Synchronization of oscillators coupled through an environment

Guy Katriel

Abstract

We study synchronization of oscillators that are indirectly coupled through their interaction with an environment. We give criteria for the stability or instability of a synchronized oscillation. Using these criteria we investigate synchronization of systems of oscillators which are weakly coupled, in the sense that the influence of the oscillators on the environment is weak. We prove that arbitrarily weak coupling will synchronize the oscillators, provided that this coupling is of the ‘right’ sign. We illustrate our general results by applications to a model of coupled GnRH neuron oscillators proposed by Khadra and Li [14], and to indirectly weakly-coupled \(\lambda - \omega\) oscillators.

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1 Introduction

The aim of this work is to investigate the dynamics of systems of oscillators which are globally coupled through an environment. An important example of such systems is populations of cells in which oscillatory reactions are taking
place [7, 10, 15, 21, 25], which ‘communicate’ via chemicals that diffuse in the surrounding medium. The ability of thousands of cells to synchronize their periodic activity is crucial for the generation of macroscopic oscillations, like circadian periodicities [2].

Consider a system of \( n \) identical dynamical systems (‘oscillators’), described by the differential equations

\[
\dot{x}_k = f(x_k, y), \quad 1 \leq k \leq n, \tag{1.1}
\]

where \( x_k \in \mathbb{R}^d \) is the state of the \( k \)-th oscillator, \( y \in \mathbb{R}^p \) is the state of the environment, and \( f : \mathbb{R}^d \times \mathbb{R}^p \to \mathbb{R}^d \) is smooth. The dynamics of each oscillator thus depends on the state of the environment. An additional equation describes the dynamics of the environmental variable \( y \)

\[
\dot{y} = g(y) + \frac{\beta}{n} \sum_{j=1}^{n} h(x_j, y), \tag{1.2}
\]

where the smooth function \( g : \mathbb{R}^p \to \mathbb{R}^p \) represents the intrinsic dynamics of the environment, and the smooth function \( h : \mathbb{R}^d \times \mathbb{R}^p \to \mathbb{R}^p \) represents the effect of the oscillators on the environment. The state of the oscillators thus influences the dynamics of the environment.

In the case of biological cells, \( x_k \) would be a vector whose components are the concentrations (in moles per unit volume) of various biochemical species in cell \( k \), and \( y \) a vector of concentrations of various biochemical species in the exterior of the cells. The parameter \( \beta \) is the ratio of the total intracellular volume to the volume of the environment: if \( V_{\text{cell}} \) is the volume of an individual cell and \( V_{\text{ext}} \) is the volume of the external environment,

\[
\beta = \frac{nV_{\text{cell}}}{V_{\text{ext}}}. \tag{1.3}
\]

In the case of biological cells, the interaction of cells and environment may occur through the diffusion and transport of chemical species across the cell membranes, and through the effects of the activation of receptors on the cell membrane. A variety of modeling studies of biochemical systems of oscillators coupled through an environment, described by equations of the form (1.1), (1.2), can be found in [1, 3, 4, 5, 8, 9, 16, 17, 22, 23, 26, 27, 28]. The framework presented above thus unifies many models of particular systems,
and allows us to obtain some basic analytical results which apply to all of them.

Since the state of each of the oscillators influences the environment, and the state of the environment in turn influences the oscillators, we obtain an indirect coupling of the oscillators. We are interested in studying the capacity of this indirect coupling to induce synchronization of the oscillators. When this happens, in the biochemical context, one refers to the relevant species which diffuse in the environment as ‘synchronizing agents’.

By a synchronized oscillation of the system \((1.1), (1.2)\) we mean a periodic solution with all the \(x_k\) identical

\[
x_1(t) = x_2(t) = ... = x_n(t) = x(t).
\]

(1.4)

The periodicity means that there exists a \(T > 0\) such that

\[
x(t + T) = x(t), \quad y(t + T) = y(t), \quad \forall t \in \mathbb{R}.
\]

(1.5)

Therefore, substituting (1.4) into (1.1), (1.2), we see that a synchronized oscillation corresponds to a periodic solution of the system

\[
\dot{x} = f(x, y), \quad \dot{y} = g(y) + \beta h(x, y).
\]

(1.6) (1.7)

The original system (1.1), (1.2) is \(nd + p\) dimensional, whereas the system (1.6), (1.7) is only \(d + p\) dimensional. Since (1.6), (1.7) do not depend on \(n\), a periodic solution of (1.6), (1.7) gives rise to a synchronized oscillation of (1.1), (1.2) for any \(n \geq 1\). Note that system (1.6), (1.7) is simply (1.1), (1.2) for the case \(n = 1\), so it describes the behavior of a single oscillator placed in the environment, and we can therefore refer to it as the single-oscillator system.

In order for a synchronized oscillation to be observable, it must be stable in the sense that it is asymptotically approached starting from an open set of initial conditions (the precise definition is recalled in section 2). A crucial point must be made here: the stability of a synchronized oscillation \(x_1(t) = ... = x_n(t) = x(t), y(t)\) refers to its stability as a solution of the full system (1.1), (1.2), and does not follow from the stability of the corresponding solution \((x(t), y(t))\) as a solution of the single-oscillator system (1.6), (1.7).
Figure 1: Three coupled Van der Pol Oscillators: Top: Graph of $v_k(t)$ vs. $t$ for $\beta = -0.5$. Bottom: $\beta = 0.5$. 
When we say that **synchronization** occurs, we mean that there exists a synchronized oscillation which is *stable as a solution of* (1.1), (1.2). A criterion for the (in)stability of a synchronized oscillation will be derived in section 3.

In order to illustrate some of the collective phenomena observed in systems of the form (1.1), (1.2) we display, in figure 1, the results of numerical simulations, in which we took three Van der Pol oscillators coupled through an environment. The dynamics of the oscillators are defined by

\[ \ddot{v}_k + (v_k^2 - 1)\dot{v}_k + v_k = y, \quad 1 \leq k \leq 3, \]

which we can convert to a first-order system (1.1), with \( d = 2, p = 1, n = 3 \), where \( x = (v, w) \) and

\[ f(x, y) = (w, (1 - v^2)w - v + y). \]

We assume now that the environmental variable evolves according to (1.2), with

\[ g(y) = -y, \quad h(x, y) = v. \]

The system of the three oscillators coupled through the environment is thus described by the equations

\[ \ddot{v}_k + (v_k^2 - 1)\dot{v}_k + v_k = y, \quad 1 \leq k \leq 3 \]

\[ \dot{y} = -y + \frac{\beta}{3}(v_1 + v_2 + v_3). \]

In the top part of figure 1 we set \( \beta = -0.5 \), and plotted the values \( v_k(t) \) (1 \( \leq k \leq 3 \)), starting at some arbitrary initial conditions. One sees that the three oscillators synchronize, so that within about 50 time units the three graphs look identical.

On the other hand, in the bottom part of figure 1 when we set \( \beta = 0.5 \) we see that the three oscillators do not synchronize. In fact they seem to tend to the type of behavior known as anti-synchronized or splay state, in which each of the three oscillators perform the same motion, but with a phase lag of \( \frac{2\pi}{3} \) among the oscillators. When many oscillators are involved, such behavior will lead to the averaging out of the oscillations, hence no periodicity will be observable at the macroscopic level.

Our aim is to obtain some understanding of phenomena of synchronization and desynchronization in oscillators coupled through an environment, such as
those demonstrated above. There is an extensive literature concerned with
the analysis of synchronization of coupled oscillators (see \[11, 18, 19\] and
references therein), but most studies deal with directly coupled oscillators,
rather than oscillators indirectly coupled through an environment. In some
numerical and theoretical studies of systems of the form \((1.1), (1.2)\), ‘steady
state’ approximation on \((1.2)\) is made in order to transform it into a directly
coupled system: the term \(\dot{y}\) on the left hand side of \((1.2)\) is replaced by 0, the
resulting algebraic equation is solved for \(y\) in terms of \(x\), and the expression
for \(y\) is substituted in \((1.1)\). Although in some cases this yields a good
approximation, it is not always so, and it is not hard to find examples in which
direct simulation shows synchronization of the ‘approximate’ system, while
the system \((1.1), (1.2)\) does not synchronize, or vice versa. In this paper we
study the indirectly coupled system without this steady-state approximation.

