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Mathematics

Analysis of circadian rhythm synchronization under the influence of pain

Análise de sincronização do ritmo circadiano sob influência da dor

Adriano De Cezaro[I], Fabiana Travessini De Cezaro[I], Stefânia da Silveira Glaeser[II]

[I]Federal University of Rio Grande, Rio Grande, RS, Brazil
[II]Instituto federal Sul-rio-grandense, Pelotas, Brazil

ABSTRACT

The synchronization of biological rhythms is of fundamental importance for health. The influence of pain on the functioning of vital functions and its effects on the synchronization of biological rhythms in human beings have been explored clinically for a long time. On the other hand, the modeling of this phenomenon can add features that are still unexplored. This bias fits the present contribution: to analyze the existence of synchronization of the circadian rhythm under the influence of external factors such as pain. To that end, we propose and investigate a model of coupled and phase oscillators that describes the sleep-wake, body temperature, and pain rhythms. The simplicity of the modeling allows one to obtain the synchronized solutions analytically as well as derive restrictions in terms of the parameters that guarantee their synchronization. The results obtained by analyzing the proposed model are accompanied by numerical simulations.

Keywords: Synchronization; Biological rhythms; Pain; PIM model

RESUMO

A sincronização dos ritmos biológicos é de fundamental importância para a saúde. A influência da dor no funcionamento das funções vitais e de seus efeitos na sincronização dos ritmos biológicos dos seres humanos é explorada clinicamente há muito tempo. Por outro lado, a modelagem deste fenômeno pode agregar características ainda inexploradas. Neste viés que se enquadra a presente contribuição: analisar a existência de sincronização do ritmo circadiano sob a influência de fatores externos como a dor. Para tal, propomos e analisamos um modelo de osciladores acoplados em fase que descrevem os ritmos do sono-vigília, temperatura corporal e dor. A simplicidade da modelagem permitiu obter as soluções sincronizadas de forma analítica e derivar restrições em termos dos parâmetros que garantem a sincronização. Os resultados obtidos pela análise do modelo proposto são acompanhados de simulações numéricas.

Palavras-chave: Sincronização; Ritmos biológicos; Dor; Modelo PIM

1 INTRODUCTION

The vast majority of living beings have biological rhythms (or biorhythms) that determine essential or alert bodily functions Tass (1999); Klerman e Hilaire (2007). Examples of these rhythms are sleep-wake, body temperature, hormone levels, blood pressure, and pain. Under normal circumstances, such rhythms change in a predictable way with a well-defined period and frequency and produce a repeating pattern or cycle of changes known as synchronization Strogatz (2000, 1987); Tass (1999); Klerman e Hilaire (2007). Typically, the sleep-wake rhythm and body temperature are coupled in phase (synchronized) with the natural ambient light. However, some modern human ways of life often interrupt normal programming, such as rotating shift work, jet lag, insomnia, or even today's social media hyperactivity, e.g., Walker (2020); Wang (2022) and references therein. Pain is another major contributor to such synchronization shifts, e.g., Palada et al. (2020); Bumgarner et al. (2021) and references therein. Although pain is subjective, understanding how this phenomenon affects the synchronous rhythmicity of body rhythms can help improve people's quality of life, e.g., Neves et al. (2022); Walker (2020); Wang (2022) and references therein. This is because changes in the synchrony of biological rhythms, known as "desynchronization,"alter the functionalities of several fundamental mechanisms, such as metabolism, hormone levels, sleep, and body temperature Neves et al. (2022); Walker (2020); Wang (2022); Palada et al. (2020); Bumgarner et al. (2021). In this contribution, we will propose a mathematical model to analyze the external effects caused by pain on the synchronization of sleep-wake rhythms and body temperature. The periodic variations observable in the circadian rhythms of sleep-wake, temperature, and, eventually, pain indicate that coupled systems of oscillators in phase are great prototypes to describe the essential properties of the investigated biological rhythms.

State of the art and paper main contributions: Synchronization of phase-coupled oscillators is studied in many areas of science, such as medicine, with applications in neuroscience, neurological therapies, psychological treatments, cardiac markers, and circadian rhythms, as we can see in Dörfler e Bullo (2014); Tass (1999); Pikovisky A (2001); Strogatz (2000, 1987); Cai et al. (2022) and references therein. Also in chemistry Kuramoto (1984); Dörfler e Bullo (2014); Rodrigues et al. (2016), reaching applications in physics, such as lasers and electronics e.g., Dörfler e Bullo (2014); Tass (1999); Pikovisky A (2001); Strogatz (2000); Cai et al. (2022); Rodrigues et al. (2016).

From a mathematical point of view, synchronization of phase-coupled oscillators gained notoriety with the initial works of Winfree and Kuramoto Winfree (2001); Kuramoto (1984). Since then, an enormous amount of related work has been done in the field. A good review of the literature and open problems in this area can be found in Dörfler e Bullo (2014); Strogatz (2000); Rodrigues et al. (2016); Bick et al. (2019); Bard et al. (2019) and references. One major question for the phase-coupled oscillators is the existence of a synchronized solution. The answer to such a question in general, on the coupling topology and the number of oscillators. e.g., Dörfler e Bullo (2014); Strogatz (2000); Rodrigues et al. (2016); Bick et al. (2019); Bard et al. (2019).

In Glaeser et al. (2023) and Contessa e De Cezaro (2017) a circadian rhythm model and synchronization results are established, described by the biological rhythms of body temperature and sleep-wake, whose model of oscillators in phase adds memory to the dynamics using fractional order derivatives. In Glaeser et al. (2018) a study of circadian rhythm synchronization with pain effects was proposed using multi-agent simulation techniques.

