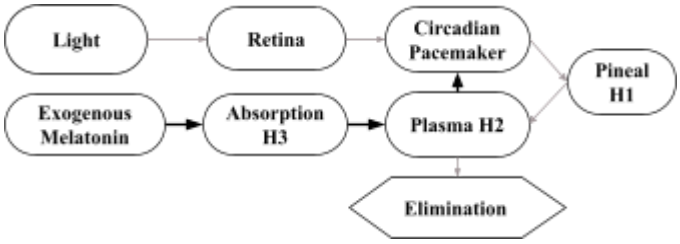


Fig. 1: Block diagram for the melatonin pathway that includes the light's effect and exogenous melatonin in the system. The darker arrows show the pathway of the exogenous melatonin.

The exogenous melatonin is consumed orally and can diffuse into the plasma through the absorption site H3. The melatonin in the plasma affects the circadian pacemaker by resetting the phase and adjusting the production of melatonin in the pineal gland.

Exogenous melatonin can be used as an alternative to cure sleep disorders such as jet-lag and insomnia, with a proper administration of dose. Although excessive melatonin intake would not be life-threatening, a high dosage can have effects on other hormones over a long period of time [4].

## II. Background

### *A) Light Effect*

In this section, we introduce the mathematical models of the light's effects and the exogenous melatonin on the circadian pacemaker. The light's effect will serve as the foundation to introduce the exogenous melatonin in the system. Light can be a stronger stimulus for phase shifting, so eliminating this variable can help us model the system solely based on exogenous melatonin. Since we are focusing on the exogenous melatonin in this project, we will simplify and assume the light's effect as constant variables.

The light exposure can alter the circadian rhythms such as pushing the sleep cycle towards a later waking time. The activation of the photoreceptors can be assumed as a forward rate constant seen in equation (1):

$$\alpha = \alpha_0 \left(\frac{I}{I_0}\right)^P \frac{I}{I+I_1} \quad (1)$$

where I is the environmental light intensity in lux.

The fraction of activated photoreceptors is modeled as below in equation (2):

$$\frac{dn}{dt} = \alpha\,(1 - n) - \beta_n \quad (2)$$

where the constant rate β is the fraction of activated photoreceptors, n that are converted into steady state.

Equation (3) is proportional to the rate of photoreceptor activation and describes the photic drive to the circadian pacemaker:

$$B = G(1 - bx) * (1 - bx_c) * \alpha(1 - n) \quad (3)$$

According to St. Hilaire, Process P is shown as the following equations:

$$\kappa\frac{dx}{dt} = x_c + \gamma(\frac{x}{3} + \frac{4x^3}{3} - \frac{256x^7}{105}) + B - \eta M \quad (4)$$

$$\kappa\frac{dx_c}{dt} = \frac{Bx_c}{3} - x(\frac{24}{f\tau_c})^2 + KB - \varsigma M \quad (5)$$

Equation (4) represents the circadian pacemaker while equation (5) represents the circadian sensitivity modulator [5].

The phase of the oscillator in this cycle is described by equation (6) below, and fits the light's effects on the circadian pacemaker to the exogenous melatonin as a constant:

$$\varphi = tan^{-1}(\frac{x}{x_c}) \quad (6)$$

*B) Exogenous Melatonin Effect*

Since the scope of our project focuses on the exogenous melatonin within the body, the next few equations will describe this exogenous melatonin model. The first equation describes the oral absorption site on top of the pineal gland and blood plasma, which is described in equation (7):

$$\frac{dH_1(t)}{dt} = -\beta_{IP}H_1(t) + A(t) \quad (7)$$

where A(t) is the circadian phase, $\beta_{IP}$ is the rate of melatonin into plasma and $H_1(t)$ is the concentration of melatonin in the pineal compartment. The concentration of melatonin in the plasma, $H_2(t)$ is described as below:

$$\frac{dH_2(t)}{dt} = \beta_{IP}H_1(t) - \beta_{CP}H_2(t) + \beta_{AP}H_3(t) \quad (8)$$

where $\beta_{CP}$ is the rate of clearance of the melatonin from the plasma and $\beta_{AP}$ is the rate of the absorption of exogenous melatonin. Lastly, since we are focusing on the exogenous melatonin, the concentration of the oral absorption site, $H_3(t)$ is incorporated in the system as well:

$$\frac{dH_3(t)}{dt} = \beta_{AP}H_3(t) \quad (9)$$

The melatonin drive to the circadian pacemaker incorporates melatonin receptor inputs from exogenous and endogenous melatonin blood plasma and is modeled by equation (10):

$$M = \frac{M_{max}}{1 - e^{\frac{H_{sat} - H_2}{\sigma}}} \quad (10)$$

Since we aimed to model the effect of exogenous melatonin, we assume that there is no interference of light in the system to try to exclude the endogenous melatonin system. Furthermore, we assume that the equal dose distribution across the blood volume. Next, we also assume that the measurement feedback system, G(s) is ideal. We also assume that all the melatonin is released into the plasma from the pineal glands. These assumptions will be realized in the methods section of this paper, but are worth noting now.