The assumptions that the dynamics of the \(n\) oscillators, and their effects on
the environment, are identical, should be considered as idealizations which
will only be satisfied in an approximate sense in any real system. However,
in studying phenomena such as synchronization, it is useful to consider the
heterogeneity of the characteristics of the oscillators as a perturbation of
an idealized system of identical oscillators, and the results in this case are
robust in the sense that results for the idealized systems will also explain
and predict the behavior of heterogenous systems, at least when the degree of
heterogeneity is sufficiently small. Indeed, if the system of identical oscillators
has a stable synchronized oscillation, then by the basic perturbation theory
of periodic solutions, any sufficiently close heterogeneous system, that is with
\(f, g, h\) in \((1.1)-(1.2)\) replaced by \(f_k, g_k, h_k\), will have a stable periodic solution
which is ‘almost synchronized’ in the sense that \(|x_j(t) - x_k(t)|\) is small for all
\(j, k\).

Another approximation implicit in the model \((1.1), (1.2)\) is that the environ-
ment is homogeneous, which, in the biochemical context, means that the
various chemicals diffuse in the environment on a time scale which is faster
than that of the reactions in the cells and the diffusion across the cell mem-
branes, or alternatively that the medium surrounding the cells is stirred.

In section 3 we prove a basic result, Theorem 3.1, which allows to determine
the (in)stability of synchronized oscillations of \((1.1), (1.2)\) in terms of the
stability of two associated linear systems with periodic coefficients. Notably,
these two linear systems, hence the stability of synchronized oscillations,
do not depend on the number \( n \) of oscillators. Theorem 3.1 thus reduces arbitrarily large problems to a pair of problems which are of fixed size, by exploiting symmetry.

In section 4 we make a general study of systems of oscillators which are \textit{weakly} coupled in the sense that they are described by (1.1),(1.2) with \(|\beta|\) small. Using Theorem 4.1 and some perturbation calculations, we prove that a system of oscillators coupled through an environment can be synchronized using an arbitrarily weak coupling, \textit{provided} that \( \beta \) is chosen to be of the ‘right’ sign, and derive a formula which tells us what this right sign is.

In sections 5 and 6 we present two examples of applications of our analytical results to specific systems.

In section 5 we apply the general Theorem 3.1 to the study of a model of periodic release of GnRH, proposed by Khadra and Li [14]. We show that whenever this model, for a single cell, produces oscillations, the oscillations of any number of cells coupled through the environment will synchronize.

In section 6 we apply Theorem 4.1 which deals with the weakly-coupled case, to the particular example of indirectly coupled \( \lambda - \omega \) oscillators, to derive explicit conditions for (de)synchronization in the weak coupling regime.

In section 7 we conclude with some comments on the applicability of the results obtained in this paper to the study of systems of the form (1.1)-(1.2).

2 Stability, instability and linearization

We recall the definitions of relevant notions of stability. Let

\[
\dot{z} = \Phi(z),
\]

where \( \Phi : \mathbb{R}^N \to \mathbb{R}^N \), be a system of differential equations. Let \( \bar{z}(t) \) be a \( T \)-periodic solution of (2.1). We denote by \( O \subset \mathbb{R}^N \) the corresponding orbit

\[
O = \{ \bar{z}(t) \mid t \in \mathbb{R} \}.
\]

\( \bar{z}(t) \) is said to be \textbf{orbitally asymptotically stable} if there exists an open set \( O \subset U \subset \mathbb{R}^N \), so that for any \( z_0 \in U \), there exists a \( \rho \) such that the solution \( z(t) \) of the initial value problem (2.1), \( z(0) = z_0 \), satisfies

\[
\lim_{t \to \infty} |z(t) - \bar{z}(t + \rho)| = 0.
\]
\( \tilde{z}(t) \) is said to be **unstable** if there exists an open set \( O \subset U \subset \mathbb{R}^N \) such that for any open set \( O \subset V \subset \mathbb{R}^N \) there exists \( z_0 \in V \) and \( \tilde{t} > 0 \) so that the solution \( z(t) \) of the initial value problem (2.1), \( z(0) = z_0 \), satisfies \( z(\tilde{t}) \notin U \).

We now recall the notion of linearized stability. With a periodic solution \( \tilde{z}(t) \) of (2.1) we associate the \( T \)-periodic linearized equation

\[
\dot{w} = \Phi'(\tilde{z}(t))w. \tag{2.2}
\]

A Floquet multiplier of (2.2) is a (generally complex) number \( \mu \) for which (2.2) has a solution \( w(t) \) satisfying

\[
w(t + T) = \mu w(t).
\]

In other words, defining the fundamental solution of (2.2) as the \( N \times N \)-matrix valued function \( H(t) \) satisfying

\[
\dot{H}(t) = \Phi'(\tilde{z}(t))H(t), \quad H(0) = I,
\]

the eigenvalues of \( H(T) \) are the Floquet multipliers associated with (2.2).

By differentiating (2.1) with respect to \( t \), we get

\[
\ddot{\tilde{z}} = \Phi'(\tilde{z}(t))\dot{\tilde{z}},
\]

so that \( \ddot{\tilde{z}} \) is a \( T \)-periodic solution of (2.2), which means that \( \mu = 1 \) is always a Floquet multiplier of the linearized equation. The periodic solution \( \tilde{z}(t) \) is said to be **non-degenerate** if \( \mu = 1 \) is a simple Floquet multiplier (that is, it is a simple eigenvalue of the matrix \( H(T) \)). It is said to be **linearly stable** if it is non-degenerate and all Floquet multipliers other than \( \mu = 1 \) have absolute values strictly less than 1. It will be said to be **linearly unstable** if there is a Floquet multiplier with absolute value strictly greater than 1.

A fundamental result (see e.g. [20], Ch. V, Theorem 8.4) states that

**Lemma 2.1** (i) A linearly stable periodic solution is orbitally asymptotically stable.

(ii) A linearly unstable solution is unstable.

From now on we will refer to linearly (un)stable periodic solutions simply as (un)stable.
It should be noted that the notions of stability defined above, and the results which will be obtained below, are local. Stability of the synchronized oscillation does not imply that synchronization will be reached from all initial conditions, but only that it will be reached with some positive probability - that is for a set of initial conditions of positive measure.

3 Criterion for stability of a synchronized oscillation

To study stability of a synchronized oscillation \( x_1(t) = \cdots = x_n(t) = x(t), y(t) \) of

\[
\begin{align*}
\dot{x}_k &= f(x_k, y), \quad 1 \leq k \leq n, \\
\dot{y} &= g(y) + \frac{\beta}{n} \sum_{j=1}^{n} h(x_j, y),
\end{align*}
\]

where \( x(t), y(t) \) is a \( T \)-periodic solution of the single-oscillator system \((1.6), (1.7)\), we linearize the system \((3.1), (3.2)\) around this solution, obtaining

\[
\begin{align*}
\dot{w}_k &= f_x(x(t), y(t))w_k + f_y(x(t), y(t))z, \quad 1 \leq k \leq n, \\
\dot{z} &= \frac{\beta}{n} h_x(x(t), y(t)) \sum_{j=1}^{n} w_j + [g'(y(t)) + \beta h_y(x(t), y(t))]z.
\end{align*}
\]

Although the system \((3.3), (3.4)\) is an \( nd + p \)-dimensional one, we will show below, using some simple linear algebra, and exploiting the symmetry of the system with respect to permutation of the oscillators, that the study of its stability reduces to the study of the stability of two linear systems, of dimensions \( d + p \) and \( d \) respectively. When \( n \) is large this is a huge reduction in the complexity of the problem.

**Theorem 3.1** Let \( x_1(t) = \cdots = x_n(t) = x(t), y(t) \) be a \( T \)-periodic synchronized oscillation of \((3.1), (3.2)\). This solution is stable if the following two conditions hold:

(C1) All of the \( d \) Floquet multipliers of the \( T \)-periodic linear equation

\[
\dot{w} = f_x(x(t), y(t))w
\]
have absolute values less than 1.

(C2) The Floquet multiplier $\mu = 1$ of the $T$-periodic linear system

$$\dot{w} = f_x(x(t), y(t))w + f_y(x(t), y(t))z,$$
$$\dot{z} = \beta h_x(x(t), y(t))w + [g'(y(t)) + \beta h_y(x(t), y(t))]z \quad (3.6)$$

is simple, and all the other $d + p - 1$ Floquet multipliers have absolute values less than 1.

If one of the Floquet multipliers of either (3.5) or (3.6) has absolute value greater than 1, then the synchronized oscillation is unstable.

