Study of internal oscillations in a dynamic system through an external signal implemented in circadian rhythms

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Abstract. Through the analysis carried out on a dynamic model that is represented as a system of ordinary differential equations that describes the behavior of the circadian cycles; we will show and analyze in the next document what are the conditions that allow the synchronization of the circadian clock oscillator with the external modification oscillator. The implementation of this type of techniques in anatomical problems is highlighted, which are rare in the literature. The implementations will be carried out through different simulations using numerical techniques and the way in which we will determine the coupling conditions of an internal cycle of the system versus external cycles will be detailed. In the final development of this work, we will be able to see in the model without an external modification signal the existence of stable limit cycles and discover the moment in which the synchronization of the internal oscillator and the external modification signal occurs. These types of problems are common when making biological models that are described by a physical analysis.

1. Introduction
Daily rhythms in physiology, metabolism and behavior are controlled by a circadian timing system, which has evolved to synchronize an organism with periodic environmental conditions, such as light-dark or temperature cycles. In mammals, the circadian system relies on autonomous cellular oscillators that reside in almost every cell in the body. Essentially, the same molecular components are arranged as transcriptional feedback loops generating cycles of approximately 24 hours at the molecular level [1].

The precise synchronization of the cycles is an essential part of the circadian organization, which generally follows hierarchically organized steps, for example, as follows: First, the periodic light detected by the eyes modifies the functioning of 20,000 neurons in the bilateral suprachiasmatic nucleus of the hypothalamus (SCN) through signals that travel along the retinohypothalamic tract [2]. Within the SCN tissue, individual neurons synchronize with each other by coupling neuropeptides that generate precise and self-sufficient oscillations of 24 hours, even in the absence of external signals [3]. Subsequently, the SCN synchronizes other peripheral tissues, however, this synchronization seems to be less coupled which can lead to rapid desynchronization when external signals are eliminated [4]. Different authors have studied in detail the dynamics present in circadian cycles, which present a highly non-linear dynamic where bifurcation diagrams, toroidal oscillations and even deterministic chaos can be found [5]; however, in most physiological situations, a modification of the internal oscillations can be observed stably, but not trivially due to the limitations of the external forces of modification.

Therefore, this document explores the conditions necessary for a robust and relatively fast synchronization of the circadian cycles in the face of a periodic external force of modification, to be able to answer under which conditions the oscillator of the circadian clock is synchronized with the
oscillator of the external signal or the existence of synchronization ranges [6]. For this, it is necessary to clarify some previous concepts about dynamical systems, such as the determination of equilibrium points, their stability, and the existence of periodic orbits. These mathematical concepts are described in the next section. On the other hand, section three describes the functioning of biological clocks as a background and section four presents the model that will be treated in this document along with some results to be highlighted. Finally, section five presents some of the conclusions about the synchronization of circadian rhythms.

2. Mathematical concepts

The use of differential equations has allowed to describe many dynamic systems of physics, mathematics, mechanics, electromagnetism, medicine, etc. quantitatively and qualitatively. However, there are still many questions to be resolved in this area as wide as differential equations are.

In this work a dynamic system of the form presented in Equation (1) will be analyzed, these are autonomous systems described by ordinary differential equations, mathematically, if $\Omega$ is an open and related region of $\mathbb{R}^n$, and $f: \Omega \to \mathbb{R}^n$ is a continuous function, then:

$$\dot{x} = f(x, \mu), \quad x \in \Omega, \mu \in \mathbb{R}^k. \tag{1}$$

The system is said to be an ordinary differential system, where $x$ is the vector of state variables and $\mu$ represents the system parameters. In addition, if there is $t_0 \in I$ and $x_0 \in \Omega$, then the system Equation (1) will be a problem of initial value, which will have a solution if it satisfies the existence and uniqueness theorem set forth below.

**Definition 1.** Balance points the balance points for the system Equation (1) are given by $\dot{x} = 0$, that is Equation (2).

$$f(x, \mu) = 0. \tag{2}$$

For a given value of $\mu$, the solution of Equation (2) will be an equilibrium point for the system Equation (1). Once the equilibrium points have been defined, it is necessary to study the classification of their stability through linearization around them, as shown. Taking $x_0$ and $\mu_0$ as equilibrium points, the system Equation (1) can be rewritten as Equation (3).

$$\dot{x} = Ax, \tag{3}$$

where $A$ is the Jacobian matrix of the system Equation (1) defined as Equation (4).

$$A = [a_{ij}] = \left[ \frac{\partial f_i}{\partial x_j} \right] \text{con } x = x_0. \tag{4}$$

The stability of each of the equilibrium points of the system of Equation (1), will depend on the eigenvalues of the matrix $A$; If all eigenvalues have a negative real part, the equilibrium point is stable known as an attractor.

