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Circadian rhythm synchronization under the influence of pain: PIM model with memory

Sincronização do ritmo circadiano sob influência da dor: Modelo PIM com memória

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ABSTRACT

In this work, we propose and analyze the existence of synchronization/dissynchronization states of in-phase and coupled oscillators that model the influence of external factors such as pain on the biological rhythms of sleep-wakefulness and body temperature under the memory effect. We show the well-posedness of the proposed model and derive analytical solutions for the oscillator system in the synchronized state. The theoretical results are accompanied by some numerical simulations that indicate that the existence of memory contributes to the synchronization of the oscillator system.

Keywords: Circadian rhythms; Synchronization; Couple oscillators; Memory

RESUMO

Neste trabalho propomos e analisamos a existência de estados de sincronização/dessincronização de osciladores em fase e acoplados que modelam a influência de fatores externos como a dor nos ritmos biológicos do sono-vígilia e temperatura corporal sob o efeito de memória. A memória é incorporada no modelo pelas derivadas de ordem fracionária do tipo Caputo. Mostramos a boa colocação do modelo proposto e derivamos soluções analíticas para o sistema de osciladores no estado de sincronia. Os resultados teóricos são acompanhados por algumas simulações numéricas que indicam que a existência de memória contribui para a sincronização do sistema de osciladores.

Palavras-chave: Ritimo circadiano; Sincronização; Osciladores acoplados; Memória

1 INTRODUCTION

Circadian rhythm, which is associated with our internal biological clock, is a natural biological process that presents endogenous and adaptive oscillations around a 24-hour period (Klerman & Hilaire, 2007; Moore-Ede et al., 1983). Although endogenous, the circadian rhythm adjusts to external stimulus called *zeitgebers*[1], which include luminosity, temperature, among others. Circadian rhythm is responsible for monitoring the cycle of activities and regulating the material and psychological rhythms of human beings, influencing digestion while awake, cell renewal, among other functions (Bumgarner et al., 2021; Neves et al., 2022; Palada et al., 2020; Walker et al., 2020; Wang et al., 2022).

Examples of rhythms that occur in the body include sleep-wake, body temperature, hormone levels, blood pressure, and pain. These rhythms usually change in a predictable manner with a specific period and frequency, resulting in a repeating pattern or a cycle of changes known as synchronization (Klerman & Hilaire, 2007; Strogatz, 1987, 2000; Tass, 1999). Desynchronization, which is a change in the timing of biological rhythms, can modify the performance of several essential processes, such as metabolism, hormone levels, sleep, and body temperature, and is responsible for health problems in humans, including cognitive problems, obesity, diabetes, and cancer, among others (Bumgarner et al., 2021; Neves et al., 2022; Palada et al., 2020; Walker et al., 2020; Wang et al., 2022).

The sleep-wake cycle and body temperature are usually in sync with the natural light in the environment. However, certain modern lifestyles can disrupt this synchronization, such as shift work, jet lag, or excessive use of social media (Walker et al., 2020; Wang et al., 2022). Pain is another factor that can cause desynchronization, as demonstrated by (Bumgarner et al., 2021; Palada et al., 2020) and the references therein.

The circadian rhythm has the ability to adapt to the local environment, given the action of external stimulus called *zeitgebers*[2]. A classic example is the ability of people to synchronize their biological rhythm after experiencing jet lag. Furthermore, the repetition of certain behaviors and routines in the new environment, under

[1] *Zeitgebers*, from the German "time giver".
[2] *Zeitgebers*, from the German "time giver".

appropriate lighting conditions, speeds up the process of synchronizing the circadian rhythm. This is the case, for example, of a person who goes to bed and gets up the same "time" that they usually do, even though they are in another time zone. Thus, *zeitgebers* function as a memory trigger that our circadian rhythm acquired during evolution and vice versa. In this work, we use memory as a synonym for the ability to retain and evoke information, characteristics present consciously or subconsciously in living beings, mainly in humans (Silverthorn, 2018). Therefore, when we talk about memory, we refer to whether or not an organism knows the existence of a past behavior and has information about what the behavior was like.

Gaining insight into the impact of the pain phenomenon and the respective memory of circadian rhythms on the synchrony of body rhythms can help improve people's quality of life. In this paper, we present a mathematical model to investigate the external influences of pain on the synchronization of sleep-wake cycles and body temperature in a model with memory. Although modeling provides a caricature of the underlined phenomena, it could provide some guidance for medical advice. The proposed methods use the fact that the circadian rhythms of sleep-wake, temperature, and eventually pain have a periodic oscillatory behavior. Hence, we assume that each of the circadian rhythms of interest is in phase oscillators coupled in a network (three-body coupling problem) by constant coupling forces. Memory is assumed to be imputed in the model by the Caputo fractional derivative in the dynamics. We show that the proposed model describes the essential properties of the investigated circadian rhythms, from which interesting properties can be deduced.

Literature overview: Synchronization of phase-coupled oscillators is a topic of research in many scientific fields, and a complete literature overview becomes almost impossible. Some examples can be found in (Bard et al., 2019; Bick et al., 2019; Cai et al., 2022; Dörfler & Bullo, 2014,1; Kuramoto, 1984; Pikovisky et al., 2001; Rodrigues et al., 2016,1; Strogatz, 1987, 2000; Tass, 1999) and references therein. Applications related to the framework presented in this article are modeling of problems in neuroscience, neurological treatments, psychological treatments, cardiac markers, and circadian rhythms, as demonstrated in (Cai et al., 2022; Contessa & Cezaro, 2017; Dörfler & Bullo, 2014; Glaeser et al., 2023b,1; Pikovisky et al., 2001; Strogatz, 1987; Tass, 1999).