There is an illuminating interpretation of the conditions (C1),(C2). Condition (C2) says that $(x(t), y(t))$ is stable as a solution of single-oscillator system (1.6),(1.7). As we noted in the introduction, this is a much weaker condition then the statement that the synchronized oscillation is stable as a solution of the system (3.1),(3.2). However Theorem 3.1 tells us that the only condition that we have to add in order to get this stronger conclusion is (C1), that is the stability of the linear system (3.5). This is the system one would obtain by looking at $x(t)$ as a periodic solution of the periodically forced system

$$\dot{x} = f(x, y(t)),$$

with $y(t)$ considered as a given forcing, and asking for the stability of $x(t)$ as a solution of this forced system.

Note that the conditions (C1),(C2) do not depend on $n$, so that we see that stability of the synchronized solution $x_1 = ... = x_n = x$, $y$, where $x,y$ is an oscillation of the single-oscillator system (1.6),(1.7) does not depend on $n \geq 2$. In other words, if two oscillators synchronize then any number of oscillators will synchronize, provided the ratio $\beta$ of the total intracellular volume to the volume of the environment is maintained fixed.

In order to apply Theorem 3.1 to a particular system, one needs to verify the conditions (C1) and (C2), so one needs to study the nonautonomous periodic systems (3.5) and (3.6), a task which may not be easy. Moreover, in general one does not have an explicit expression for the periodic oscillation $\bar{x}(t)$, so that even writing down these systems is not possible. Therefore in general the verification of these conditions will involve numerical computations. There are, however, systems for which the conditions can be verified
based on general considerations. Such an example is presented in section 5. In addition, Theorem 3.1 is useful for deriving other general results, as we demonstrate in the investigation of weakly coupled oscillators in section 4.

Proof of Theorem 3.1: Written in matrix notation, the system (3.3), (3.4) is

\[
\begin{pmatrix}
\dot{w}_1 \\
\vdots \\
\dot{w}_n \\
\dot{z}
\end{pmatrix} = A(t) \begin{pmatrix}
w_1 \\
\vdots \\
w_n \\
z
\end{pmatrix},
\]

where

\[
A(t) = \begin{pmatrix}
a(t) & 0 & \cdots & 0 & b(t) \\
0 & a(t) & 0 & 0 & b(t) \\
0 & \cdots & \cdots & 0 & \vdots \\
0 & \cdots & 0 & a(t) & b(t) \\
c(t) & c(t) & \cdots & c(t) & d(t)
\end{pmatrix},
\]

\[a(t) = f_x(x(t), y(t)), \quad b(t) = f_y(x(t), y(t)),\]

\[c(t) = \frac{\beta}{n} h_x(x(t), y(t)), \quad d(t) = g'(y(t)) + \beta h_y(x(t), y(t)).\]

In order to determine the stability of the synchronized oscillation, we wish to find the Floquet multipliers of (3.7). The solution of (3.7) given by

\[
\begin{pmatrix}
w_1 \\
\vdots \\
w_n \\
z
\end{pmatrix} = \begin{pmatrix}
x \\
\vdots \\
y
\end{pmatrix},
\]

(3.8)

corresponds to the Floquet multiplier 1. The synchronized oscillation is linearly stable if this is the only solution corresponding to the Floquet multiplier 1, and the other Floquet multipliers have absolute values less than 1. We now display more solutions of (3.7) and their corresponding Floquet multipliers. Assume that \(w : \mathbb{R} \to \mathbb{R}^d\) satisfies (3.5). Then by direct inspection one sees
that

\[
\begin{pmatrix}
  w \\
  -w \\
  0 \\
  \vdots \\
  \vdots \\
  0
\end{pmatrix},
\begin{pmatrix}
  w \\
  0 \\
  -w \\
  \vdots \\
  \vdots \\
  0
\end{pmatrix}, \ldots,
\begin{pmatrix}
  w \\
  0 \\
  0 \\
  \vdots \\
  \vdots \\
  0
\end{pmatrix}
\]

are linearly independent solutions of (3.7). Thus the \( d \) Floquet multipliers of (3.5) are also Floquet multipliers of (3.7), and condition (C1) implies that these Floquet multipliers have absolute values less than 1. Since each of these Floquet multipliers correspond to \( n - 1 \) eigenvectors, we have accounted for \( (n - 1)d \) of the \( nd + p \) Floquet multipliers.

We note also that if \( w, z \) is a solution of (3.6) then

\[
\begin{pmatrix}
  w \\
  \vdots \\
  w \\
  z
\end{pmatrix}
\]

is a solution of (3.7). Thus the Floquet multipliers of (3.6) are also Floquet multipliers of (3.7), and condition (C2) implies that these Floquet multipliers, except the one corresponding to (3.8), have absolute values less than 1. Since (3.6) is a \( d + p \) system we have now another \( d + p \) Floquet multipliers. We have thus accounted for all \( nd + p \) Floquet multipliers of (3.7), and shown that under conditions (C1) and (C2), the system (3.7) is stable. The argument for instability is similar. ■

4 Synchronization of oscillators weakly coupled through an environment

In this section we consider the system (3.1), (3.2), under the assumption that the coupling of the oscillators to the environment is weak, in the sense that \(|\beta|\) is small. We will use Theorem 3.1 and perturbation calculations, to obtain information on the (in)stability of synchronized oscillations in this regime.
Note that, in the biochemical context, in view of (1.3) the weak coupling case arises when the volume of the environment is large relative to the total intracellular volume, hence the secretion of a synchronizing agent into the environment by a cell has only a weak effect on the concentration of this synchronizing agent in the environment.

When $\beta = 0$, the oscillators do not influence the environment, hence they are also uncoupled from each other. We assume that in such a case the environment has a steady state $\bar{y}$, and that when the environment is in the state $\bar{y}$ the oscillators have a periodic solution $\bar{x}(t)$:

**Assumption 4.1**  
(i) The equation

$$\dot{y} = g(y)$$  

has a stable steady state $\bar{y}$, that is $g(\bar{y}) = 0$, and that the eigenvalues of the matrix

$$A = g'(\bar{y})$$

have negative real parts.

(ii) The equation

$$\dot{x} = f(x, \bar{y})$$

has a non-degenerate $T_0$-periodic solution $\bar{x}(t)$.

Part (i) of Assumption 4.1 holds, for example, in the simplest case, in which the dynamics in the environment is ‘trivial’, consisting simply of the decay of the various species, so that $g(y) = -Dy$, where $D$ is a diagonal matrix whose diagonal coefficients are the various rates of decay, and $\bar{y} = 0$. We mention here a paper of Watanabe (see [24], Theorem 3), which includes a perturbation result for synchronized oscillations of systems of the form (3.1), (3.2) when $|\beta| \to 0$ in the case that $g \equiv 0$, a case which is excluded by Assumption 4.1.

When $\beta = 0$ the oscillators are uncoupled, so they will not be able to synchronize, and the most we can expect, in case that $\bar{x}(t)$ is a stable periodic solution of (4.2), is that oscillator $k$ will tend to $\bar{x}(t + \rho_k)$ with different and unrelated values of $\rho_k$. We shall show that for $|\beta| > 0$ sufficiently small there is a synchronized oscillation, but the stability of this oscillation depends on the sign of $\beta$: there exists a number $\sigma$ such the synchronized oscillation is
stable if $\sigma \beta > 0$, and is unstable if $\sigma \beta < 0$. We shall give an explicit formula for computing $\sigma$.

**Theorem 4.1** Assume that Assumption 4.1 holds. Then there exists $\beta_0 > 0$ and smooth functions $T(\beta)$, $x(\beta, t)$, $y(\beta, t)$, with

\[ T : (-\beta_0, \beta_0) \rightarrow (0, \infty), \]
\[ x : (-\beta_0, \beta_0) \times \mathbb{R} \rightarrow \mathbb{R}^d, \quad y : (-\beta_0, \beta_0) \times \mathbb{R} \rightarrow \mathbb{R}^p, \]

and

\[ T(0) = T_0, \quad x(0, t) = \bar{x}(t), \quad y(0, t) = \bar{y}, \]

so that:

(i) For all $|\beta| < \beta_0$,

\[ x_1(t) = x_2(t) = \ldots = x_n(t) = x(\beta, t), \quad y(t) = y(\beta, t) \quad (4.3) \]

is a synchronized oscillation of the system (3.1), (3.2), with period $T(\beta)$.