**Theorem 1.** Existence and uniqueness $\Omega \subset \mathbb{R}^n$ an open region, $f: \Omega \to \mathbb{R}^n$ locally Lipschitz, $x_0 \in \Omega$ then exists at $> 0$ and a single solution $x: I := (-a, a) \to \mathbb{R}^n$ of the problem. Equation (5).

$$\dot{x} = f(x), \quad x(t_0) = x_0. \tag{5}$$

From the existence and uniqueness theorem we have that for each $x \in \Omega$, there is a single solution called local flow defined by $\phi_t(x) := \phi(t, x)$, which will present two types of trajectories important for the analysis of the global behavior of the system Equation (1) known as fixed points and periodic orbits.
Definition 2. For the system Equation (1), it is said that a point \( p \in \Omega \) is a fixed point if it is satisfied that \( \phi_t (p) = p, \forall t \in \mathbb{R} \). Now, it is said that a solution \( \phi_t (x) \) is periodic if \( \phi_{T} (x) = x \) with \( T > 0 \).

In the study of the dynamics of the systems of differential equations, a very important task is the determination of periodic orbits in these systems, in the literature there are several criteria to solve the problem that range from the criteria for non-existence, such as the theorem from gradient systems to criteria for existence, where the most used theorem is the Poincaré-Bendixson theorem, which will be treated next.

Theorem 2. Poincaré-Bendixson Criteria Let \( M \) be an open subset of \( \mathbb{R}^2 \) and \( f \in C^1 (M, \mathbb{R}^2) \). Let's fix a point \( x \in M, \sigma \in \{\pm\} \) and suppose that \( \omega_{\sigma} (x) \neq \emptyset \) is compact, connected and only has a number (finite at most) of fixed points. Then one of the following cases occurs:

1. \( \omega_{\sigma} (x) \) is a fixed orbit.
2. \( \omega_{\sigma} (x) \) is a regular periodic orbit.
3. \( \omega_{\sigma} (x) \) is a set (finite at most) of fixed points \( \{x_i\}_{i=1}^n \) and a single closed orbit \( \gamma(x) \) such that
   \[
   \omega_{\pm} \in \{x_i\}_{i=1}^n.
   \]

All living beings, animals and plants have biological cycles determined by the rhythms of the environment such as the light or seasonal changes of the earth [7]. It is known that all living beings have a regular change between light and dark, which demonstrates the biological periodicity 24 hours a day, during this period there are sleep and wake activities. Sleep activity is a normal, active, procedural, reversible, periodic phenomenon with the most prominent feature that the perceptual disconnection with the environment. While vigil activity or state is a physiological, behavioral, and psychic conscious phenomenon [8].

Biological rhythm is defined as the regular variation of an organic function related to the course of time. According to the biological variations of time, there are different types of biological rhythms, these are: (i) circadians, (ii) infraradians, and (iii) ultradians. The first of these is related to activities around the day, that is, they have periods of approximately 24 hours; the infradian rhythms are those regular variations recorded in a time greater than 24 hours, while the ultradian rhythms are recorded in a time less than 24 hours. The term circadian rhythm etymologically means cycle close to 24 hours; however, some authors consider that this cycle varies between 24 hours and 25 hours [9].

In mammals, biological functions expressed in a circadian manner include: the sleep-wake cycle, the synthesis and hormonal release and the regulation of body temperature, among others. The oscillations of these functions are generated and organized by a pacemaker or circadian clock structure: the suprachiasmatic nucleus (NSQ) located in the hypothalamus is responsible for synchronizing the organism with its environment. The precise synchronization of these rhythms is an essential part of the circadian organization, which generally follows hierarchically organized steps.

The signal is sent from the NSQ through the retinohyothalamus tract when the training or modification force is low. The NSQ sends signals of modifications to the peripheral clocks and can be modeled by an oscillator, which can be influenced by external forces such as the social environment, temperature change and feeding cycles. This work will be based on the study of the dynamics of the model proposed by [10], which describes an analysis of the effect of external modification forces [11].

The dynamic equation that models the behavior of a peripheral and internal clock is given by Equation (6) [5].

\[
Z = (\mu + i\omega) \cdot z - z|z|^2 + Fe^{i\Omega t}, \tag{6}
\]

where \( \mu \) is a parameter of the oscillator, \( \omega \) is the intrinsic frequency, \( \Omega \) is the extrinsic frequency and \( F \) will be the external training or modification signal that will act on the oscillator.
3. Results and discussion

In this section we will analyze the models of the circadian clock oscillator without modification signal and with modification signal; this will allow us to understand under what conditions the oscillator of the circadian clock is synchronized with the oscillator of the external signal F or the existence of synchronization ranges.