The modeling of the sleep-wake cycle and body temperature as two coupling oscillators was first proposed in (Strogatz, 1987). The sinc/dessyncronization results in (Strogatz, 1987) were generalized in (Glaeser et al., 2023b; **?**) assumed that the dynamics of the two coupling oscillators (sleep-wake cycle and body temperature) have memory (fractional circadian rhythms). The authors of (Glaeser et al., 2018) proposed the use of multi-agent simulation techniques to investigate the relationship between circadian rhythm synchronization and pain effects. In (Glaeser et al., 2023a) analytical results for the sinc/dessyncronization for the coupling oscillator model of the sleep-wake cycle and body temperature influenced by pain (PIM model) were obtained. Since the dynamics in the model proposed in (Glaeser et al., 2023a) was based on integer derivatives (that is, a local operator), no memory was considered.

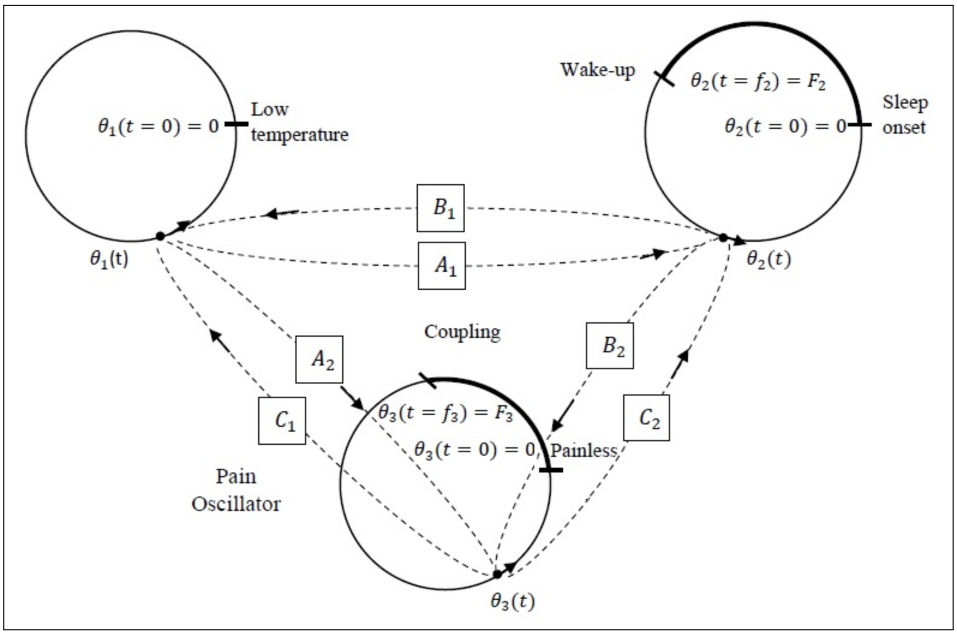
Main contributions: In this manuscript, we generalize the results obtained by the authors in (Glaeser et al., 2023a), for the PIM model with memory. Memory is assumed to be input into the model by a Caputo-type fractional dynamics of the coupling oscillators.

The results are distributed in the manuscript as follows: In Section 2, we will introduce the fractional dynamic PIM model. It is characterized by a topology of phase-coupled oscillators that characterize sleep-wake, body temperature, and pain, where the dynamics of iteration is driven by fractional derivatives of Caputo type. In Subsection 2.1, we show the well-posedness of the fractional PIM model. We also show why the proposed model has memory. Section 3, we derive sufficient conditions for partial and total synchronization for the proposed fractional PIM model. In Section 4, we provide numerical evidence to support the theoretical findings discussed earlier. The last section of this contribution is Section 5, which is devoted to the final conclusions and potential future developments.

2 MODELING THE CIRCADIAN RHYTHM AS A SYSTEM OF COUPLED OSCILLATORS WITH FRACTIONAL DYNAMICS

From a modeling perspective, the periodic fluctuations seen in the circadian rhythm of sleep-wake, temperature, and pain suggest that coupled oscillator systems are excellent models for describing the fundamental characteristics of biological rhythms. These were the main arguments used by (Strogatz, 1987) in its seminar paper. Here, we adopt a similar strategy, assuming that the interactions of the circadian rhythms of sleep-wake, temperature, and pain are given, respectively, by the phase oscillators $\theta_1(t), \theta_2(t)$ and $\theta_3(t)$ that are weakly coupled to each other (as represented by Figure 1).

Figure 1 – Fractional PIM model



Source: The authors

Caption: Coupling form of phase oscillators that describe the biological rhythm of body temperature $\theta_1(t)$, sleep-wake $\theta_2(t)$ and pain $\theta_3(t)$.

Moreover, the dynamics interaction consists of three oscillators mutually coupled and moving in a counterclockwise direction, given by

$$D^\alpha \theta_1(t) = \omega_1^\alpha - B_1^\alpha \cos(2\pi(\theta_2(t) - \theta_1(t))) - C_1^\alpha \cos(2\pi(\theta_3(t) - \theta_1(t))) \quad (1)$$

$$\theta_2(t) = 0 \quad (2)$$

$$\theta_3(t) = 0, \quad (3)$$

for $t \in [0, f_3[$,

$$D^\alpha \theta_1(t) = \omega_1^\alpha - B_1^\alpha \cos(2\pi(\theta_2(t) - \theta_1(t))) - C_1^\alpha \cos(2\pi(\theta_3(t) - \theta_1(t))) \quad (4)$$

$$\theta_2(t) = 0 \quad (5)$$

$$D^\alpha \theta_3(t) = \omega_3^\alpha + A_2^\alpha \cos(2\pi(\theta_1(t) - \theta_3(t))) - B_2^\alpha \cos(2\pi(\theta_2(t) - \theta_3(t))), \quad (6)$$

for $t \in \ [f_3, f_2[$ e

$$D^\alpha\theta_1(t) = \omega_1^\alpha - B_1^\alpha \cos(2\pi(\theta_2(t) - \theta_1(t))) - C_1^\alpha \cos(2\pi(\theta_3(t) - \theta_1(t))) \tag{7}$$

$$D^\alpha\theta_2(t) = \omega_2^\alpha + A_1^\alpha \cos(2\pi(\theta_1(t) - \theta_2(t))) + C_2^\alpha \cos(2\pi(\theta_3(t) - \theta_2(t))) \tag{8}$$

$$D^\alpha\theta_3(t) = \omega_3^\alpha + A_2^\alpha \cos(2\pi(\theta_1(t) - \theta_3(t))) - B_2^\alpha \cos(2\pi(\theta_2(t) - \theta_3(t))). \tag{9}$$

for $t \geq f_2$.