(ii) Letting $q(t)$ denote the $T_0$-periodic solution of the linear equation

\[ \dot{q}(t) = -[f_x(\bar{x}(t), \bar{y})]^* q(t), \quad (4.4) \]

normalized so that

\[ \int_0^{T_0} \langle q(s), \dot{x}(s) \rangle ds = 1, \quad (4.5) \]

we have the following asymptotic formula for the period $T(\beta)$ of the above synchronized oscillation as $\beta \rightarrow 0$:

\[ \frac{T(\beta)}{T_0} = 1 - \beta \int_0^{T_0} \int_0^{T_0} \langle f_y(\bar{x}(s), \bar{y})e^{rA} h_x(\bar{x}(s-r), \bar{y}), q(t) \rangle ds dr + O(\beta^2). \quad (4.6) \]

(iii) If $\bar{x}(t)$ is stable as a periodic solution of (4.2), then defining

\[ \sigma = \int_0^{T_0} \int_0^{\infty} \langle f_y(\bar{x}(s), \bar{y})e^{rA} h_x(\bar{x}(s-r), \bar{y}), \dot{\bar{x}}(s-r), q(s) \rangle dr ds, \quad (4.7) \]

we have that, for $0 < |\beta| < \beta_0$, (4.3) is stable as a solution of (3.1), (3.2) if $\sigma \beta > 0$, and unstable if $\sigma \beta < 0$.

(iv) If $\bar{x}(t)$ unstable as a periodic solution of (4.2), then (4.3) is unstable as a solution of (3.1), (3.2) for any $0 < |\beta| < \beta_0$.  


We recall a fundamental result regarding the perturbation of a non-degenerate periodic solution of a differential equation, when the equation is perturbed.

**Lemma 4.1** Let

\[ \dot{x} = \Phi(\beta, x), \quad (4.8) \]

where \( \Phi : \mathbb{R} \times \mathbb{R}^N \to \mathbb{R}^N \) is smooth, be a differential equation parameterized by the parameter \( \beta \). Assume that when \( \beta = 0 \), \( (4.8) \) has a \( T_0 \)-periodic solution \( \bar{x}(t) \), which is non-degenerate. Then there exists \( \beta_0 > 0 \) such that if \( |\beta| < \beta_0 \) then \( (4.8) \) has a non-degenerate \( T(\beta) \)-periodic solution \( x(\beta, \cdot) \), where \( T : (-\beta_0, \beta_0) \to (0, \infty) \) and \( x : (-\beta_0, \beta_0) \times \mathbb{R}^N \to \mathbb{R}^N \) are smooth functions satisfying

\[ T(0) = T_0, \quad x(0, t) = \bar{x}(t), \quad \forall t \in \mathbb{R}, \]

and if \( \bar{x}(t) \) is a linearly (un)stable solution of \( (4.8) \) for \( \beta = 0 \), then \( x(\beta, \cdot) \) is a linearly un(stable) solution of \( (4.8) \) for \( |\beta| < \beta_0 \).

**Proof of Theorem 4.1** The existence of the synchronized oscillation, that is a periodic solution of

\[ \dot{x} = f(x, y), \quad (4.9) \]
\[ \dot{y} = g(y) + \beta h(x, y) \quad (4.10) \]

for \( |\beta| \) sufficiently small, is an application of Lemma 4.1. Indeed, by Assumption 4.1 when \( \beta = 0 \), \( (4.9), (4.10) \) has the non-degenerate \( T_0 \)-periodic solution \( x(t) = \bar{x}(t), y(t) = \bar{y} \), which is perturbed to a \( T(\beta) \)-periodic solution \( x(\beta, t), y(\beta, t) \) of \( (4.9), (4.10) \) for \( |\beta| \) small, which gives the synchronized oscillation of \( (3.1), (3.2) \) and proves part (i).

If \( \bar{x}(t) \) is stable as a periodic solution of \( (4.2) \), and since all the eigenvalues of \( A \) have negative real parts, we have that, for \( \beta = 0 \), \( x(t) = \bar{x}(t), y(t) = \bar{y} \) is stable as a solution of \( (4.9), (4.10) \), hence by Lemma 4.1 \( x(\beta, t), y(\beta, t) \) is a stable solution of \( (4.9), (4.10) \) for \( |\beta| < \beta_0 \). Thus condition (C2) of Theorem 3.1 holds for this solution.

On if \( \bar{x}(t) \) is unstable as a periodic solution of \( (4.2) \), then Lemma 4.1 implies that (C2) does not hold for \( |\beta| < \beta_0 \), hence by Theorem 3.1 the synchronized oscillation is unstable as a solution of \( (3.1), (3.2) \), so that we have part (iv) of the Theorem.

To prove part (iii), we need to determine the circumstances under which condition (C1) of Theorem 3.1 holds for the synchronized oscillation when \( |\beta| > 0 \) is small.
For the following computations it will be convenient to normalize the period of the periodic solutions to $T_0$ by setting
\[ \tau(\beta) = \frac{T(\beta)}{T_0}, \quad (4.11) \]
so that $u(\beta, t), v(\beta, t)$ are $T_0$-periodic with respect to $t$, and satisfy
\[ u_t(\beta, t) = \tau(\beta)f(u(\beta, t), v(\beta, t)), \quad (4.12) \]
\[ v_t(\beta, t) = \tau(\beta)[g(v(\beta, t)) + \beta h(u(\beta, t), v(\beta, t))]. \quad (4.13) \]

To verify condition (C1) of Theorem 3.1 we need, defining
\[ a(\beta, t) = \tau(\beta)f_x(u(\beta, t), v(\beta, t)), \quad (4.14) \]
to check whether all $d$ Floquet multipliers of the $T_0$-periodic linear equation
\[ \dot{w} = a(\beta, t)w, \quad (4.15) \]
have absolute value less than 1.

Setting $\beta = 0$ in (4.14) we have $a(0, t) = f_x(\bar{x}(t), \bar{y})$, so in this case (4.15) reduces to
\[ \dot{w} = f_x(\bar{x}(t), \bar{y})w. \quad (4.16) \]
(C1) does not hold for $\beta = 0$, since (4.16) has the Floquet multiplier $\mu = 1$, corresponding to the $T_0$-periodic solution $w(t) = \dot{\bar{x}}(t)$. However, by our assumption that $\bar{x}(t)$ is a stable solution of (4.2), all other Floquet multipliers of (4.16) are smaller than 1 in absolute value, and by continuity this remains true for (4.15) when $|\beta| > 0$ is sufficiently small. Our task, then, is to determine in what way the Floquet multiplier $\mu = 1$ for $\beta = 0$ is perturbed when $|\beta| > 0$ is small. Stability of the synchronized oscillation corresponds to the perturbed Floquet multiplier being inside the unit disk of the complex plane. We thus assume that the Floquet multiplier $\mu = 1$ of (4.15) is perturbed to $\mu(\beta)$ for $|\beta| > 0$, where $\mu(\beta)$ is a real-valued smooth function of $\beta$ with $\mu(0) = 1$ - the justification for which is the well-known lemma on perturbation of simple eigenvalues (see e.g. [13], Theorem 5.4). Thus for $|\beta|$ small there is a solution $w(\beta, t)$ of
\[ w_t(\beta, t) = a(\beta, t)w(\beta, t), \]
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satisfying
\[ w(\beta, t + T_0) = \mu(\beta)w(\beta, t), \quad \forall t \in \mathbb{R}, \]
\[ w(0, t) = \dot{x}(t). \]

Defining
\[ \eta(\beta) = \log(\mu(\beta)), \]
\[ \tilde{w}(\beta, t) = e^{-\eta(\beta)t}w(\beta, t) \]
we have that
\[ \eta(0) = 0, \]
and \( \tilde{w}(\beta, t) \) satisfies
\[ \tilde{w}_t(\beta, t) = [a(\beta, t) - \eta(\beta)I]\tilde{w}(\beta, t), \quad (4.17) \]
\[ \tilde{w}(\beta, t + T_0) = \tilde{w}(\beta, t), \quad \forall t \in \mathbb{R}, \quad (4.18) \]
\[ \tilde{w}(0, t) = \dot{x}(t). \quad (4.19) \]

Stability for small \( \beta > 0 \) will hold if \( \eta'(0) < 0 \), which will imply that \( \eta(\beta) < 0 \) and hence \( |\mu(\beta)| < 1 \). Similarly, stability for small \( \beta < 0 \) will hold if \( \eta'(0) > 0 \). Part (iii) of the Theorem will be proved by showing that
\[ \eta'(0) = -\sigma, \quad (4.20) \]
where \( \sigma \) is given by (4.7) and the rest of the proof is devoted to this computation of \( \eta'(0) \).