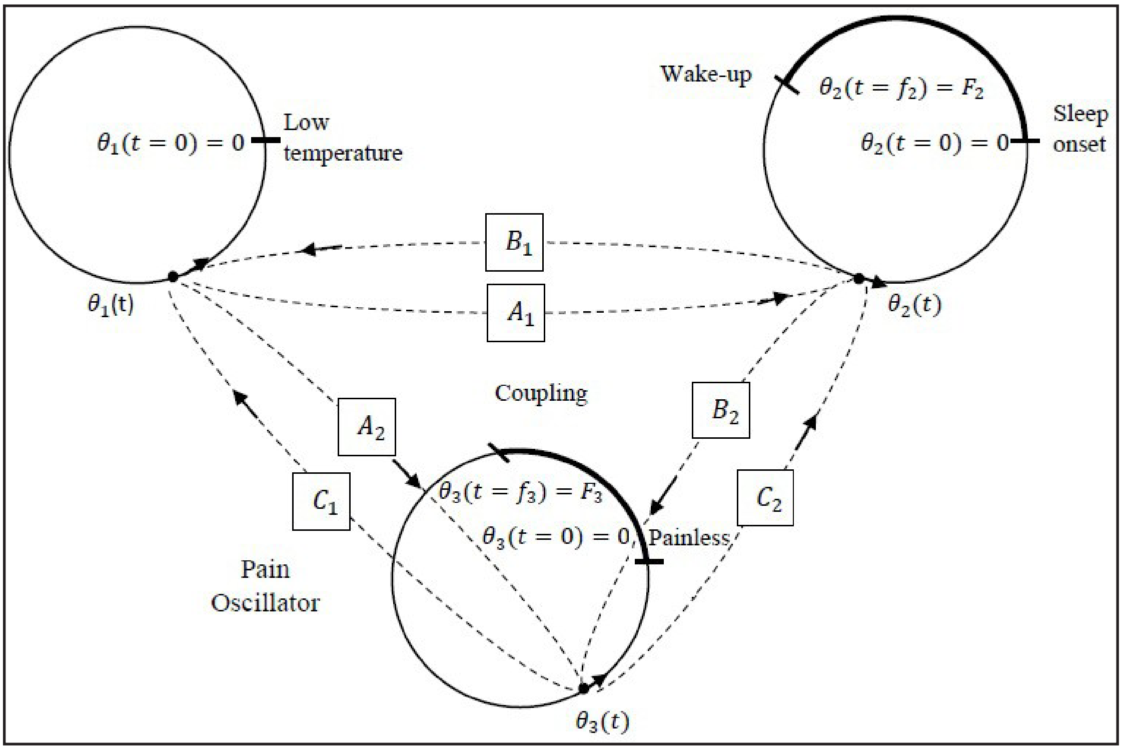
In this contribution, we will focus on establishing the analytical results of total or partial synchronization for three coupled phase oscillators, that model sleep-wake rhythms, body temperature, and pain. The proposed model is called the PIM (pain- influenced model). The total and partial synchronization results obtained in this contribution can be interpreted as a generalization of the results obtained by Strogatz (1987) for two coupled phase oscillators (sleep-wake and body temperature). The following are the main findings and the organization of the manuscript:

1. In Section 2, we will introduce the dynamic model and topology of phase-coupled oscillators that characterize sleep-wake, body temperature, and pain. In Subsection 2.1, we will show that the proposed model is well-posed, that is, it has a unique solution that continuously depends on the initial data and the model parameters.
2. In Subsection 2.2, we obtain the partially and fully synchronized solutions analytically. We will also show how such synchronized solutions depend on the model parameters, allowing us to deduce conditions on the parameters that guarantee the existence of synchronization.
3. In Section 3, we present numerical results that support the theoretical results previously presented.
4. Section 4 is reserved for the final conclusions and future developments of this contribution.

2 PIM MODEL

The PIM model, which we are proposing in this contribution, consists of three nonlinear oscillators, both in phase and weakly coupled. The phases that represent sleep-wake rhythms, body temperature, and pain are described, respectively, by $\theta 1(t)$, $\theta 2(t)$ and.

Figure 1 – PIM model topology



Source: Authorship

$\theta_3(t)$, moving in a counterclockwise direction. The dynamic equations (according to the coupling topology described in Figure 1) of the PIM model are given by

$$\theta_1'(t) = \omega_1 - B_1\cos(2\pi(\theta_2(t)-\theta_1(t))) - C_1\cos(2\pi(\theta_3(t)-\theta_1(t))) \tag{1}$$
$$\theta_2(t) = 0 \tag{2}$$
$$\theta_3(t) = 0, \tag{3}$$

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

$$\theta_1'(t) = \omega_1 - B_1\cos(2\pi(\theta_2(t)-\theta_1(t))) - C_1\cos(2\pi(\theta_3(t)-\theta_1(t))) \tag{4}$$
$$\theta_2(t) = 0 \tag{5}$$
$$\theta_3'(t) = \omega_3 + A_2\cos(2\pi(\theta_1(t)-\theta_3(t))) - B_2\cos(2\pi(\theta_2(t)-\theta_3(t))), \tag{6}$$

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

$$\theta_1'(t) = \omega_1 - B_1\cos(2\pi(\theta_2(t)-\theta_1(t))) - C_1\cos(2\pi(\theta_3(t)-\theta_1(t))) \tag{7}$$
$$\theta_2'(t) = \omega_2 + A_1\cos(2\pi(\theta_1(t)-\theta_2(t))) + C_2\cos(2\pi(\theta_3(t)-\theta_2(t))) \tag{8}$$
$$\theta_3'(t) = \omega_3 + A_2\cos(2\pi(\theta_1(t)-\theta_3(t))) - B_2\cos(2\pi(\theta_2(t)-\theta_3(t))). \tag{9}$$

for $t \geq f_2$.

In equations (1)-(9), $\omega_i = \frac{1}{\tau_i}$ is the intrinsic frequency of oscillator i, where τ_i is the period in hours of oscillator i, for $i = 1,2,3$. These values are always positive and not null. The coupling forces are determined by the parameters A_l, B_l, and C_l, with $l = 1, 2$, which determine how much each oscillator influences the others (we can see the coupling forces in Figure 1).

According to the coupling topology shown in Figure 1, sleep will be defined as a fraction f_2 of the dynamics described by the oscillator $\theta_2(t)$. We will then assume that rest (corresponding to sleep time) remains for the entire interval $[0,f_2[$. In other words, we assume that:

$$\theta_2(t=0) = 0\,. \tag{10}$$

When the vigil begins, we must have

$$\theta_2(t=f_2) = F_2\,. \tag{11}$$

A fraction f_3 of the dynamics of the oscillator $\theta_3(t)$ will define the absence of pain, that is, when an organism does not experience pain. Analogously to what was done above, let's assume that the pain does not manifest itself throughout the interval $[0,f_3[$. And so, we have to

$$\theta_3(t=0) = 0\,. \tag{12}$$

Furthermore, $\theta_3(t) = 0$ for any $0 < t < f_3$. When the pain comes, we have to

$$\theta_3(t=f_3) = F_3\,. \tag{13}$$

It is important to emphasize that the values f_2 and f_3 are not necessarily the same. Assume that $f_2 > f_3$ to fix the ideas. Other cases can be analyzed analogously. We can therefore interpret that the pain manifests itself when the organism is still in the sleep stage. Body temperature peaks in the late afternoon and declines significantly in the early morning, according to Wang (2022). Thus, barring a change of scale and to facilitate the analysis, we will consider that

$$\theta_1(t=0)=0\,. \tag{14}$$

meaning that the “phase”' of oscillator $\theta_1(t)$ is located at zero. See Figure 1.