In (1)-(9), $\omega_i = \tau_i^{-1}$ is the intrinsic frequency and τ_i is the period in hours of the oscillator $i = 1, 2, 3$. The positive parameters A_l, B_l and C_l, with $l = 1, 2$, are the coupling strengths that determine how much each oscillator influences the others. Note that some coupling force parameters may be preceded by a negative signal since the oscillators move in a counterclockwise direction. Furthermore, $D^\alpha(\cdot)$ is the Caputo fractional derivative operator (Diethelm, 2004), of order $\alpha \in]0, 1]$. All the model parameters in (1)-(9) are raised to the power of the order of derivatives α, so that the time corresponds to $(\text{time})^{-1}$, see (Diethelm, 2004).

The model (1)-(9) assumes that sleep time is defined as a fraction f_2 of the oscillator $\theta_2(t)$. Therefore, $\theta_2(t) = 0$ for any $0 < t < f_2$. As a result, we have $\theta_2(t = 0) = 0$ as the corresponding initial condition. When the vigil begins, we have $\theta_2(t = f_2) = F_2$. The absence of pain, that is, when an organism does not present pain, will be defined by a fraction f_3 of the cycle $\theta_3(t)$. We then assume that pain does not occur throughout the interval $[0, f_3[$, consequently, $\theta_3(t) = 0$ for any $0 < t < f_3$. It results in the initial condition $\theta_3(t = 0) = 0$. When pain arises, we have $\theta_3(t = f_3) = F_3$. It is important to emphasize that the values f_2 and f_3 are not necessarily the same. To fix the ideas, we assume that $f_2 > f_3$. The other cases can be analyzed in a similar way. The assumption that $f_2 > f_3$ can interpret that pain manifests itself when the body is still in the sleep stage. Finally, body temperature peaks in the late afternoon and then declines significantly in the early morning hours (Hasting et al., 2003). Thus, at less than a scale factor, we will assume that the initial condition $\theta_1(t = 0) = 0$ is satisfied.

2.1 Well-posedness for the fractional PIM model and memory effects

In this subsection, we will prove the well-posedness of the nonlinear fractional system of three coupled oscillators (1)-(9) with homogeneous initial conditions and for orders of derivatives $\alpha \in]0,1]$.

Lemma 1. *Let $\alpha \in]0,1]$. Then*

i) There is a unique continuous solution $(\theta_1(t),0,0)^T$ for the fractional PIM (1)-(9) *with homogeneous initial conditions in the interval $[0,f_3]$.*

ii) There is a unique continuous solution $(\theta_1(t),0,\theta_3(t))^T$ for fractional PIM (1)-(9) *with $\theta_1(f_3)=F_3$, $\theta_2(f_3)=\theta_3(f_3)=0$ in the interval $[f_3,f_2]$.*

iii) There is a unique continuous solution $(\theta_1(t),\theta_2(t),\theta_3(t))^T$ for fractional PIM (1) -(9) *with $\theta_1(t=f_2)=\theta_1(f_2)$ and $\theta_2(f_2)=0$ and $\theta_3(f_2)=F_2$ for $t>f_2$.*

Proof. Since $\cos(X)\le 1+|X|$, it follows that the right-hand side of the system (1) -(9), is continuous with respect to Lipschitz continuous with respect to the second argument in any of the intervals of the lemma assertions. Therefore, from (Diethelm, 2004, Theorems 8.7 - 8.11), it follows the existence and uniqueness of a continuous solution $(\theta_1(t),0,0)$ for some $T^*>0$. Furthermore, (Diethelm, 2004, Corolary 6.3), guarantees the continuous extension of the solution in $[0,f_3]$, concluding item i). In particular, $\theta_1(f_3):=F_3$ is well defined. Repeating the same arguments as above, we arrive at the conclusion stated at item ii) and iii), respectively. □

Theorem 2. *Let $\alpha \in]0,1]$. Then fractional PIM* (1)-(9) *has a unique piecewise-continuous solution.*

The solution continuously depends on the initial conditions, the parameters of the system, and the order of the derivatives $\alpha \in]0,1]$.

Proof. The existence and uniqueness follow from the lemma 1. The continuous dependence of the solution on the initial conditions, the model parameters and the fractional order α follows from (Diethelm, 2012, Theorems 6.7 - 6.11). □

Next, we justify the "memory" effect of the fractional derivatives in the dynamics of the fractional PIM modelo (1)-(9).

It follows from the factional integration in each line of the model (1)-(9) with order α that the solution $\theta_j(t)$ satisfies the Volterra system of equations.

$$\theta_j(t)=\frac{1}{\Gamma(\alpha)}\int_0^t (t-s)^{\alpha-1} f_j(s,\theta_1(s),\theta_2(s),\theta_3(s)))ds. \tag{10}$$

where f_j corresponding the right function of the j-line on the hand side of the fractional PIM model (1)-(9), for $j = 1, 2, 3$, respectively. Moreover, $\Gamma(z)$ is the Gamma function (Diethelm, 2004).