Differentiating (4.17) with respect to \( \beta \) we have
\[ \tilde{w}_\beta(\beta, t) = [a_\beta(\beta, t) - \eta'(\beta)I]\tilde{w}(\beta, t) \]
\[ + [a(\beta, t) - \eta(\beta)I]\tilde{w}_\beta(\beta, t) \]
and putting \( \beta = 0 \) and rearranging we get
\[ \tilde{w}_\beta(0, t) - f_x(\bar{x}(t), \bar{y})\tilde{w}_\beta(0, t) = [a_\beta(0, t) - \eta'(0)I]\dot{x}(t). \quad (4.21) \]

Taking the inner product of both sides of (4.21) with \( q(t) \) (defined as the \( T_0 \)-periodic solution of (4.4)) and integrating over \([0, T_0]\), noting that, using integration by parts and (4.4) we have
\[
\int_0^T \langle \tilde{w}_\beta(0, s) - f_x(\bar{x}(s), \bar{y})\tilde{w}_\beta(0, s), q(s) \rangle ds \\
= - \int_0^T \langle \tilde{w}_\beta(0, s), \dot{q}(t) + [f_x(\bar{x}(s), \bar{y})]^*q(s) \rangle ds = 0, \quad (4.22)
\]
we get
\[
\int_0^{T_0} \langle [a_\beta(0, s) - \eta'(0)I] \dot{x}(s), q(s) \rangle ds = 0. \tag{4.23}
\]
Using (4.5) and (4.23) we get
\[
\eta'(0) = \int_0^{T_0} \langle a_\beta(0, s) \dot{x}(s), q(s) \rangle ds. \tag{4.24}
\]
From (4.14) we have
\[
a(\beta, t) \dot{x}(t) = \tau(\beta) f_x(u(\beta, t), v(\beta, t)) \dot{x}(t),
\]
and differentiating this with respect to \( \beta \) we get,
\[
a_\beta(\beta, t) \dot{x}(t) = \tau'(\beta) f_x(u(\beta, t), v(\beta, t)) \dot{x}(t)
+ \tau(\beta) f_{xx}(u(\beta, t), v(\beta, t))[u_\beta(t), \dot{x}(t)]
+ \tau(\beta) f_{xy}(u(\beta, t), v(\beta, t))[\dot{x}(t), v_\beta(\beta, t)]. \tag{4.25}
\]
Putting \( \beta = 0 \) in (4.25) we have
\[
a_\beta(0, t) \dot{x}(t) = \tau'(0) \dot{x}(t) + f_{xx}(\bar{x}(t), \bar{y})[u_\beta(0, t), \dot{x}(t)]
+ f_{xy}(\bar{x}(t), \bar{y})[\dot{x}(t), v_\beta(0, t)]. \tag{4.26}
\]
Differentiating (4.12) with respect to \( \beta \) we have
\[
u_{\beta t}(\beta, t) = \tau'(\beta) \dot{x}(t) + \tau(\beta) f_x(u(\beta, t), v(\beta, t)) u_\beta(t)
+ \tau(\beta) f_y(u(\beta, t), v(\beta, t)) v_\beta(t), \tag{4.27}
\]
and setting \( \beta = 0 \) in (4.27) we get
\[
u_{\beta t}(0, t) = \tau'(0) \dot{x}(t) + f_x(\bar{x}(t), \bar{y}) u_\beta(0, t) + f_y(\bar{x}(t), \bar{y}) v_\beta(0, t). \tag{4.28}
\]
Differentiating (4.28) with respect to \( t \) we get
\[
u_{\beta tt}(0, t) = \tau'(0) \ddot{x}(t) + f_{xx}(\bar{x}(t), \bar{y})[\dot{x}(t), u_\beta(0, t)]
+ f_x(\bar{x}(t), \bar{y}) u_{\beta t}(0, t)
+ f_{xy}(\bar{x}(t), \bar{y})[\dot{x}(t), v_\beta(0, t)] + f_y(\bar{x}(t), \bar{y}) v_{\beta t}(0, t). \tag{4.29}
\]
Combining (4.26) and (4.29) we get
\[
a_\beta(0, t) \dot{x}(t) = u_{\beta tt}(0, t) - f_x(\bar{x}(t), \bar{y}) u_{\beta t}(0, t) - f_y(\bar{x}(t), \bar{y}) v_{\beta t}(0, t),
\]
\[18\]
which we can also write as

\[ a_\beta(0, t) \dot{x}(t) + f_y(\bar{x}(t), \bar{y}) v_{\beta t}(0, t) = u_{\beta t}(0, t) - f_x(\bar{x}(t), \bar{y}) u_{\beta t}(0, t). \]  

(4.30)

Taking the inner product of (4.30) with \( q(t) \) and integrating over \([0, T_0]\), and noting that, using (4.4), the right-hand side vanishes, we get

\[ \int_0^{T_0} \langle a_\beta(0, s) \dot{x}(s), q(s) \rangle ds + \int_0^{T_0} \langle f_y(\bar{x}(s), \bar{y}) v_{\beta t}(0, s), q(s) \rangle ds = 0, \]

which, together with (4.24), gives

\[ \eta'(0) = - \int_0^{T_0} \langle f_y(\bar{x}(s), \bar{y}) v_{\beta t}(0, s), q(s) \rangle ds. \]

(4.31)

We now compute \( v_\beta(0, t) \). Differentiating (4.13) with respect to \( \beta \) and setting \( \beta = 0 \), we have

\[ v_{\beta t}(0, t) - Av_{\beta}(0, t) = h(\bar{x}(t), \bar{y}). \]

(4.32)

Solving (4.32) for \( v_{\beta}(0, t) \), we get

\[ v_{\beta}(0, t) = e^{tA} v_{\beta}(0, 0) + \int_0^{t} e^{rA} h(\bar{x}(t-r), \bar{y}) dr, \]

(4.33)

and using the fact that \( v_{\beta}(0, t) \) and \( \bar{x}(t) \) are \( T_0 \)-periodic we have

\[ v_{\beta}(0, 0) = [I - e^{T_0 A}]^{-1} \int_0^{T_0} e^{rA} h(\bar{x}(-r), \bar{y}) dr. \]

(4.34)

We have

\[ \int_0^{\infty} e^{rA} h(\bar{x}(-r), \bar{y}) dr = \sum_{k=0}^{\infty} \int_0^{T_0} e^{(r+kT_0)A} h(\bar{x}(kT_0 - r), \bar{y}) dr \]

\[ = \left[ \sum_{k=0}^{\infty} e^{kT_0 A} \right] \int_0^{T_0} e^{rA} h(\bar{x}(-r), \bar{y}) dr = [I - e^{T_0 A}]^{-1} \int_0^{T_0} e^{rA} h(\bar{x}(-r), \bar{y}) dr, \]

where we have used the periodicity of \( \bar{x}(t) \), and the fact that the geometric series converges because the eigenvalues of \( A \) have negative real parts. Therefore (4.34) can be rewritten as

\[ v_{\beta}(0, 0) = \int_0^{\infty} e^{rA} h(\bar{x}(-r), \bar{y}) dr. \]

(4.35)
From (4.33) and (4.35) we have
\[ v_\beta(0, t) = e^{tA} \int_0^\infty e^{rA} h(\bar{x}(-r), \bar{y}) dr + \int_0^t e^{rA} h(\bar{x}(t-r), \bar{y}) dr \]
\[ = \int_0^\infty e^{rA} h(\bar{x}(t-r), \bar{y}) dr + \int_0^t e^{rA} h(\bar{x}(t-r), \bar{y}) dr \]
\[ = \int_0^\infty e^{rA} h(\bar{x}(t-r), \bar{y}) dr, \]  \hspace{1cm} (4.36)
and, using (4.32) and (4.36),
\[ v_\beta(0, t) = h(\bar{x}(t), \bar{y}) + Av_\beta(0, t) \]  \hspace{1cm} (4.37)
\[ = A \int_0^\infty e^{rA} [h(\bar{x}(t-r), \bar{y}) - h(\bar{x}(t), \bar{y})] dr \]
\[ = \int_0^\infty \frac{d}{dr} [e^{rA}][h(\bar{x}(t-r), \bar{y}) - h(\bar{x}(t), \bar{y})] dr \]
\[ = e^{rA} [h(\bar{x}(t-r), \bar{y}) - h(\bar{x}(t), \bar{y})] \bigg|_{r=0}^{r=\infty} - \int_0^\infty e^{rA} \frac{d}{dr} h(\bar{x}(t-r), \bar{y}) dr \]
\[ = \int_0^\infty e^{rA} h_x(\bar{x}(t-r), \bar{y}) \dot{x}(t-r) dr. \]