We also note that melatonin is converted from serotonin by arylalkylamine N-acetyltransferase (AA-NAT) enzyme, and the time when the enzyme is activated and producing melatonin is described by equation (11):

$$A(\varphi) = ae^{-rM_{2\pi}(\varphi_{on} - \varphi_{off})} \quad \text{for } \varphi_{on} < \varphi < \varphi_{off} \quad (11)$$

where $\varphi_{on}$ and $\varphi_{off}$ are the phases when melatonin synthesis is turned on and off, and $M_{2\pi}$ describes a cyclic process for the phase input [6].

Having described the mathematical model obtained from the literature [5, 6] surrounding the effects of light and exogenous melatonin in blood plasma melatonin concentration, we will now modify this framework to fit the scope of our project's goals.

## III. Methods

*A) Light Effect*

To utilize the light effects and exogenous melatonin effects on the concentration of melatonin in the blood plasma, we need to make several key assumptions to simplify our mathematical model. First, since we are primarily interested in the effects of exogenous melatonin (the melatonin one would ingest), we assume we can ignore the effects of light on the circadian pacemaker by assuming the environmental light intensity *I* in equation (1) is equal to zero lux. This assumption means equations (1) and (3) equal zero, therefore modifying the following light effect equations as described:

$$\frac{dn}{dt} = -\beta_n \quad (2.1)$$

$$\kappa\frac{dx}{dt} = x_c + \gamma(\frac{x}{3} + \frac{4x^3}{3} - \frac{256x^7}{105}) - \eta M \quad (4.1)$$

$$\kappa\frac{dx_c}{dt} = -x(\frac{24}{f\tau_c})^2 - \varsigma M \quad (5.1)$$

Now that the light effects are condensed to essentially two equations, equation (4.1) and (5.1) since equation (2.1) is a constant, we can assume that we ignore the effects of light in our model and therefore choose to focus on the equations for the exogenous melatonin. For the exogenous melatonin, we further simplify our model by limiting the time phase of the model to only when the arylalkylamine N-acetyltransferase (AA-NAT) enzyme is activated and synthesizing melatonin. Under this assumption, equation (11) can be used. Without this restricted time assumption, we would need to use equation (6) in conjunction with a modified form of equation (11), but our assumption appropriately simplifies our model to the scope of this paper.

After simplifying our system to two light-effect equations and the three exogenous melatonin effects from equations (7), (8), and (9), we used Simulink to produce a block diagram for visualizing the system and understanding the behavior of the circadian pacemaker in the presence of exogenous melatonin. This time-domain block diagram for this system is shown in Fig. 2, with both systems connected by the melatonin drive equation (10).

*B) Exogenous Melatonin Effect*

Since the scope of our project focuses on the exogenous components of melatonin from equations (7), (8), and (9), we further simplify our model and look at this component specifically. Before building a transfer function that appropriately models the exogenous effect of blood melatonin concentration, we need to linearize and take the Laplace Transform of out exogenous melatonin equations, as shown below:

$$sH_1(s) = -\beta_{IP}H_1(s) + A(s) \quad (12)$$

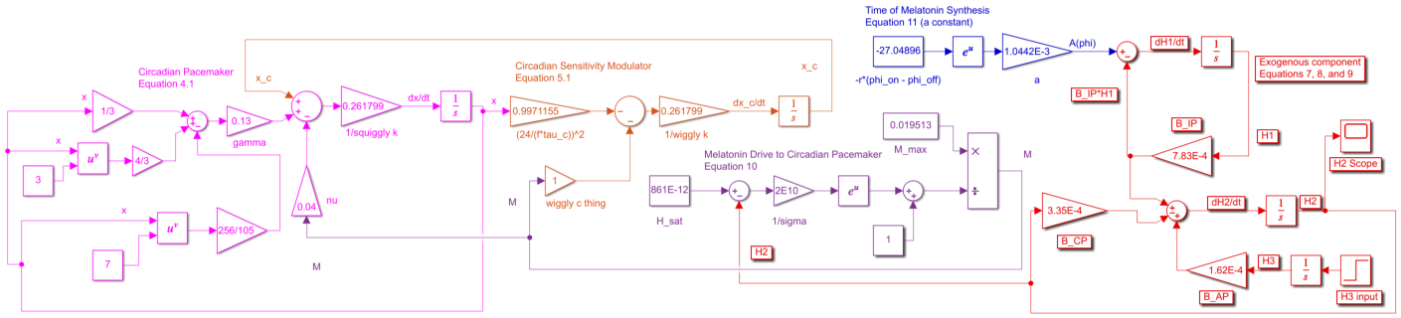


Fig. 2: The entire block diagram for the simplified light and exogenous effects of melatonin. The light effect component is colored pink (equation 4.1) and orange (equation 5.1), the melatonin synthesis time is colored blue (equation 11), the exogenous component is colored red (equations 7, 8, and 9), and the melatonin drive connecting the two systems is colored purple (equation 10).

$$sH_2(s) = \beta_{IP}H_1(s) - \beta_{CP}H_2(s) + \beta_{AP}H_3(s) \quad (13)$$

$$sH_3(s) = -\beta_{AP}H_3(s) \quad (14)$$

Since we are looking at blood plasma melatonin concentration, we will set this as our output $H_2(s)$ and the melatonin concentration at the oral absorption site $H_3(s)$ as the input. This produces the simplified transfer function for our model in equation (15).

$$H(s) = \frac{output}{input} = \frac{H_2(s)}{H_3(s)} = \frac{\frac{\beta_{IP}\frac{A(s)}{s+\beta_{IP}}}{s+\beta_{CP}}}{H_3(s)} \quad (15)$$

It is worth noting that our transfer function is defined in terms of the function input, which generally is not advised, but to work around this we make one more assumption: we assume our subject is ingesting a 2mg dose of melatonin (as prescribed for insomniac patients [7]). When accounting for the concentration of this dosage in a person's blood (estimated 5 L [5]), we calculate a concentration of 1722 mol/L $H_3(s)$ concentration.

Once accounting for the variables included in our transfer function (see Table 2 in the Appendix) along with our $H_3$ concentration, we can further simplify our exogenous melatonin transfer function to the following:

$$H(s) = \frac{output}{input} = \frac{H_2(s)}{H_3(s)} = \frac{8.48\times10^{-22}}{s^2+1.12\times10^{-3}s+2.05\times10^{-10}} \quad (15.1)$$

We modeled this transfer function equation (15.1) in Simulink using a transfer function block. The Simulink block model for the exogenous melatonin using equations (7), (8), and (9) is shown in Fig. 3, and Fig. 4 shows the Simulink block transfer function diagram using equation (15.1). These models were used for the results described in the following section.

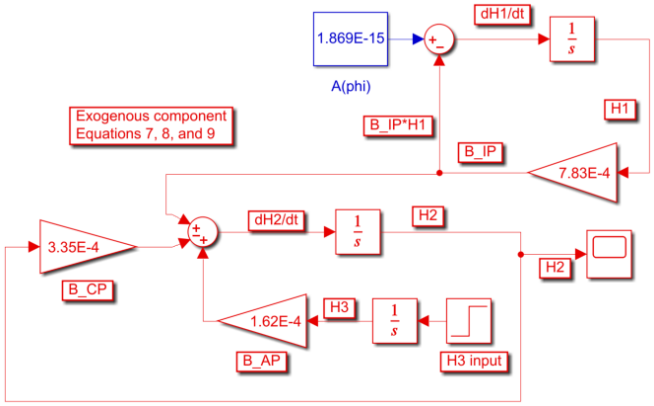


Fig. 3: The Simulink block diagram for the exogenous components of the melatonin concentrations. This model utilized equations (7), (8), and (9).

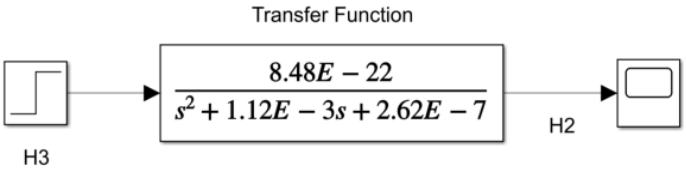


Fig. 4: The Simulink block diagram for the transfer function described in equation (15.1). This utilized the Laplace Transform equations (12), (13), and (14) into one transfer function block in Simulink.