From (10), it follows that any of the coordinates $\theta_j(t)$ of the solution for the fractional PIM model (1)-(9) is such that, for any time $t_1 \leq t_2$,

$$\theta_j(t_2) - \theta_j(t_1) = \frac{1}{\Gamma(\alpha)} \int_0^{t_1} [(t_2 - s)^{\alpha-1} - (t_1 - s)^{\alpha-1}] f_j(s, \theta_1(s), \theta_2(s), \theta_3(s)) ds + \frac{1}{\Gamma(\alpha)} \int_{t_1}^{t_2} (t_2 - s)^{\alpha-1} f_j(s, \theta_1(s), \theta_2(s), \theta_3(s))) ds \,. \tag{11}$$

When $\alpha = 1$, the expression within parentheses in equation (11) is zero, resulting in the nullification of the first integral in equation (11). Therefore, to calculate the solution $\theta_j(t)$ of the PIM model (with derivative of order 1 as studied in (Glaeser et al., 2023a)) at t_2, it depends only on the value of $\theta_j(t_1)$ and the functions f_j corresponding to the right-hand side of (1)-(9). However, if $\alpha < 1$, then the first integral does not vanish in general. As a result, the history of the dynamics from 0 to t_2 must be considered to evaluate the solution $\theta_j(t_2)$ of the fractional PIM model (1)-(9). This phenomenon we call "memory".

3 SYNCHRONIZATION FOR THE FRACTIONAL PIM MODEL

In this section, we will analyze the synchronization results for the fractional PIM model (7)-(9).

Definition 1 ((Strogatz, 2000))**.** *Two phase oscillators are said to be synchronized in the interval $[a, b]$ if and only if, for all $t \in [a, b]$, the phase difference between the oscillators is constant.*

It follows from the Definition 1 and the results in Theorem 2 that synchronization only makes sense for $t \geq f_2$, that is, when the equations of the fractional PIM model are given by equations (7)-(9).

3.1 Total synchronization for Fractional PIM Model

It follows from the Definition (1) that total synchronization occurs when $\theta_1(t) = \theta_2(t) + K_2 = \theta_3(t) + K_3$. For simplicity, assume that $K_2 = K_3 = 0$[3]. Therefore, it follows from the equations (7)-(9) that the fractional PIM model, during synchronization, is such that

$$\begin{aligned} D^\alpha\theta_1(t) &= \omega_1^\alpha - B_1^\alpha - C_1^\alpha \\ D^\alpha\theta_2(t) &= \omega_2^\alpha + A_1^\alpha + C_2^\alpha \\ D^\alpha\theta_3(t) &= \omega_3^\alpha + A_2^\alpha - B_2^\alpha. \end{aligned} \quad (12)$$

Integrating on both sides of (13) with order α and using the conditions that $\theta_2(f_2) = F_2$, and $\theta_3(f_3) = F_3$, we obtain that the total synchronized solution is given by

$$\begin{aligned} \theta_1(t) &= \frac{(\omega_1^\alpha - B_1^\alpha - C_1^\alpha)}{\alpha\,\Gamma(\alpha)} t^\alpha\,, \\ \theta_2(t) &= \frac{(\omega_2^\alpha + A_1^\alpha + C_2^\alpha)}{\alpha\Gamma(\alpha)}(t - f_2)^\alpha + F_2\,, \\ \theta_3(t) &= \frac{(\omega_3^\alpha + A_2^\alpha - B_2^\alpha)}{\alpha\,\Gamma(\alpha)}(t - f_3)^\alpha + F_3\,. \end{aligned} \quad (13)$$

In the following, we will make some considerations about the total synchronization for the fractional PIM model (7)-(9).

- The hipoteses that $K_2 = K_3 = 0$ above are the same as to translate the total synchronized solutions of $\theta_2(t)$ and $\theta_3(t)$ to the origin. In these cases, we have $f_2 = f_3 = 0$, as well as $F_2 = F_3 = 0$ in (13).

- For $\alpha = 1$, (13) are the same conditions as obtained in (Glaeser et al., 2023a).

- Furthermore, since the Caputo fractional derivative of a constant is zero (Diethelm, 2004), it follows from (13) that, a sufficient condition for the total synchronization

[3]Otherwise, a change of variables $\tilde{\theta}_j = \theta_j(t) - K_j$, for $j = 2, 3$ in the fractional PIM model (7)-(9) shall be considered, which does not affect the analyses.

of the fractional PIM model, is given by

$$\begin{aligned} A_1^\alpha + B_1^\alpha &= |\omega_1^\alpha - \omega_2^\alpha| \\ A_2^\alpha + C_1^\alpha &= |\omega_1^\alpha - \omega_3^\alpha| \\ B_2^\alpha + C_2^\alpha &= |\omega_3^\alpha - \omega_2^\alpha|. \end{aligned} \tag{14}$$

The conditions (14) are the generalized Winfree conditions for syncrhonization (Strogatz, 2000).

3.2 Partial synchronization for the fractional PIM model

We will assume that two phase oscillators, $\theta_1(t)$ and $\theta_2(t)$, are synchronized with each other, but not necessarily with the third, $\theta_3(t)$. The other cases can be studied in a similar way. According to Definition 1 (with $K_1 = 0$), the dynamic equations of the fractional PIM model, during such partial synchronization, fulfill

$$D^\alpha \theta_1(t) = \omega_1^\alpha - B_1^\alpha - C_1^\alpha \cos(2\pi(\theta_3(t) - \theta_1(t))) \tag{15}$$

$$D^\alpha \theta_2(t) = \omega_2^\alpha + A_1^\alpha + C_2^\alpha \cos(2\pi(\theta_3(t) - \theta_2(t))) \tag{16}$$

$$D^\alpha \theta_3(t) = \omega_3^\alpha + A_2^\alpha \cos(2\pi(\theta_1(t) - \theta_3(t))) - B_2^\alpha \cos(2\pi(\theta_2(t) - \theta_3(t))). \tag{17}$$