Substituting the expression (4.37) for \( v_\beta(0, t) \) into (4.31), we get (4.20), as we wanted. We now prove part (ii). We rewrite (4.28) as
\[ u_\beta(0, t) - f_x(\bar{x}(t), \bar{y}) u_\beta(0, t) = \tau'(0) \dot{x}(t) + f_y(\bar{x}(t), \bar{y})(v_\beta(0, t)). \]  \hspace{1cm} (4.38)
Taking the inner product of (4.38) with \( q(t) \) and integrating over \([0, T_0]\) using the fact that, due to (4.4), the left-hand side vanishes and (4.5), we get
\[ \tau'(0) = -\int_0^{T_0} \langle f_y(\bar{x}(s), \bar{y}) v_\beta(0, s), q(s) \rangle ds. \]  \hspace{1cm} (4.39)
Substituting the expression (4.36) for \( v_\beta(0, s) \) into (4.39), we get
\[ \tau'(0) = -\int_0^\infty \int_0^{T_0} \langle f_y(\bar{x}(s), \bar{y}) e^{rA} h(\bar{x}(s-r), \bar{y}), q(t) \rangle dsdr \]
which, in view of (4.11) implies (4.6).  \hspace{1cm} ■
5 Application to a model for the pulsatile secretion of GnRH

In this section we apply Theorem 3.1 to study a mathematical model, presented by Khadra and Li [14], whose aim is to explain the synchronization of the periodic (with period approximately 1 hour) secretion of GnRH (gonadotropin-releasing hormone) by GnRH neurons in the hypothalamus. The explanation proposed for this synchronization phenomenon, based on a range of experimental results, is that the GnRH neurons have receptors for GnRH, so that the concentration of GnRH in the environment influences their dynamics by binding to these receptors, thus inducing an indirect coupling leading to synchronization.

We very briefly describe the mechanisms involved in the model of [14], and refer to that paper for details. The binding of GnRH to the receptors on a GnRH neuron activates three types of G-protein $G_s$, $G_q$, $G_i$ in the cell, and the concentrations of their activated subunits $\alpha_s, \alpha_q, \alpha_i$ in the cell are denoted by $S, Q, I$, respectively. $\alpha_s$ activates the production of cAMP, whose concentration is denoted by $A$. $\alpha_q$ induces the release of Ca$^{2+}$, whose concentration is denoted by $C$, from intracellular stores. $C$ and $A$ act in synergy to induce the secretion of GnRH from the neuron. $G$ denotes the concentration of GnRH in the external environment. These causal relations are modeled by the following differential equations:

\begin{align*}
\dot{S} &= \nu_S H_S(G) - k_S S, \\
\dot{Q} &= \nu_Q H_Q(G) - k_Q Q, \\
\dot{I} &= \nu_I H_S(G) - k_I I, \\
\dot{C} &= \nu_C F_C(C, Q)[C_{ER} - C) - k_C C, \\
\dot{A} &= b_A + \nu_A F_A(S, I) - k_A A, \\
\dot{G} &= b_G + \nu_G F_G(C, A) - k_G G,
\end{align*}

(5.1) (5.2) (5.3) (5.4) (5.5) (5.6)

where all the parameters, and the nonlinearities $H_S, H_Q, H_I, F_C, F_A, F_G$, are positive. In [14] these nonlinearities are taken as:

\begin{align*}
H_S(G) &= \frac{G^4}{K_S^4 + G^4}, \quad H_Q(G) = \frac{G^2}{K_Q^2 + G^2}, \quad H_I(G) = \frac{G^2}{K_I^2 + G^2}, \\
F_C(C, Q) &= Q, \quad F_A(S, I) = \frac{h_I S}{I + h_I}, \quad F_G(C, A) = (AC)^3.
\end{align*}

(5.7)
For our results we do not need to assume these specific forms.

When dealing with \( n \) GnRH neurons coupled through the GnRH in their environment, the model becomes [14] (1 \( \leq k \leq n \))

\[
\dot{S}_k = \nu_S H_S(G) - k_S S_k, \quad (5.8)
\]

\[
\dot{Q}_k = \nu_Q H_Q(G) - k_Q Q_k, \quad (5.9)
\]

\[
\dot{I}_k = \nu_I H_S(G) - k_I I_k, \quad (5.10)
\]

\[
\dot{C}_k = J_{IN} + [l + \nu_C F_C(C_k Q_k)](C_{ER} - C_k) - k_C C_k, \quad (5.11)
\]

\[
\dot{A}_k = b_A + \nu_A F_A(S_k, I_k) - k_A A_k, \quad (5.12)
\]

\[
\dot{G} = b_G + \frac{\nu_G}{n} \sum_{j=1}^{n} F_G(C_j, A_j) - k_G G, \quad (5.13)
\]

where \( S_k, Q_k, I_k, C_k, A_k \) are intracellular concentrations of the various species in neuron \( k \), and \( G \) is the concentration of GnRH in the intercellular medium.

We are going to prove results which say that if a single neuron, placed in the environment, performs periodic oscillations (in other words if the system (5.1)-(5.6) has a stable periodic solution), then a population of such neurons will synchronize (in the sense that the synchronized oscillation is stable).

The following simple lemma will be used.

**Lemma 5.1** Assume \( a(t) \) satisfies

\[
a(t) \geq a_0 > 0, \quad \forall t > 0,
\]

and \( f(t) \) satisfies

\[
\dot{f}(t) + a(t)f(t) = y(t) \quad (5.14)
\]

where

\[
|y(t)| \leq m e^{-kt} \quad \forall t > 0 \quad (5.15)
\]

with \( k > 0 \). Then \( f(t) \) converges exponentially to 0 as \( t \rightarrow \infty \): there exist \( m', k' > 0 \) so that

\[
|f(t)| \leq m' e^{-k't} \quad \forall t > 0.
\]
Proof: \( f \) can be written explicitly as
\[
\begin{align*}
f(t) &= \exp\left(-\int_0^t a(s)ds\right)f(0) + \int_0^t \exp\left(-\int_s^t a(r)dr\right)y(s)ds.
\end{align*}
\]
Therefore, using (5.14), (5.15) we have
\[
|f(t)| \leq \exp(-ta_\ast)|f(0)| + me^{-a_\ast t} \int_0^t e^{(a_\ast-k)s}ds.
\]
which gives the exponential decay. \( \square \)

We assume that the system (5.1)-(5.6) has a stable periodic solution \( S(t), Q(t), I(t), C(t), A(t), G(t) \) (that is, we assume that a single neuron performs oscillations). Condition (C2) of Theorem 3.1 holds by this assumption. To obtain the stability of this solution as a synchronized oscillation of (5.8)-(5.13), we need, according to Theorem 3.1, to verify (C1), that is to show that the Floquet multipliers of the periodic equation system
\[
\begin{align*}
\dot{\tilde{S}} &= -k_S \tilde{S} \\
\dot{\tilde{Q}} &= -k_Q \tilde{Q} \\
\dot{\tilde{I}} &= -k_I \tilde{I} \\
\dot{\tilde{C}} &= -\left[I + k_C + \nu_C F_C(C(t), Q(t)) + \frac{\partial F_C}{\partial C}(C(t), Q(t))(C_{ER} - C(t))\right] \tilde{C} \\
&\quad + \frac{\partial F_C}{\partial Q}(C(t), Q(t))(C_{ER} - C(t)) \tilde{Q}, \\
\dot{\tilde{A}} &= \nu_A \frac{\partial F_A}{\partial S}(S(t), I(t)) \tilde{S} + \nu_A \frac{\partial F_A}{\partial I}(S(t), I(t)) \tilde{I} - k_A \tilde{A}.
\end{align*}
\]
have absolute values less than 1, or in other words that any solution of this system decays to 0 at an exponential rate as \( t \to \infty \). Let \( \tilde{S}(t), \tilde{Q}(t), \tilde{I}(t), \tilde{C}(t), \tilde{A}(t) \) be a solution of (5.16)-(5.20). From (5.16)-(5.18) we get that
\[
\begin{align*}
\tilde{S}(t) &= \tilde{S}(0)e^{-k_S t}, \\
\tilde{Q}(t) &= \tilde{Q}(0)e^{-k_Q t}, \\
\tilde{I}(t) &= \tilde{I}(0)e^{-k_I t},
\end{align*}
\]
so that these components certainly decay exponentially.
Substituting (5.21) into (5.20) we have
\[ \dot{\tilde{A}} + k_A \tilde{A} = \nu_A \frac{\partial F_A}{\partial S}(S(t), I(t))\tilde{S}(0)e^{-k_A t} + \nu_A \frac{\partial F_A}{\partial I}(S(t), I(t))\tilde{I}(0)e^{-k_A t}. \] (5.22)

The right-hand side of (5.22) decays exponentially, and \( k_A > 0 \), hence, by Lemma 5.1, \( A(t) \) decays exponentially.