## IV. Results

After running the simulation on Simulink, we have determined that at the 100th second, the melatonin concentration in the blood plasma is higher when exogenous melatonin is present. The graphs and the tabulation of results are shown below:

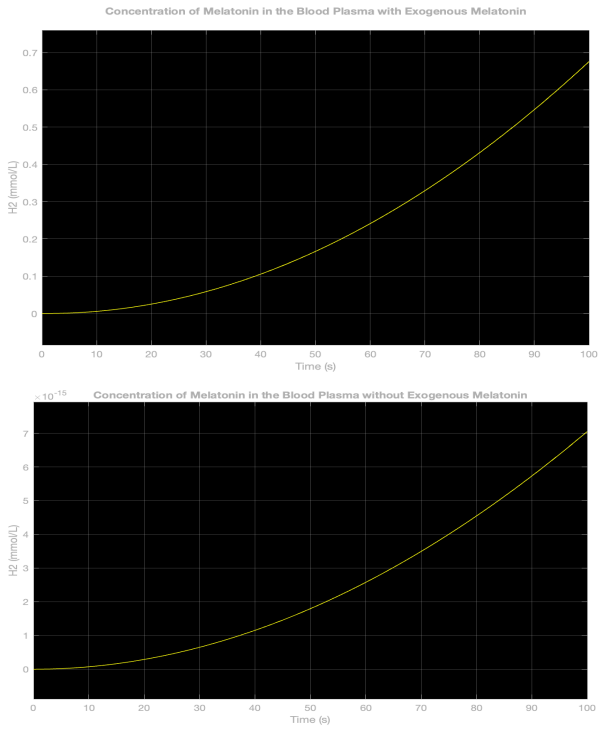


Fig. 3 & 4: The waveforms of the concentration of melatonin in blood plasma $H_2$ with the presence and absence of exogenous melatonin.

TABLE 1

| | Without exogenous melatonin | With exogenous melatonin |
|---|---|---|
| Concentration of melatonin in blood plasma at t = 100s | $7 \times 10^{-15}$ mol/L | 0.7 mol/L |

The result of the concentration of melatonin in blood plasma with and without the exogenous melatonin at t = 100s.

While both graphs show an increasing pattern, the one with the exogenous melatonin increases much faster. Without the exogenous melatonin, the amount of melatonin produced endogenously is virtually 0. This is not surprising since we are only looking at a timespan of 100 seconds. Nevertheless, we see the huge discrepancy between the presence and absence of exogenous melatonin from this simulation.

## V. Conclusions

Due to the various assumptions made in our model, it does not reflect the reality of melatonin concentration in the blood plasma during complete darkness. Our graph shows the melatonin concentration continues to grow to infinity because it does not take into account the effect of melatonin receptors being saturated after a certain point.

However, it does reflect the fact that as a person takes in exogenous melatonin supplements, the amount of melatonin in the blood plasma increases dramatically after a certain period of time. The graphs shown can help us visualize how slow the rate of endogenous melatonin production is and that relying solely on it may not be enough for some people who suffer from insomnia.

Quantifying the effect of this increase in melatonin in the blood to the time that a person may fall asleep is not the aim of this study, therefore we cannot make the connection that more melatonin causes a person to fall asleep earlier using this model. Further studies need to be done that take into account many of the assumptions we made and better reflect the causal relationship between melatonin and sleep time.

In conclusion, the model we have made, and the assumptions we have used, does reflect that taking exogenous melatonin causes a higher concentration of melatonin in the blood. This model does not, however, infer that more melatonin results in a shift in the circadian rhythm since more work would need to be done to build off our model and confirm this.

## Acknowledgment

Foremost, we would like to express our deepest appreciation to our instructor, Dr. Gert Cauwenberghs for his advice and guidance on our project. We also would like to extend our sincere gratitude to BENG 122A TAs for leading us to work on this project. We are grateful for what they have offered us.

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## Appendix

TABLE 2

| Parameter | Value and Units | Parameter | Value and Units |
|---|---|---|---|
| $I_0$ | 9500 lux | η | 0.04 |
| $I_1$ | 100 lux | ς | 0.54 |
| $\alpha_0$ | 0.1 sec | $\beta_{IP}$ | $7.83 * 10^{-4} sec^{-1}$ |
| β | 0.007 sec | $\beta_{CP}$ | $3.35 * 10^{-4} sec^{-1}$ |
| p | 0.5 | $\beta_{AP}$ | $1.62 * 10^{-4} sec^{-1}$ |
| r | 15.36 sec | a | $1.04 * 10^{-3} sec^{-1}$ |
| G | 37 | $\phi_{on}$ | 6.113 |
| b | 0.4 | $\phi_{off}$ | 4.352 |
| γ | 0.13 | δ | 500 sec |
| κ | $\frac{12}{\pi} h$ | $M_{max}$ | 0.019513 |
| $\tau_C$ | 24.1 h | $H_{sat}$ | 861 pmol/L |
| f | 0.99729 | σ | 50 pmol/L |
| m | $7\ sec^{-1}$ | $H_3$ (input) | 1722 mol/L |

This table shows the parameters used in our calculations [6].