Conditions from equations (10)-(14) justify the initial conditions for the proposed PIM model, (1)-(9). It is worth mentioning that in the dynamic equations of the PIM model, (1)-(9) some parameters of the coupling forces can be preceded by the negative sign. The justification is given by the movement of the oscillators in the counterclockwise direction. Thus, if the coupling force contributes to the movement of the oscillator that receives it, then the signal that precedes this force is positive, otherwise, if the coupling force retards the movement of the oscillator that receives it, then the signal that precedes such a force shall be negative. The PIM model with $A_2 = B_2 = C_1 = C_2 = 0$ is the phase oscillator proposed by Strogatz (1987) to analyze body temperature and sleep-wake rhythms. Hence the proposed PIM model is a generalization of the model proposed by Strogatz(1987).

2.1 Well-posedness for the PIM model

In this subsection, we formulate the well-posedness results of the PIM model (1)-(9) with initial conditions (10)-(14). First, we have to prove auxiliary results.

Lemma 2.1. *Assume that the PIM dynamics' general assumptions are correct, with initial conditions (10)-(14). Then, for* $t \in [0, f_3]$*, there exists a unique continuous solution* $(\theta_1(t), 0, 0)^T$*. Such a solution depends continuously on the initial conditions and the model parameter described in the equations (1)-(14).*

Proof: Since $cos(X) \leq 1 + |X|$, it follows that the right-hand side of system (1), is continuous with respect to $t \in [0, f_3]$ and Lipschitz continuous with respect to the second argument. Therefore, it follows from the classical theory of differential equations, see Strogatz (1994), that there is a unique continuous solution in the interval $[0, K^*]$, for some

$K^* > 0$, which depends only on the parameters of equation (1), the Lipschitz constant and the initial conditions. It follows from conditions (2)-(3) and (10)-(14) that such a solution is given by $(\theta_1(t), 0, 0)^T$.

Since *cos(X)* is uniformly bounded, it follows from Strogatz (1994) that the solution has a continuous extension to the interval $[0, f_3]$.

Now, we can formulate the following result, which also covers the second part of the system (1)-(9).

Lemma 2.2. *Let the general assumptions holding true and assume* $F_3 = 0$. *Then:*

i) *There is a unique continuous solution* $(\theta_1(t),0,\theta_3(t))^T$ *for the system (1)-(6) with initial conditions (10)-(14) in the interval* $[0,K^{**}]$, *for some* $K^{**} > 0$.

ii) *The solution* $(\theta_1(t),0,\theta_3(t))^T$ *of the system (1)-(6) with initial conditions (10)-(14) depend continuously on the initial conditions (1)-(6) and on the system parameters.*

iii) *The solution* $(\theta_1(t),0,\theta_3(t))^T$ *of the system (1)-(6) can be continuously extended to the interval* $[0,f_2]$.

Proof: Because $\theta_2(t)$ and $\theta_3(t)$ are both zero in $[0, f_3]$, items (i) and (ii) are true in $[0, f_3]$ using arguments similar to those used in Lemma 2.1. As a result, $\theta_1(f_3)$ is well defined.

The lemma statements are then reduced to the case of (1)-(6) with initial conditions $\theta_1(t = f_3)$ and $\theta_2(t = f_3) = \theta_3(t = f_3) = F_3 = 0$. The remained lemma statements are proved using the same arguments as in Lemma 2.1 for the interval $[f_3, f_2]$. The combination of the results above concludes the statements of Lemma 2.2.

Theorem 2.1. *Let* $F_2 = F_3 = 0$. Then:

1. There exist a unique continuous solution $(\theta_1(t),\theta_2(t),\theta_3(t))^T$ for the system (1)-(9) with initial conditions (10)-(14) in the interval $[0,K]$, for some $K > 0$.
2. The solution $(\theta_1(t),\theta_2(t),\theta_3(t))^T$ for the system (1)-(9) with initial conditions (10)-(14) continuously depends on the initial conditions (10)-(14) and on the system parameters.
3. The solution (10)-(14) can be continuously extended to the interval $[0,\infty[$.

Proof: It follows from Lemmas 2.1 and 2.2 that the conclusion for items i) and ii) holds true in the interval $[0, f_2]$, since θ_2(t) is identically zero in $[0, f_2]$. As a result, $\theta_1(f_2)$ and $\theta_3(f_2)$ are well defined.

It remained to prove Theorem 2.1 statement with initial conditions $\theta_1(t = f_2) = \theta_1(f_2)$, $\theta_2(t = f_2) = F_2 = 0$ and $\theta_3(t = f_2) = \theta_3(f_2)$. It turns out that such a result is the result of arguments similar to those used in Lemmas 2.1 and 2.2, which prove the existence of a unique and continuous solution $(\theta_1(t), \theta_2(t), \theta_3(t))^T$ in the interval $[f_2, K^{***}]$. Furthermore, because cos(X) = |X|, it follows from Strogatz (1994), which can be extended continuously to the interval $[f_2, \infty]$. Putting together the two results above, we conclude the statements of Theorem 2.1.

In the case of $F_3 \neq 0$, we cannot prove the continuity of $\theta_3(t)$ in $[0, \infty]$ because $\theta_3(t) = 0$ for $t \in [0, f_3]$. Similarly, in the case of $F_2 \neq 0$, we cannot prove the continuity of $\theta_2(t)$ in $[0, \infty]$ because the assumption $\theta_2(t) = 0$ for $t \in [0, f_2]$ prevents us from doing so. On the other hand, we can consider a piecewise continuous solution $(\theta_1(t),0,0)^T$ in $[0,f_3[$ given by Lemma 2.1, $(\theta_1(t),0,\theta_3(t))^T$ in $[f_3,f_2[$ given by Lemma 2.2 and $(\theta_1(t),\theta_2(t),\theta_3(t))^T$ in $[f_2,\infty[$, as in Theorem 2.1. Specifically, it is possible to prove that the solution $(\theta_1(t), \theta_2(t), \theta_3(t))^T$ is continuously differentiable in $]f_2, \infty[$ using the general theory of the existence of a solution for ODE's Strogatz (1994). The latter is sufficient for the synchronization results that we will establish, as this makes sense only for $t \geq f_2$, as we will see below.