Substituting (5.21) into (5.19) we get
\[ \dot{\tilde{C}} + K(t)\tilde{C} = \frac{\partial F_C}{\partial Q}(C(t), Q(t))(C_{ER} - C(t))\tilde{Q}(0)e^{-k_Q t}, \] (5.23)

where
\[ K(t) = l + k_C + \nu_C F_C(C(t), Q(t)) + \frac{\partial F_C}{\partial C}(C(t), Q(t))(C_{ER} - C(t)). \] (5.24)

The right-hand side of (5.24) decays exponentially, so to use Lemma 5.1 in order to show that \( \tilde{C}(t) \) decays exponentially, we must show that
\[ \min_{t \in \mathbb{R}} K(t) > 0. \] (5.25)

If we assume that \( F_C \) does not depend on \( C \), so that
\[ \frac{\partial F_C}{\partial C}(C, Q) = 0, \] (5.26)

which holds in the case of (5.7), then
\[ K(t) = l + k_C + \nu_C F_C(C(t), Q(t)) \geq l + k_C > 0, \]

hence (5.25) holds. We thus have

**Proposition 5.1** Assume that (5.26) holds and that the system (5.1)-(5.6) has a stable periodic solution \( S(t), Q(t), I(t), C(t), A(t), G(t) \). Then, for any \( n \geq 1 \), the synchronized oscillation \( S_k(t) = S(t), Q_k(t) = Q(t), I_k(t) = I(t), A_k(t) = A(t) \) (\( 1 \leq k \leq n \)), \( G(t) \) is a stable solution of (5.8)-(5.13).

Proposition 5.1 covers the case in which the nonlinearities are given by (5.7), but we now also derive a sufficient condition for synchronization without
assuming (5.26). As explained in [14] there is evidence for positive feedback of Ca$^{2+}$ concentration on Ca$^{2+}$ release, so that we assume

$$\frac{\partial F_C}{\partial C}(C, Q) \geq 0.$$  \hspace{1cm} (5.27)

We note that (5.4) implies that

$$\dot{C}(t) = 0 \Rightarrow C(t) = \frac{J_{IN} + [l + \nu_C F_C(C(t), Q(t))] C_{ER}}{k_C + l + \nu_C F_C(C(t), Q(t))}$$

and since

$$0 < \frac{J_{IN} + [l + \nu_C F_C(C(t), Q(t))] C_{ER}}{k_C + l + \nu_C F_C(C(t), Q(t))} \leq \max \left( \frac{J_{IN} + l C_{ER}}{k_C + l}, C_{ER} \right),$$

we have that if $\dot{C}(t) = 0$ then

$$0 < C(t) \leq \max \left( \frac{J_{IN} + l C_{ER}}{k_C + l}, C_{ER} \right),$$ \hspace{1cm} (5.28)

so that in particular (5.28) holds at the minimum and maximum points of $C(t)$ (recall that $C(t)$ is periodic), hence (5.28) holds for all $t$. If we assume that

$$C_{ER} > \frac{J_{IN} + l C_{ER}}{k_C + l},$$

then we get $C(t) < C_{ER}$ for all $t$, hence from (5.24) and (5.27) we get that (5.26) holds. We thus obtain

**Proposition 5.2** Assume that (5.27) and

$$C_{ER} k_C > J_{IN}$$ \hspace{1cm} (5.29)

hold, and that the system (5.1)-(5.6) has a stable periodic solution $S(t)$, $Q(t)$, $I(t)$, $C(t)$, $A(t)$, $G(t)$. Then, for any $n \geq 1$, the synchronized oscillation $S_k(t) = S(t)$, $Q_k(t) = Q(t)$, $I_k(t) = I(t)$, $A_k(t) = A(t)$ ($1 \leq k \leq n$), $G(t)$ is a stable solution of (5.8)-(5.13).

The biologically reasonable values of the parameters given in [14], $C_{ER} = 2.5 \mu M$, $k_C = 5100 \text{ min}^{-1}$, $J_{IN} = 0.2 \frac{\mu M}{\text{min}}$, are well within the range satisfying
so that proposition 5.2 applies and assures that synchronization will occur, even if the nonlinearity \( F_C \) depends on both \( Q \) and \( C \).

We remark that Khadra and Li also give a simplified version of their model ([14], eqs. 8-9). Proving the stability of synchronized oscillations of this simplified model (assuming that a single cell has a stable oscillation), by verifying condition (C1) of 3.1 is even easier than in the case of the full model, and no restriction on the parameters or nonlinearities is needed in this case.

6 Synchronization of indirectly coupled \( \lambda - \omega \) oscillators

\( \lambda - \omega \) oscillators are given by the equations

\[
\begin{align*}
\dot{u} &= \lambda(\sqrt{u^2 + v^2})u - \omega(\sqrt{u^2 + v^2})v \\
\dot{v} &= \omega(\sqrt{u^2 + v^2})u + \lambda(\sqrt{u^2 + v^2})v,
\end{align*}
\]

(6.1)

where \( \omega, \lambda : [0, \infty) \rightarrow \mathbb{R} \) are given functions. Introducing polar coordinates \( r, \theta \) in the \( u, v \)-plane, we can write (6.1) as

\[
\begin{align*}
\dot{r} &= \lambda(r)r, \\
\dot{\theta} &= \omega(r).
\end{align*}
\]

It is then seen immediately that if \( r_0 > 0 \) is such that \( \lambda(r_0) = 0 \) then

\[
\begin{align*}
\bar{u}(t) &= r_0 \cos(\omega_0 t), \\
\bar{v}(t) &= r_0 \sin(\omega_0 t),
\end{align*}
\]

where \( \omega_0 = \omega(r_0) \). Moreover, if \( \lambda'(r_0) < 0 \) then this periodic solution is stable, and if \( \lambda'(r_0) > 0 \) it is unstable.

In the particular case

\[
\lambda(r) = 1 - r^2, \quad \omega(r) = 1 + \gamma(1 - r^2)
\]

we get the Ginzburg-Landau oscillator, which in terms of \( A = u + iv \) can be written as

\[
\dot{A} = (1 + i(\gamma + 1))A - (1 + i\gamma)|A|^2A.
\]

(6.2)

When \( \gamma = 0 \) this is known as the ‘radial isochron clock’ [12], or ‘Poincaré oscillator’ [6].
We shall assume that 
\[ \lambda(1) = 0, \quad \lambda'(1) < 0, \]
\[ \omega(1) = 1. \]
so that (6.1) has the stable periodic solution
\[ \bar{u}(t) = \cos(t), \quad \bar{v}(t) = \sin(t). \]

The existence of an explicitly-known periodic solution facilitates analytical study of weakly-coupled \( \lambda - \omega \) oscillators without resort to numerical calculations. \( \lambda - \omega \) oscillators have been used to address a variety of questions related to coupled and forced oscillators - see [25], page 163 for references.