Since $\theta_1(t)$ and $\theta_2(t)$ are synchronized and the Caputo fractional derivative of a constant is zero, hence, $D^\alpha(\theta_1(t) - \theta_2) = 0$. Therefore, it follows from (15)-(16) that

$$\omega_1^\alpha - \omega_2^\alpha - B_1^\alpha - A_1^\alpha - C_1^\alpha \cos(2\pi(\theta_3(t) - \theta_1(t))) - C_2^\alpha \cos(2\pi(\theta_3(t) - \theta_2(t))) = 0. \tag{18}$$

Define the phase difference as

$$\psi_4(t) = \theta_1(t) - \theta_3(t) = \theta_2(t) - \theta_3(t). \tag{19}$$

It follows from (18) and (19), that

$$\psi_4(t) = \frac{1}{2\pi} \arccos \frac{\Omega_4 - E_4}{D_4}, \tag{20}$$

where $\Omega_4 = \omega_1^\alpha - \omega_2^\alpha$ is the difference of the intrinsic frequencies of the synchronized oscillators; $E_4 = A_1^\alpha + B_1^\alpha$ is the sum of the coupling strengths between synchronized oscillators; and $D_4 = C_1^\alpha + C_2^\alpha$ is the sum of the oscillator coupling strengths $\theta_3(t)$, all of them depending on the memory level α.

Here is an interesting consequence of (20). Since the domain of the function $\arccos \in]-1,1[$, then the oscillator $\theta_3(t)$ synchronizes to the system generated by the oscillators $\theta_1(t)$ and $\theta_2(t)$ if

$$|D_4| > |\Omega_4 - E_4| \iff |C_1^\alpha + C_2^\alpha| > |(\omega_1^\alpha - \omega_2^\alpha) - (A_1^\alpha + B_1^\alpha)|. \tag{21}$$

Therefore, (21) implies that the synchronization of $\theta_3(t)$ with the system generated by $\theta_1(t)$ and $\theta_2(t)$ depends on the coupling forces C_1 and C_2, which come from $\theta_3(t)$, from the intensity of synchronization between oscillators $\theta_1(t)$ and $\theta_2(t)$, and the memory parameter α. From this follow the following comments:

- If the oscillators $\theta_1(t)$ and $\theta_2(t)$ are strongly coupled, that is, if $E_3 >> |\Omega_3|$, then the $\theta_3(t)$ oscillator will only synchronize with the $\theta_1(t)$ and $\theta_2(t)$ oscillators if the coupling strengths influenced by the system memory, $C_1^\alpha + C_2^\alpha$, is large. Therefore, pain will have to strongly influence at least one of the oscillators, body temperature, or sleep-wake.

- If the oscillators $\theta_1(t)$ and $\theta_2(t)$ are weakly coupled but still synchronized, that is, if $E_3 > |\Omega_3|$, but $E_3 - |\Omega_3| \cong 0$, then the $\theta_3(t)$ oscillator will synchronize with the oscillators $\theta_1(t)$ and $\theta_2(t)$ even though the coupling strengths $C_1^\alpha + C_2^\alpha$ are relatively small. Therefore, it is enough for pain to at least weakly influence one of the oscillators, body temperature or sleep-wake, for it to synchronize with the others.

Remark 1. *We conjecture that if the intensity of synchronization between oscillators $\theta_1(t)$ and $\theta_2(t)$ with the memory effect is low, then synchronization with $\theta_3(t)$ is made easier. In the latter case, pain becomes frequent on a daily basis. We plan to examine this supposition by utilizing real data in future works.*

By substituting equation (20) into the system equations (15)-(17), it follows that during the partial synchronization of $\theta_1(t)$ and $\theta_2(t)$, we obtain that

$$D^\alpha\theta_1(t) = \frac{C_1^\alpha\omega_2^\alpha + C_2^\alpha\omega_1^\alpha + A_1^\alpha C_1^\alpha - B_1^\alpha C_2^\alpha}{C_1^\alpha + C_2^\alpha} \quad (22)$$

$$D^\alpha\theta_2(t) = \frac{C_1^\alpha\omega_2^\alpha + C_2^\alpha\omega_1^\alpha + A_1^\alpha C_1^\alpha - B_1^\alpha C_2^\alpha}{C_1^\alpha + C_2^\alpha} \quad (23)$$

$$D^\alpha\theta_3(t) = \frac{((\omega_1^\alpha - \omega_2^\alpha) - (A_1^\alpha + B_1^\alpha))(A_2^\alpha - B_2^\alpha)}{C_1^\alpha + C_2^\alpha} + \omega_3^\alpha. \quad (24)$$

The integration of both sides of the identities in fractional order α yields the synchronized solution

$$\begin{aligned}
\theta_1(t) &= \frac{(C_1^\alpha\omega_2^\alpha + C_2^\alpha\omega_1^\alpha + A_1^\alpha C_1^\alpha - B_1^\alpha C_2^\alpha)}{\alpha\,\Gamma(\alpha)(C_1^\alpha + C_2^\alpha)}\, t^\alpha \\
\theta_2(t) &= \frac{(C_1^\alpha\omega_2^\alpha + C_2^\alpha\omega_1^\alpha + A_1^\alpha C_1^\alpha - B_1^\alpha C_2^\alpha)}{\alpha\,\Gamma(\alpha)(C_1^\alpha + C_2^\alpha)}\, (t - f_2)^\alpha + F_2 \\
\theta_3(t) &= \left(\frac{((\omega_1^\alpha - \omega_2^\alpha) - (A_1^\alpha + B_1^\alpha))(A_2^\alpha - B_2^\alpha)}{\alpha\,\Gamma(\alpha)(C_1^\alpha + C_2^\alpha)} + \frac{\omega_3^\alpha}{\alpha\,\Gamma(\alpha)}\right)(t - f_3)^\alpha + F_3.
\end{aligned} \quad (25)$$

From the analytical solution (25) for the synchronized fractional PIM model, we can make some comments as follows.