2.2 Synchronization results for the PIM model

In this subsection, we will analyze the existence of synchronized analytical solutions for the PIM model (1)-(14).

Definition 2.1. *We say that two oscillators in phase are synchronized if and only if the phase difference between them is constant. Therefore, three oscillators in phase are synchronized if they are pairwise synchronized.*

According to Definition 2.1, synchronization of the PIM model oscillators (1)-(14) makes sense only when $\theta_2(t) \neq 0$ and $\theta_3(t) \neq 0$, because otherwise these oscillators do not influence each other and do not influence the oscillator $\theta_1(t)$. As a result, we will only consider synchronization for the PIM model for $t \geq f_2$.

2.2.1 Partial synchronization

We assume that two oscillators, $\theta_1(t)$ and $\theta_2(t)$, are synchronized but not individually synchronized with the third oscillator, $\theta_3(t)$, because we want to identify the influence of pain on the synchronization of sleep-wake and body temperature oscillators.Therefore, we have a partial synchronization. Hypothetically, this situation can be interpreted as a strongly synchronized organism in terms of sleep-wake and body temperature, for which we will analyze the influence of pain on these rhythms.

With the assumption that oscillators $\theta_1(t)$ and $\theta_2(t)$ are synchronized, Definition 2.1 states that the phase difference $\theta_1(t) - \theta_2(t) = k_4$ during synchronization. Consequently,

$$\theta_1'(t) - \theta_2'(t) = 0\,, \tag{15}$$

during synchronization. We can deduce from the initial conditions that k4 = 0. Furthermore, because cos(0) = 1, the dynamics equations of the PIM model during partial synchronization are given by

$$\theta_1'(t) = \omega_1 - B_1 - C_1 \cos(2\pi(\theta_3(t) - \theta_1(t)))\,, \tag{16}$$
$$\theta_2'(t) = \omega_2 + A_1 + C_2 \cos(2\pi(\theta_3(t) - \theta_2(t)))\,, \tag{17}$$
$$\theta_3'(t) = \omega_3 + A_2 \cos(2\pi(\theta_3(t) - \theta_1(t))) - B_2 \cos(2\pi(\theta_3(t) - \theta_2(t)))\,. \tag{18}$$

It follows from equations (15)-(16)-(17) that

$$\omega_1 - \omega_2 - A_1 - B_1 - C_1 \cos(2\pi(\theta_3(t) - \theta_1(t))) - C_2 \cos(2\pi(\theta_3(t) - \theta_2(t))) = 0\,. \tag{19}$$

Let us define the phase difference (which is true because, by assumption, θ1(t) = θ2(t)) during synchronization as

$$\psi_3(t) = \theta_1(t) - \theta_3(t) = \theta_2(t) - \theta_3(t)\,. \tag{20}$$

From equations (19) and (20), we have

$$\Omega_3 - E_3 - D_3\cos(2\pi\psi_3(t)) = 0 \quad \iff \psi_3(t) = \frac{1}{2\pi}\arccos\left(\frac{\Omega_3 - E_3}{D_3}\right), \tag{21}$$

where $\Omega_3 = \omega_1 - \omega_2$ is the difference of the intrinsic frequencies of the synchronized oscillators; $E_3 = A_1 + B_1$ is the sum of the coupling forces between the synchronized oscillators; and $D_3 = C_1 + C_2$ is the sum of the coupling forces of oscillator $\theta_3(t)$.

Remark 2.1. It is worth noting that, because the domain of the arccos(·) $\in]-1,1[$, oscillator θ3(t) is synchronized with the system generated by the previously synchronized oscillators θ1(t) and θ2(t) if

$$D_3 \geq |\Omega_3 - E_3| \quad \iff C_1 + C_2 \geq |\omega_1 - \omega_2 - (A_1 + B_1)|\,. \tag{22}$$

As a result of equation (22), we can deduce that the synchronization of oscillator $\theta_3(t)$ with the system of synchronized oscillators $\theta_1(t)$ and $\theta_2(t)$ (of sleep-wake and temperature) is dependent on the coupling forces C_1 and C_2 relative to oscillator $\theta_3(t)$, as well as the intensity of synchronization between the oscillators $\theta_1(t)$ and $\theta_2(t)$.

To the Remark 2.1, we can add the following remarks:

- Synchronization (or desynchronization) occurs regardless of the influence of oscillators $\theta_1(t)$ and $\theta_2(t)$ on oscillator $\theta_3(t)$ because equations (21) and (22) are independent of A_2 and B_2. In other words, it is pain that influences sleep-wake rhythms and body temperature, and this is in agreement with our hypotheses.
- If θ_1(t) and $\theta_2(t)$ oscillators are strongly coupled, that is, if $|E_3| >> |\Omega_3|$, where >> means much larger. Then, according to equation (22), oscillator $\theta_3(t)$ will only synchronize with oscillators $\theta_1(t)$ and $\theta_2(t)$ if the sum of the coupling forces C_1 and C_2 is large enough. Therefore, pain will have to strongly influence at least one of the oscillators, sleep-wake or body temperature.
- If the oscillators $\theta_1(t)$ and $\theta_2(t)$ are weakly coupled. In other words, $|E_3| > |\Omega_3|$, but the difference $E_3 - \Omega_3$ is small. Then, equation (22) implies that oscillator $\theta_3(t)$ will synchronize with oscillators $\theta_1(t)$ and

$\theta_2(t)$, even if the sum of the coupling forces C_1 and C_2 is relatively small. Therefore, it is enough for the pain to slightly influence one of the oscillators, sleep-wake or body temperature, for it to synchronize with the others.

Given the preceding remarks, we can conjecturing that if the intensity of synchronization between oscillators $\theta_1(t)$ and $\theta_2(t)$ is low, synchronization with $\theta_3(t)$ is facilitated. In the latter case, the pain has a high possibility of becoming frequent in everyday life. Such conjecture will be investigated in future contributions using real data.