3.1. Oscillator model without modification signal

For the analysis of this model of the oscillator we will take from Equation (4) to \( F = 0 \), in addition we will transform the polar coordinate system to Cartesian coordinates by changing the variable \( z = x + i \), this results in the following system of differential Equations (7).

\[
\begin{align*}
\dot{x} &= \mu x - \omega y - x^3 - xy^2, \\
\dot{y} &= \mu y + \omega x - y^3 - yx^2.
\end{align*}
\] (7)

In polar coordinates with \( z(t) = R(t)e^{i\theta}(t) \), the model is described by the system of Equations (8).

\[
\begin{align*}
\dot{z} &= \Re e^{i\theta} + i\Re e^{i\theta}, \\
\dot{R} &= R(\mu - R^2), \\
\dot{\theta} &= \omega.
\end{align*}
\] (8)

It is necessary for the system without external signal for the oscillator modification, that is, the system Equation (5) and Equation (6) there is an equilibrium point at the origin \((0,0)\) which will be an unstable fixed point for all \( R < \sqrt{\mu} \). When \( R = \sqrt{\mu} \) the system presents a stable periodic orbit as well as for \( R > \sqrt{\mu} \) since it satisfies the conditions of the Poincaré-Bendixson theorem, the isochrons of Figure 1 show this behavior that regardless of the initial conditions, the orbits of the system will be taken to the limit cycle [12].

![Figure 1. Presence of limit cycles for different values of \( \mu \).](image)

3.2. Oscillator model with modification signal

In the analysis of this model, the external signal \( F \) must be different from zero, the polar and Cartesian coordinates are very useful but in this case they do not eliminate the time dependence for \( e^{-i\Omega t} \), therefore the following variable change will be used: \( \Delta = \omega - \Omega \) in order to transform the system into an autonomous system and establish a frame of reference in which \( F \) is constant and static. Thus, we obtain the system of Equation (9).
\[ \begin{align*}
x' &= \mu x - \Delta y - x^3 - xy^2 + F, \\
y' &= \mu y + \Delta x - y^3 - yx^2. 
\end{align*} \tag{9} \]

To determine under what conditions the oscillator is synchronized with the external stimulus applied through \( F \), the phase plane for different values of \( \Delta \) and \( F \) will be shown in Figure 2. In Figure 2(a) we can see the existence of three equilibrium points, two of them saddle points and the other unstable. In Figure 2(b) a single point of equilibrium is observed. Figure 2 shows an idea of how the equilibrium points of the system move before the variations of the external signal \( F \); It can be seen that only the nucinal \( x' \) is the one that varies since it is this one that depends on the external signal of modification.

![Figure 2](image.png)

**Figure 2.** Phase plane for different values of \( \Delta \) and \( F \); (a) two of them saddle points and the other unstable; (b) a single point of equilibrium is observed.

In order to summarize the occurrence of stable equilibrium points when varying \( \Delta \) and \( F \), Figure 3. shows that within the yellow triangle there will be presence of at least one stable equilibrium point for the system, this graph is known as Arnold languages, used for the analysis of the coupling of oscillatory systems.

![Figure 3](image.png)

**Figure 3.** Different zones for equilibrium points with respect to the \( \Delta - F \) plane.
Additionally, in order to observe the effects of $\Delta$ variations on the amplitude and relative phase angle of equilibrium points, Figure 4 is available for different values of $F \in [0,1]$. It is observed that the amplitude is maximum when $\Delta = 0$, the amplitude varies quadratically while the phase is in the form of an odd function.

![Figure 4](image_url)

**Figure 4.** Variations of amplitude and phase with respect to $\Delta$, for different values of $F$.

### 4. Conclusions

For the analysis of the model without external modification signal it was possible to observe the existence of periodic orbits, stable limit cycles with amplitude of their radii equal to $\sqrt{\mu}$, therefore for very large $\mu$ very large limit cycles will be obtained.

For the model with the external signal, it was possible to observe the existence of stable equilibrium points only on the region $\Delta = \pm F$, this fact was verified with the construction of Figure 3 defined as the Arnold language. Figure 4 shows the variation of the amplitude of the equilibrium point for different values of $F$. The maximum amplitude is reached when $\Delta= 0$, which makes sense since it means that the phase difference is zero therefore both Oscillators are synchronized. When $\Delta= \pm F$, the amplitude is zero, which also makes sense because it corresponds to the limit result found in Figure 3.

Synchronization of the internal oscillator and the external modification signal occurs when the phase difference $\Delta$ is between the values $F$ and $-F$. The timing is robust when $F$ is very large and $\Delta$ very small. Qualitative analysis on many occasions for this type of problem is more appropriate than quantitative analysis, since the information obtained from the phase diagram on many occasions is sufficient to describe the system.

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