- The phase difference between the oscillators $\theta_1(t)$ and $\theta_2(t)$ is zero when we move the synchronized solution from $\theta_2(t)$ to the origin, which is the same as setting $f_2 = F_2 = 0$.
- From the solutions (25), it is evident that the phase difference between $\theta_1(t)$ and $\theta_3(t)$, as well as the phase difference between $\theta_2(t)$ and $\theta_3(t)$, is not constant, even when $f_2 = f_3 = F_2 = F_3 = 0$. This implies that the oscillators are not synchronized.
- In the case where $\alpha = 1$, the synchronized solutions coincide with those of the PIM model with integer derivatives studied in (Glaeser et al., 2023a)
- It is deduced from (25) that the analytical solutions for the synchronized oscillators $\theta_1(t)$ and $\theta_2(t)$ are determined by their intrinsic frequencies, the coupling strengths of the interaction between them, the coupling forces they receive from the oscillator $\theta_3(t)$ and the memory parameter α. However, the intrinsic frequency of $\theta_3(t)$ and the coupling forces of $\theta_1(t)$ and $\theta_2(t)$ to $\theta_3(t)$ do not affect the solutions. In conclusion, oscillators that are in sync rely solely on their interactions with each other and any external influences they may receive.

4 NUMERICAL SIMULATIONS

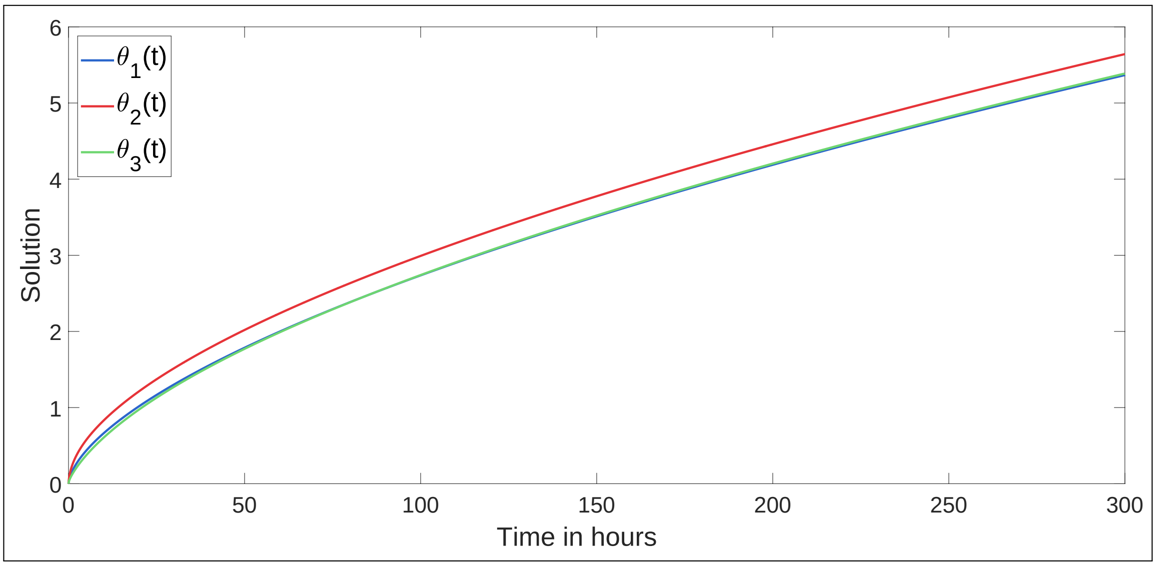
In this section, we will present some numerical simulations, which represent the synchronization situations studied above. It is important to note that the results presented for synchronization and desynchronization are concerned with the phase difference (refer to Definition 1) rather than the rhythms themselves. According to (26) the expected behavior of synchronized rhythms are given by parallel ”curves” for $\alpha \neq 1$ and parallel lines for $\alpha = 1$ (see Glaeser et al. (2023a)). In all simulations, the solutions were transferred to the origin; this is equivalent to considering $f_2 = f_3 = F_2 = F_3 = 0$. The other parameters in each of the simulations are presented, respectively, by each line of the table 1.

Table 1 – Table with the parameter values corresponding to each of the simulations

Parameter values								
A_1	A_2	B_1	B_2	C_1	C_2	τ_1	τ_2	τ_3
0,0008	0,004	0,0007	0,009	0,0016	0,0045	18	20	34
0,005	0,0003	0,009	0,0006	0,00028	0,0001	20	22	32
0,0003	0,0002	0,0001	0,00035	0,0006	0,0004	17	20	28

Source: the authors (2024)

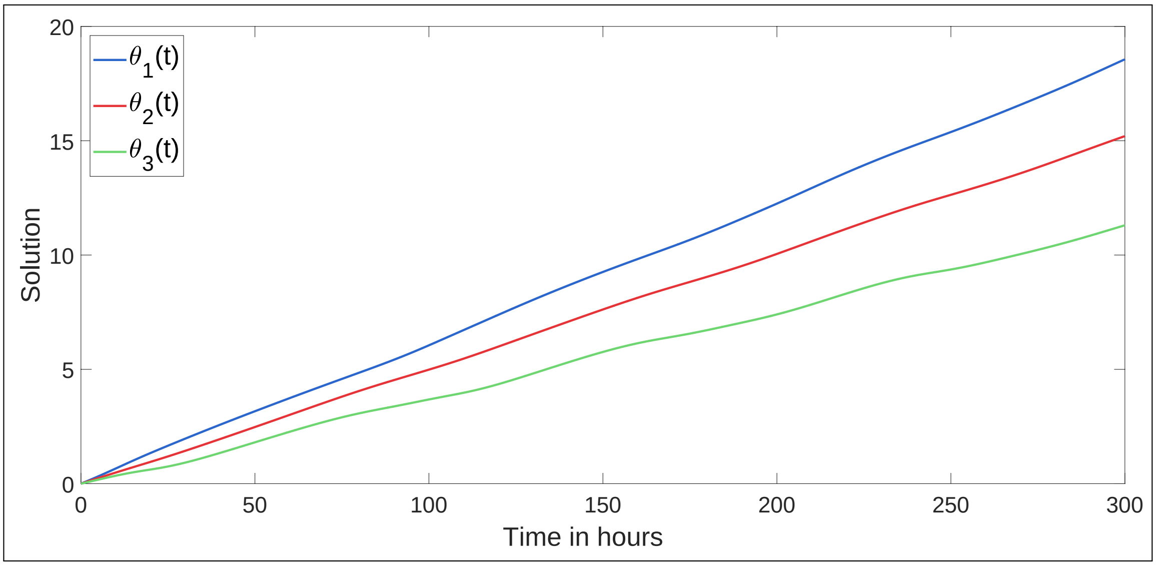
Figure 2 – Total synchronization



Source: the authors (2024)
Caption: Parameters according to the first line of Table 1 and with $\alpha = 0.6$. Total synchronization