Remark 2.2. *Starting with the assumption that the oscillators $\theta_1(t)$ and $\theta_3(t)$ are synchronized, we can derive the constraint that guarantees synchronization of $\theta_2(t)$ with synchronized systems of $\theta_1(t)$ and $\theta_3(t)$, which is given by*

$$|B_1 - B_2| \geq |\omega_1 - \omega_3 - (A_2 + C_1)|\,. \tag{23}$$

It follows from (23) that $\theta_2(t)$ synchronization with the synchronized systems given by $\theta_1(t)$ and $\theta_3(t)$ is directly related to the synchronization intensity between the oscillators $\theta_1(t)$ and $\theta_3(t)$ with the coupling forces that come out of the oscillator $\theta_2(t)$.

In the previous case, for the pain oscillator to be synchronized with the body temperature and sleep-wake system, it was necessary that the sum of the coupling forces of the pain oscillator be greater than the synchronization intensity of the other two biological rhythms. Now, where the biological rhythm of sleep-wake seeks to synchronize with the synchronized system of pain and body temperature, one of its coupling forces works in the opposite way to total synchronization: the B_2 coupling force of sleep-wake with pain influences the desynchronization of the biological sleep-wake rhythm. In other words, pain synchronized with body temperature hinders the synchronized behavior of the sleep-wake rhythm, and, therefore, if pain is frequent in everyday life, the intervals between sleep and wakefulness tend to be deregulated. Thus, for the synchronization of sleep-wake with the body temperature and pain system to occur, a strong coupling of sleep-wake with body temperature is necessary in order to overcome the intensity of synchronization of the rhythm of body temperature with the rhythm of pain and overcome the sleep-wake coupling force with pain.

Therefore, we conjecture that if the synchronization intensity between oscillators $\theta_1(t)$ and $\theta_3(t)$ is low and $\theta_2(t)$ influences $\theta_1(t)$ more than $\theta_3(t)$, then the synchronization of $\theta_2(t)$ with the system defined by $\theta_1(t)$ and $\theta_3(t)$ is facilitated.

Remark 2.3. *Let oscillators $\theta_2(t)$ and $\theta_3(t)$ be synchronized. Analogously to Remark 2.1 and 2.2, synchronization of $\theta_1(t)$ with the system generated by $\theta_2(t)$ and $\theta_3(t)$ is guaranteed if*

$$|A_1 - A_2| > |\omega_2 - \omega_3 - (B_2 + C_2)|\,. \tag{24}$$

Hence, similarly to what was previously mentioned, from Remark (2.3) we can conjecture that if the synchronization intensity between oscillators $\theta_2(t)$ and $\theta_3(t)$ is low and $\theta_1(t)$ influences $\theta_2(t)$ more than $\theta_3(t)$, then the synchronization of the sleep-wake rhythm $\theta_1(t)$ with the system that involves the rhythms of body temperature and pain is facilitated. In the latter case, if the periods of sleep and wakefulness are well regulated and pain is frequent in everyday life, the body temperature will only have a well-behaved daily cycle if it is strongly related to the sleep-wake periods and not to the pain. As above mentioned, such conjecture will be investigated using real data in future contributions.

2.2.2 Existence of an explicit solution for the phase oscillator during partial synchronization

In this subsection, we will derive an explicit solution for the phase oscillator during partial synchronization.

Assumes that the oscillators $\theta_1(t)$ and $\theta_2(t)$ are partial synchronized (the other cases can be treated analogously). We obtain by substituting (21) in the equations of the system (16)- (18), that

$$\theta_1'(t) = \frac{C_1\omega_2 + C_2\omega_1 + A_1C_1 - B_1C_2}{C_1 + C_2}\,, \tag{25}$$

$$\theta_2'(t) = \frac{C_1\omega_2 + C_2\omega_1 + A_1C_1 - B_1C_2}{C_1 + C_2}\,, \tag{26}$$

$$\theta_3'(t) = \frac{((\omega_1 - \omega_2) - (A_1 + B_1))(A_2 - B_2)}{C_1 + C_2} + \omega_3\,. \tag{27}$$

Integrating from both sides of equations 25-(27), using the initial conditions, we obtain that the synchronized solution is given by

$$\theta_1(t) = \frac{C_1\omega_2 + C_2\omega_1 + A_1C_1 - B_1C_2}{C_1 + C_2}t\,, \tag{28}$$

$$\theta_2(t) = \frac{C_1\omega_2 + C_2\omega_1 + A_1C_1 - B_1C_2}{C_1 + C_2}(t - f_2) + F_2\,, \tag{29}$$

$$\theta_3(t) = \left(\frac{((\omega_1 - \omega_2) - (A_1 + B_1))(A_2 - B_2)}{C_1 + C_2} + \omega_3\right)(t - f_3) + F_3\,. \tag{30}$$

Below, we make some comments regarding the obtained explicit solutions for the oscillator in partial synchronization for the PIM model, given by (28)-(30).

- Equations (28) and (29) shows that the explicit solutions of the synchronized oscillators $\theta_1(t)$ and $\theta_2(t)$ depend only on their intrinsic frequencies, the coupling forces of the interaction between them, and the coupling forces they receive from oscillator $\theta_3(t)$, but do not depend on the intrinsic frequency of $\theta_3(t)$. In other words, body temperature and sleep-wake oscillators, when synchronized, are not influenced by the period of pain, only by the coupling forces.
- Because the phase difference is constant, oscillators $\theta_1(t)$ and $\theta_2(t)$ are synchronized, as shown by equations (28) and (29). In particular, for $F_2 = \frac{C_1\omega_2+C_2\omega_1+A_1C_1-B_1C_2}{C_1+C_2} f_2$ the phase difference is null, for any $t \geq 0$. Hence, the above assumptions can be justified for such a choice of F_2.

Finally, the frequency of "commitment"' $\omega^{*} := \theta_1(t) = \theta_2(t)$ adopted by the system during synchronization, can be obtained directly from (25) (or equivalently from (26)), and is given by

$$\omega^* = \frac{C_1\omega_2 + C_2\omega_1 + A_1C_1 - B_1C_2}{C_1 + C_2}\,. \tag{31}$$

The commitment frequency ω^{*} given by (31), is different from the intrinsic frequency ω_i for the oscillator $\theta_i(t)$, for $i = 1, 2$, from the quantity

$$\delta\omega_1 = \omega^* - \omega_1 = \frac{C_1(\omega_2 - \omega_1) + A_1C_1 - B_1C_2}{C_1 + C_2}\,, \tag{32}$$

$$\delta\omega_2 = \omega^* - \omega_2 = \frac{C_2(\omega_1 - \omega_2) + A_1C_1 - B_1C_2}{C_1 + C_2}\,. \tag{33}$$

We are going to analyze two interesting cases regarding equations (32) and(33). The comparison with real data will be postponed to a future contribution. We assume that pain only influences the sleep-wake rhythm, for example, from the use of medication that blocks interaction with body temperature. We have $C_2 = 0$ in this case. According to (32) and (33) the intrinsic frequencies in this case ω_1 and ω_2 are translated by $\delta\omega_1^{*} = (\omega_2 - \omega_1) + A1$ and $\delta\omega_2^{*} = A1$, respectively. In particular, $\theta_2(t)$'s commitment frequency is only committed to the coupling strength received from $\theta_1(t)$. If, on the other hand, we assume that pain only influences the rhythm of body temperature, such as from the use of medication that blocks the interaction with sleep-wakefulness, $C_1 = 0$, we get from (32) and (33) that $\delta\omega^{*} = -B_1$ *and* $\delta\omega^{*} = (\omega_1 - \omega_2) - B_1$. As a result, the oscillator's commitment frequency $\theta_1(t)$ is only committed to the coupling strength it receives from $\theta_2(t)$.

Finally, the results obtained so far during the synchronization of oscillators $\theta_1(t)$ and $\theta_2(t)$ differ significantly from those obtained by Strogatz (1987). In particular, it follows from the above analysis that results in (32) and (33), in the case that pain is considered in the modeling of the problem, it influences in a non-trivial way the synchronization of body temperature and sleep-wake rhythms.

2.2.3 Total synchronization

Under the assumption that they are fully synchronized, we will begin the synchronization analysis for oscillators $\theta_1(t)$, $\theta_2(t)$, and $\theta_3(t)$ in the PIM model. According to Definition 2.1, the phase difference between any two of the oscillators must be constant. Since the PIM model remains equivalent in terms of translations of the phase differences (see equations (1)-(14)), we can assume, without loss of generality, that the phase difference between any two of the oscillators is null. Since $cos(0) = 1$, it follows from the dynamic equations of the PIM model (7)-(9) (since the analysis will be done for $t \geq f_2$) that the total synchronized solution satisfies

$$\theta_1'(t) = \omega_1 - B_1 - C_1 \,, \tag{34}$$
$$\theta_2'(t) = \omega_2 + A_1 + C_2 \,, \tag{35}$$
$$\theta_3'(t) = \omega_3 + A_2 - B_2 \,. \tag{36}$$

It follows, from the integration of equations (34)-(36) and conditions (10)-(14), that the synchronized solutions for the PIM model are given by

$$\theta_1(t) = (\omega_1 - B_1 - C_1)t \,, \tag{37}$$
$$\theta_2(t) = (\omega_2 + A_1 + C_2)(t - f_2) + F_2 \,, \tag{38}$$
$$\theta_3(t) = (\omega_3 + A_2 - B_2)(t - f_3) + F_3 \,. \tag{39}$$

Next, we emphasize some comments regarding full synchronization for the PIM model:

- From the Definition 2.1 and (37)-(39), during total synchronization, we have

$$\omega_1 - B_1 - C_1 = \omega_2 + A_1 + C_2 = \omega_3 + A_2 - B_2 \,. \tag{40}$$

In other words, the total synchronization condition between the three phase oscillators is satisfied when the intrinsic frequencies of each oscillator, influenced by the two coupling forces it receives from the other two oscillators, are equal. The intrinsic frequency of each oscillator is influenced by the coupling forces of the other two oscillators in the same way that the oscillators are coupled: if the coupling force contributes to the movement of the receiving oscillator, then the force is positive; otherwise, it is negative.

2.2.4 A sufficient condition for total synchronization

In this subsection, we will explore a sufficient condition for the total synchronization of the oscillators, that can be seen as a generalization of the restrictions of Winfree (2001) for three oscillators, given by

$$\begin{aligned} A_1 + B_1 &> |\omega_1 - \omega_2|\,, \\ A_2 + C_1 &> |\omega_1 - \omega_3|\,, \\ A_2 + C_2 &> |\omega_2 - \omega_3|\,. \end{aligned} \tag{41}$$

For that fate, assume that $\theta_1(t)$ is synchronized with $\theta_3(t)$ and $\theta_2(t)$ is synchronized with $\theta_3(t)$. Without lost of generality, assume that it phase difference is given by $\theta_1(t) - \theta_3(t) = 1/4$ *and* $\theta_2(t) - \theta_3(t) = 1/4$.

Let $\psi_{12}(t) := \theta_1(t) - \theta_2(t)$. It follows from (7)-(8) that

$$\psi_{12}'(t) = \omega_1 - \omega_2 - (A_1 + B_1)\cos(2\pi\psi_{12}(t))\,.$$

As a result, the phase difference $\psi_{12}(t)$ is constant, and then $\psi'(t) = 0$, if and only if

$$(A_1 + B_1)\cos(2\pi\psi_{12}(t)) = \omega_1 - \omega_2\,.$$

Since $|\cos(x)| \leq 1$, the first inequality in (41) is satisfied.

Similarly, if we assume that $\theta_1(t)$ is synchronized with $\theta_2(t)$ and $\theta_2(t)$ is synchronized with $\theta_3(t)$, and the phase difference is given by $\theta_1(t) - \theta_2(t) = 1/4$ *and* $\theta_2(t) - \theta_3(t) = 1/4$. Then an analogous argument as presented above, using equations (7) and (9), will show that the second inequality in (41) will holds. And, if we assume that $\theta_1(t)$ is synchronized with $\theta_2(t)$ and $\theta_1(t)$ is synchronized with $\theta_3(t)$ with phase differences is given by $\theta_1(t) - \theta_2(t) =$

1/4 and $\theta_1(t) - \theta_3(t) = 1/4$. Then, using the analogous argument presented above, using equations (8) and (9), will show that the third inequality in (41) will holds.

Tabela 1 – Table with the parameter values used in the numerical simulations

Example	A_1	A_2	B_1	B_2	C_1	C_2	τ_1	τ_2	τ_3
1	0.009	0.005	0.008	0.002	0.007	0.006	23	24	25
2	0.001	0.004	0.006	0.009	0.0016	0.0045	22	20	34
3	0.0008	0.004	0.0007	0.009	0.0016	0.0045	18	20	34

3 NUMERICAL SIMULATIONS

In this section, we present simulated numerical results for the PIM model proposed to model the circadian rhythm of sleep-wake, body temperature, and pain. The simulations presented are the result of synchronized analytical solutions for the model, obtained in Section 2.2. Furthermore, the simulations reflect the phase of the analyzed rhythms.