Figures 2-3 illustrate the simulations performed with the parameters in the first row of Table 1. It should be noted that when $\alpha = 0.6$ (Figure. 2), the system is completely synchronized, while for $\alpha = 1$ (Figure. 3), the system is completely desynchronized. This example demonstrates that memory can be used to synchronize rhythms.

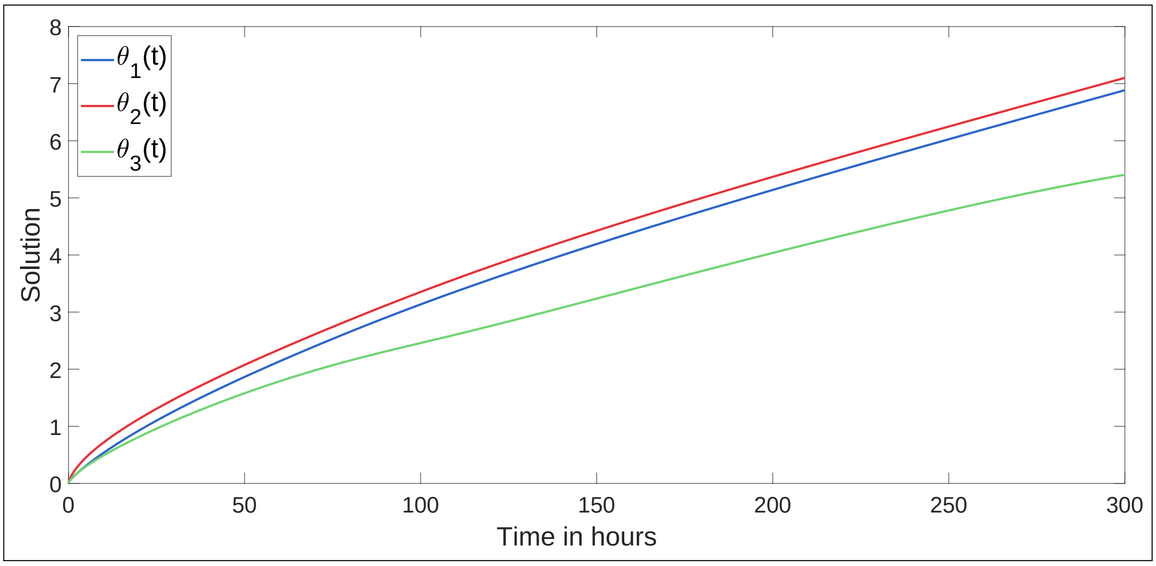
Figure 3 – Total desynchronization



Source: the authors (2024)

Caption: Parameters according to the first line of Table 1 and with $\alpha = 1$

Figure 4 – Partial synchronization

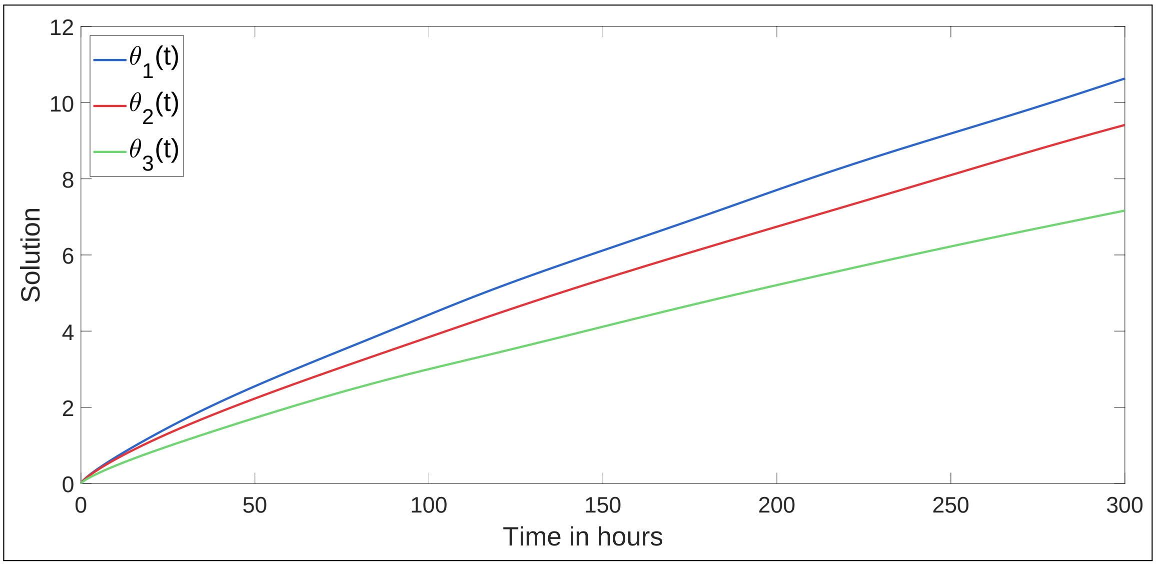


Source: the authors (2024)

Caption: Parameters according to the second line of Table 1 and with $\alpha = 0.7$

Figures 4 and 5 illustrate the simulations conducted for the parameters in the second and third lines of Table 1, with derivative orders of $\alpha = 0.7$ and $\alpha = 0.8$, respectively. The results of the simulations suggest partial synchronization in Figure 4 and complete desynchronization in Figure 5.