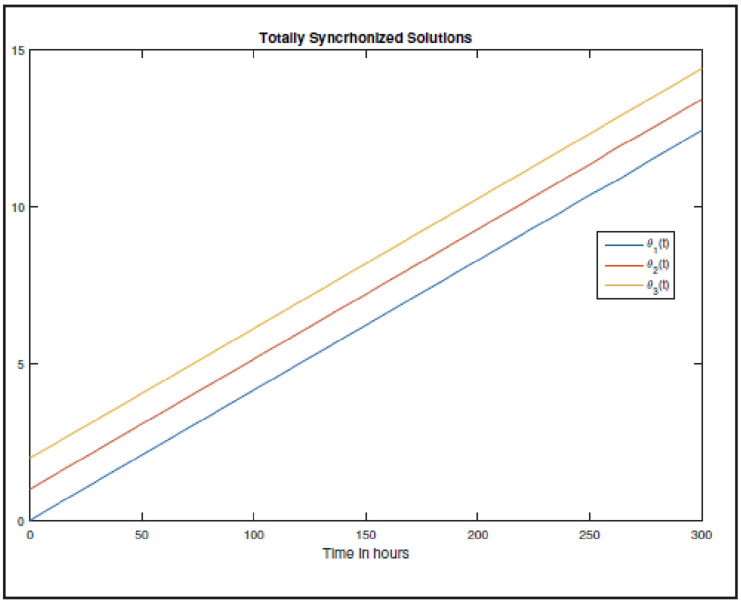
It is important to point out that none of the parameters used in the simulations that we will present in this contribution were calibrated from real data. Our approach is restricted to presenting simulated scenarios, for which the parameters are chosen to satisfy the generalized Winfree's restrictions derived in equation 41. In the numerical simulations, we do not use the derived synchronized explicit solutions because the generalized Winfree's restrictions 41 are sufficient conditions for synchronization (desynchronization). Instead, we use the explicit Runge-Kutta *(4,5)* to solve numerically the system (1)-(9) with initial conditions (10)-(14). See for more details regarding the explicit Runge-Kutta *(4,5)* method.

As the intrinsic frequency ω_i of each oscillator $\theta_i(t)$ is inversely proportional to the period τ_i(in hours), for $i = 1,2,3$, then in the simulations, we chose the parameter τ_i, which reflects the interval, in hours, that the biological rhythm described by oscillator $\theta_i(t)$ completes its respective cycle. For the coupling forces, we assume that the oscillators are weakly coupled. In this way, we restrict the choice for the coupling forces to the interval *[0, 0.1]*. We note that such a restriction is necessary because, otherwise, for coupling forces greater than *0.1*, the generalized Winfree restrictions (41) are automatically satisfied for reasonable choices of period τ_i. Furthermore, as our analysis is focused on the synchronization of the oscillators, we will analyze the solutions of the models only from the moment that all of them are active in the system. Thus, in all simulations, we will adopt both $f_2 = f_3 = 0$, and $F_2 = F_3 = 0$, so that the initial conditions of the model is homogeneous. Finally, the simulations are run for a finite final time$T$ = 300h, which is equivalent to 12 + 1/2 days. In Table 1, we present the parameter values used in the simulations of Examples 1, 2 and 3, respectively.

Example 1 - Total Synchronization The parameters for this scenario are presented in the first line of Table 1. The values defined for τ_1, τ_2 and τ_3 indicate that the body temperature rhythm has a period of 23 hours, that the sleep-wake rhythm has a period of 24 hours, and that the pain rhythm has a period of 25 hours, respectively. Given the values of C_2 and B_2 in the first line of Table 1, the values of the coupling forces, which describe the relationship between the oscillators in this simulated scenario, can be interpreted as indicating that pain influences the sleep-wake rhythm more than vice versa. Each line of the generalized Winfree's restrictions, given by (41), is satisfied, indicating the synchronization of the oscillators two by two and, thus, the total synchronization of the system.

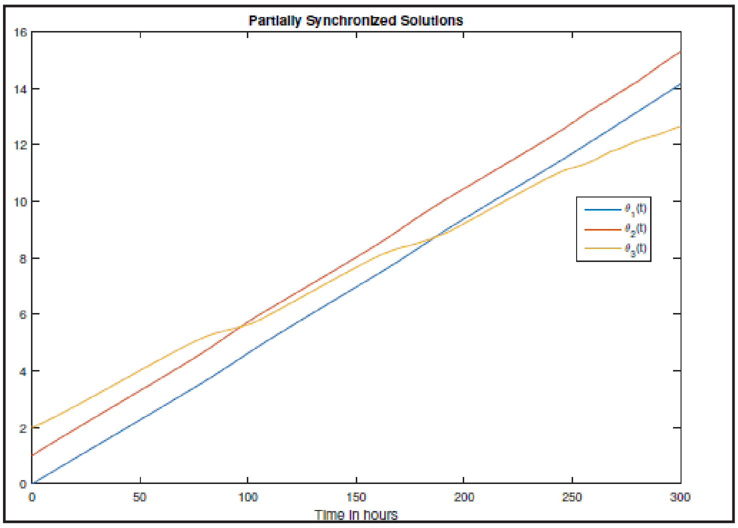
In Figure 2, we present the numerical result of the simulation of the PIM model solutions, given by the system of equati- ons (7)-(9). It is possible to observe that the phase difference between the three oscillators is constant, which implies the total synchronization of the oscillators in the model, according to Definition 2.1

Figure 2 – Totally synchronized solution of the PIM model, for the parameters in the first line of Table 1



Source: Authorship

Figure 3 – Partially synchronized solution of the PIM model, for the parameters in the second line of Table 1



Source: Authorship

A possible interpretation for the situation where body temperature, sleep-wake, and pain rhythms are fully synchronized is that the pain has become chronic.

Example 2 – Partial Synchronization The parameters for this example are presented in the second line of Table 1. In this example, the choice of parameters τ1,

τ_2 and τ_3 indicates that the body temperature rhythm period is 22 hours, the sleep-wake rhythm period is 20 hours, and the pain rhythm period is 34 hours, respectively. From the values of the other parameters, we can see that the biological rhythms of body temperature, sleep-wake, and pain do not strongly influence each other, as the coupling forces are relatively small. We also observe that only one of the generalized Winfree constraints, given by (41), is satisfied. This corresponds to the synchronization of oscillators $\theta_1(t)$ and $\theta_2(t)$ only, indicating that the system is only partially synchronized. In Figure 3, we present the numerical result of the simulation of the solutions of the PIM model, given by the system of equations (7)-(9) with the parameters corresponding to the present example.

As shown in Figure 3, the phase difference between oscillators $\theta_1(t)$ and $\theta_2(t)$ is constant, whereas the same phenomenon does not occur with respect to oscillator $\theta_3(t)$. Therefore, we have a partial synchronization of the model oscillators, according to Definition 2.1.

The disturbances that occur in the phases of oscillators $\theta_1(t)$ and $\theta_2(t)$, as shown in Figure 3, are an interesting fact to highlight. These disturbances can be interpreted as the influence of pain on a system whose body temperature rhythm and sleep-wake rhythm are strongly synchronized. Pain disturbs the system, but not to the point of desynchronizing these biological rhythms.

Example 3 – Total desynchronization The parameters for this example are presented in the third row of Table 1. The parameters used for the simulation in this example have the following peculiarities: The body temperature rhythm period is 18 hours, the sleep-wake rhythm period is 20 hours, and the period of the pain rhythm is 34 hours; The body temperature rhythm influences the sleep-wake rhythm more than the opposite ($A_1 > B_1$); the body temperature rhythm has a greater influence on the pain rhythm than the opposite ($A_2 > C_1$); just as the sleep-wake rhythm has a greater influence on the pain rhythm than the opposite ($B_2 > C_2$). We also observe that none of the generalized Winfree constraints, given by equation (41), are verified for the choice of parameters in this example. So we have total system desynchronization.

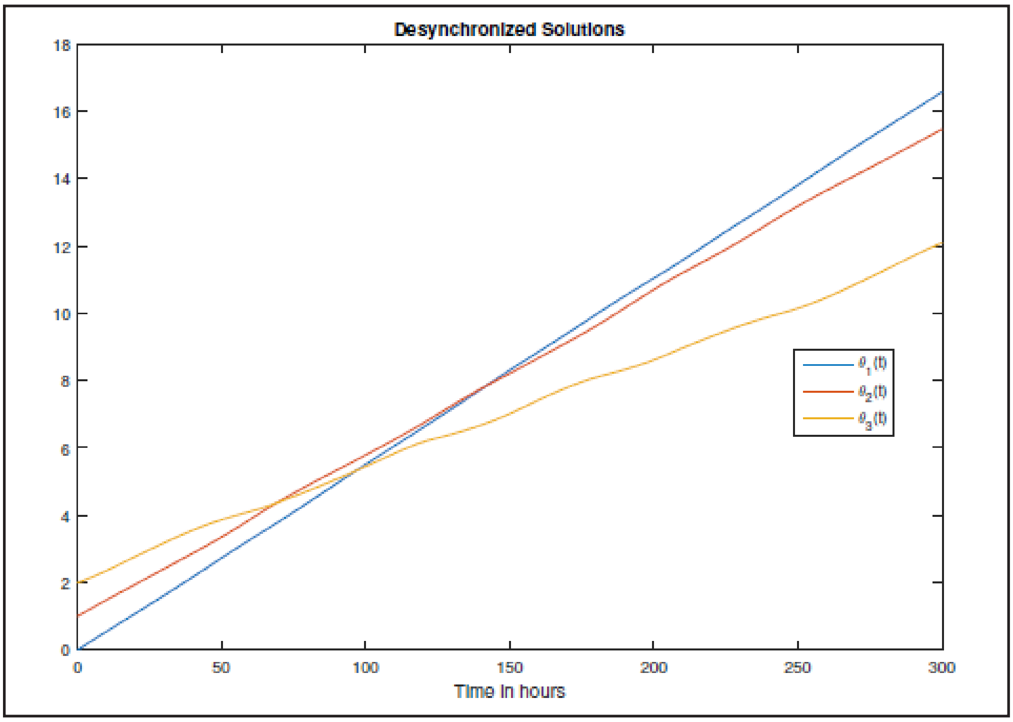
In Figure 4, we present the numerical result of the simulation of the solutions of the PIM model, given by the system of equations (7)-(9) with the parameters corresponding to the present example. It is worth noting that the phase difference between oscillators $\theta_1(t)$ and $\theta_2(t)$ grows with t, as does the phase difference between oscillators $\theta_1(t)$ and $\theta_3(t)$ and between oscillators $\theta_2(t)$ and $\theta_3(t)$. Hence, the numerical results agree with the theoretical conditions that indicate a total desynchronization of the system.

4 CONCLUSIONS

In this contribution, we propose a model with three phase-coupled oscillators, called the PIM model, which allows a simple mathematical treatment of the solutions, obtained analytically, to investigate the influence of pain on the synchronization of sleep- wake rhythms and body temperature. We establish the well-posedness of the system solutions for partial and total synchronization. We show how such synchronized solutions depend on the model parameters, thus allowing us to deduce conditions on the parameters that guarantee the existence of synchronization. The aforementioned results are numerically exemplified.

Extensions of the results presented in this contribution for the PIM (1)-(9) model with non-zero f_2, f_3, F_2 and F_3 (discontinuous solutions), generalizations for the case where pain comes and goes at random time intervals, as well as how the calibration of parameters and comparison with real data will be the result of future investigations.

Figure 4 – Desynchronized solution of the PIM model, for the parameters in the third line of Table 1



Source: Authorship

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AUTHORSHIP CONTRIBUTIONS

1 – Adriano De Cezaro

PhD in Mathematics, Professor at the Institute of Mathematics, Statistics and Physics
https://orcid.org/0000-0001-8431-9120 • decezaromtm@gmail.com
contribution: Conceptualization; Formal Analysis; Investigation; Methodology; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

2 – Fabiana Travessini De Cezaro

PhD in Mathematics, Professor at the Institute of Mathematics, Statistics and Physics
https://orcid.org/0000-0001-9401-5315 • fabi.travessini@gmail.com
contribution: Conceptualization; Formal Analysis; Investigation; Methodology; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

3 – Stefânia da Silveira Glaeser

PhD in Computational Modeling
https://orcid.org/0009-0009-4170-0808 • stefaniaglaeser@gmail.com
contribution: Conceptualization; Formal Analysis; Investigation; Methodology; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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