Figure 5 – Total desynchronization



Source: the authors (2024)
Caption: Parameters according to the third line of Table 1 and with $\alpha = 0.8$

5 CONCLUSIONS AND FUTURE DIRECTIONS

This paper presents a model to investigate the impact of external factors, such as pain, on the synchronization / desynchronization of biological sleep-wake rhythms and body temperature when memory is taken into account. The model is an extension of the models studied in (Glaeser et al., 2023a,2; Strogatz, 1987), as it considers a larger number of oscillators and the presence of memory given by fractional order derivatives. We demonstrate the well-posedness of the proposed model and derive analytical solutions for the synchronized oscillator system. Numerical simulations suggest that the presence of memory contributes to the synchronization of the oscillator system.

The numerical results suggest that a bifurcation analysis should be performed to determine the memory (order α of the derivative) at which the oscillators are synchronized. Additionally, a comparison with real data should be performed for the purpose of calibration and model validation. It will be addressed in future contributions.

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REFERENCES

Bard, E., Youngmin, P., & Dan, W. (2019). Recent advances in coupled oscillator theory. *Recent advances in coupled oscillator theory*, 377:1 – 16.

Bick, C., Goodfellow, G., Laing, C. R., & Martens, E. A. (2019). Understanding the dynamics of biological and neural oscillator networks through mean-field reductions: a review. *arXiv*, *10*(9):1–43.

Bumgarner, J. R., Walker, W. H., & Nelson, R. J. (2021). Circadian rhythms and pain. *Neuroscience Biobehavioral Reviews*, *129*:296–306.

Cai, Z., Zheng, Z., & Xu, C. (2022). Exact dynamics of phase transitions in oscillator populations with nonlinear coupling. *Communications in Nonlinear Science and Numerical Simulation*, *107*:106–129.

Contessa, N. & Cezaro, A. (2017). Derivadas fracionárias na modelagem do ritmo circadiano. *Scientia Plena*, *13*(4):1–43.

Diethelm, K. (2004). *The analysis of fractional differential equations*. (Lectutes Notes in Mathematics). Springer.

Diethelm, K. (2012). The mean value theorems and a nagumo-type uniqueness theorem for caputo's fractional calculus. *Fractional Calculus and Applied Analysis*, 15(2):304–313.

Dörfler, F. & Bullo, F. (2014). Synchronization in complex networks of phase oscillators: A survey. *Automatica*, *50*(6):1539–1564.

Glaeser, S. S., Cezaro, F., & Cezaro, A. (2023a). Analysis of circadian rhythm synchronization under the influence of pain. *Ciência e Natura*, *45*(16):1–14.

Glaeser, S. S., Cezaro, F., & Cezaro, A. (2023b). Synchronization of the circadian rhythms with memory: A simple fractional-order dynamical model based on two coupled oscillators. *Trends in Comput. Appl. Mathematics*, *1*(1):1–15.

Glaeser, S. S., Santos, A. T., Cezaro, A., Machado, C. M. d. S., & Adamatti, D. F. (2018). Modeling of circadian rhythm under influence of pain: an approach based on multi-agent simulation. *ADCAIJ: Advances in Distributed Computing and Artificial Intelligence Journal*, *7*(2):17–25.

Hasting, M., Reddy, A., & Maywood, E. (2003). A clockwork web: circadian timing in brain and periphery, in health and disease. *Nature Reviews Neuroscience*, *4*:649–661.

Klerman, E. B. & Hilaire, M. S. (2007). Review: On mathematical modeling of circadian rhythms, performance, and alertness. *Journal of Biological Rhythms*, *22*(2):91–102.

Kuramoto, Y. (1984). *Chemical Oscillations, Waves, and Turbulence*. Berlin: Springer.

Moore-Ede, M. C., Czeisler, C. A., & Richardson, G. S. (1983). Circadian timekeeping in health and disease. *New England Journal of Medicine*, *309*(9):530–536.

Neves, A. R., Albuquerque, T., Quintela, T., & Costa, D. (2022). Circadian rhythm and disease: Relationship, new insights, and future perspectives. *Journal of Cellular Physiology*, *237*(8):3239–3256.

Palada, V., Gilron, I., Canlon, B., Svensson, C. I., & Kalso, E. (2020). The circadian clock at the intercept of sleep and pain. *PAIN*, *161*(5):894–900.

Pikovisky, A., Rosemblum, M., & Kurths, J. (2001). *Synchronization: A Universal Concept in Nonlinear Sciences* (1th ed). Cambridge University Press.

Rodrigues, F. A., Peron, T. K. D., Ji, P., & Kurths, J. (2016). The kuramoto model in complex networks. *Physics Reports*, *610*:1–98.

Silverthorn, D. (2018). Human Physiology: An Integrated Approach (1th ed). Pearson.

Strogatz, S. H. (1987). Human sleep and circadian rhythms: a simple model based on two coupled oscillators. *J. Math. Biol*, *25*:327–347.

Strogatz, S. H. (2000). From kuramoto to crawford: exploring the onset of synchronization in populations of coupled oscillators. *Physica D*, *143*:1–20.

Tass, P. A. (1999). *Phase Resetting in Medicine and Biology: Stochastic Modelling and Data Analysis*. New York: Springer.

Walker, W., Walton, J., & DeVries, A. (2020). Circadian rhythm disruption and mental health. *Transl Psychiatry*, *10*(28):1–13.

Wang, W., Yuan, R., & Mitchell, J. (2022). Desynchronizing the sleep-wake cycle from circadian timing to assess their separate contributions to physiology and behaviour and to estimate intrinsic circadian period. *Nature Protocols*, *10*(28):1–15.

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