We will use Theorem 4.1 to study a system of \( n \) indirectly coupled \( \lambda - \omega \) oscillators (\( 1 \leq k \leq n \))

\[ \dot{u}_k = \lambda \left( \sqrt{u_k^2 + v_k^2} \right) u_k - \omega \left( \sqrt{u_k^2 + v_k^2} \right) v_k + F(u_k, v_k)y, \quad (6.3) \]
\[ \dot{v}_k = \omega \left( \sqrt{u_k^2 + v_k^2} \right) u_k + \lambda \left( \sqrt{u_k^2 + v_k^2} \right) v_k, \quad (6.4) \]
\[ \dot{y} = -\alpha y + \frac{\beta}{n} \sum_{j=1}^{n} (au_j + bv_j), \quad (6.5) \]

where \( \alpha > 0 \), in the weakly coupled case \( |\beta| \to 0 \). We will obtain conditions on the function \( F \) and on the parameters \( \alpha, a, b \) which ensure that the synchronized oscillation, which exists for \( |\beta| \) small, is (un)stable.

The system (6.3)-(6.5) is of the form (3.1), (3.2), with \( d = 2, \ p = 1, \)
\[ x = \begin{pmatrix} u \\ v \end{pmatrix}, \]
\[ f(x, y) = \begin{pmatrix} \lambda(\sqrt{u^2 + v^2})u - \omega(\sqrt{u^2 + v^2})v + F(u, v)y \\ \omega(\sqrt{u^2 + v^2})u + \lambda(\sqrt{u^2 + v^2})v \end{pmatrix}, \]
\[ g(y) = -\alpha y \]
\[ h(x, y) = au + bv, \]
When $\beta = 0$, the uncoupled system satisfies Assumption 4.1: the equation (4.1) has the stable stationary solution $\bar{y} = 0$, and the equation (4.2) is the $\lambda - \omega$ oscillator, with the solution

$$\bar{x}(t) = \begin{pmatrix} \cos(t) \\ \sin(t) \end{pmatrix}.$$

We have

$$f_x(\bar{x}(t), 0) = \begin{pmatrix} \cos(t)(\lambda'(1) \cos(t) - \omega'(1) \sin(t)) & \sin(t)(\lambda'(1) \cos(t) - \omega'(1) \sin(t)) - 1 \\ \cos(t)(\omega'(1) \cos(t) + \lambda'(1) \sin(t)) + 1 & \sin(t)(\omega'(1) \cos(t) + \lambda'(1) \sin(t)) \end{pmatrix}.$$

One can check by inspection that

$$q(t) = \begin{pmatrix} q_1(t) \\ q_2(t) \end{pmatrix} = \frac{1}{2\pi} \begin{pmatrix} \lambda'(1) \sin(t) + \omega'(1) \cos(t) \\ -\lambda'(1) \cos(t) + \omega'(1) \sin(t) \end{pmatrix},$$

is the $2\pi$-periodic solution of the equation (4.4), where the coefficient $\frac{1}{2\pi}$ is taken to achieve the normalization (4.5).

We compute also

$$f_y(x, y) = \begin{pmatrix} F(u, v) \\ 0 \end{pmatrix},$$

$$h_x(x, y) = \begin{pmatrix} a \\ b \end{pmatrix},$$

$$f_y(\bar{x}(s), 0)e^{rA}h_x(\bar{x}(s - r), 0) = e^{-\alpha y} \begin{pmatrix} aF(\bar{u}(s), \bar{v}(s)) \\ bF(\bar{u}(s), \bar{v}(s)) \end{pmatrix},$$

$$f_y(\bar{x}(s), 0)e^{rA}h_x(\bar{x}(s - r), 0)\dot{x}(s - r) = e^{-\alpha r} \begin{pmatrix} aF(\bar{u}(s), \bar{v}(s))\dot{u}(s - r) + bF(\bar{u}(s), \bar{v}(s))\dot{v}(s - r) \\ 0 \end{pmatrix},$$

$$\langle f_y(\bar{x}(s), 0)e^{rA}h_x(\bar{x}(s - r), 0)\dot{x}(s - r), q(s) \rangle$$

$$= e^{-\alpha r}[aF(\bar{u}(s), \bar{v}(s))\dot{u}(s - r) + bF(\bar{u}(s), \bar{v}(s))\dot{v}(s - r)]q_1(s)$$

$$= \frac{e^{-\alpha r}}{2\pi}[-aF(\cos(s), \sin(s))\sin(s - r) + bF(\cos(s), \sin(s))\cos(s - r)]$$

$$\times [\lambda'(1) \sin(s) + \omega'(1) \cos(s)],$$

28
hence

\[
\sigma = \frac{b}{2\pi} \int_{0}^{2\pi} F(\cos(s), \sin(s)) [\lambda'(1) \sin(s) + \omega'(1) \cos(s)] \int_{0}^{\infty} \cos(s - r)e^{-\alpha r} dr ds
\]

\[- \frac{a}{2\pi} \int_{0}^{2\pi} F(\cos(s), \sin(s)) [\lambda'(1) \sin(s) + \omega'(1) \cos(s)] \int_{0}^{\infty} \sin(s - r)e^{-\alpha r} dr ds
\]

\[= \frac{1}{\alpha^2 + 1} \left[(b - \alpha a)[\omega'(1)C_2 + \lambda'(1)C_1] + (a + \alpha b)[\omega'(1)C_3 + \lambda'(1)C_2] \right]
\]

where

\[C_1 = \frac{1}{2\pi} \int_{0}^{2\pi} F(\cos(s), \sin(s)) \sin^2(s) ds,\]

\[C_2 = \frac{1}{2\pi} \int_{0}^{2\pi} F(\cos(s), \sin(s)) \cos(s) \sin(s) ds,\]

\[C_3 = \frac{1}{2\pi} \int_{0}^{2\pi} F(\cos(s), \sin(s)) \cos^2(s) ds.\] (6.6)

From Theorem 4.1 we thus obtain

**Proposition 6.1** Assuming \( \lambda'(1) \neq 0 \) and \( \alpha \neq 0 \), there exists \( \beta_0 > 0 \) such that for \( |\beta| < \beta_0 \) \((6.3)-(6.5)\), has a synchronized oscillation, and we have

(i) If \( \lambda'(1) < 0 \) and

\[(b - \alpha a)[\omega'(1)C_2 + \lambda'(1)C_1] + (a + \alpha b)[\omega'(1)C_3 + \lambda'(1)C_2] > 0,\] (6.7)

where \( C_1, C_2, C_3 \) are defined by (6.6), then the synchronized oscillation is stable for \( \beta > 0 \) and unstable for \( \beta < 0 \).

(ii) If \( \lambda'(1) < 0 \) and the reverse inequality to (6.7) holds, then the synchronized oscillation is unstable for \( \beta > 0 \) and stable for \( \beta < 0 \).

(iii) If \( \lambda'(1) > 0 \) then the synchronized oscillation is unstable for all \( |\beta| < \beta_0 \).

In the case of coupled Ginzburg-Landau oscillators (6.2), where we have \( \lambda'(1) = -2, \omega'(1) = -2\gamma \), we get

**Corollary 6.1** There exists \( \beta_0 > 0 \) such that for \( |\beta| < \beta_0 \) the system of coupled Ginzburg-Landau oscillators \( 1 \leq k \leq n \):

\[\dot{u}_k = [1 - (u_k^2 + v_k^2)]u_k - [1 + \gamma - \gamma(u_k^2 + v_k^2)]v_k + F(u_k, v_k)y,\]
\[
\dot{v}_k = [1 + \gamma - \gamma(u_k^2 + v_k^2)]u_k + [1 - (u_k^2 + v_k^2)]v_k,
\]
\[
\dot{y} = -\alpha y + \frac{\beta}{n} \sum_{j=1}^{n} (au_j + bv_j),
\]

has a synchronized oscillation, which is stable if
\[
\beta[(b - \alpha a)(\gamma C_2 + C_1) + (a + \alpha b)(\gamma C_3 + C_2)] < 0, \quad (6.8)
\]
and unstable if the reverse inequality holds, where \(C_1, C_2, C_3\) are defined by (6.6).

7 Discussion

We summarize here the basic insights provided by the analytical results given by Theorems 3.1 and 4.1, and make some remarks about the possibilities for applying these results to the study of specific systems.

Theorem 3.1 shows that the study of synchronization, that is the determination of (in)stability of a synchronized solution of (3.1), (3.2), which is a system of size \(nd + p\), reduces to the study of the study of two linear systems of dimensions \(d\) (equation 3.5) and \(d + p\) (equation 3.6), associated with a periodic oscillation of a single oscillator. As we have demonstrated in section 5, for certain systems this result can be used to prove synchronization without resort to numerical computations, but in general this will not be the case. However, as we have noted, Theorem 3.1 has the following implication which is significant in general: if the system (3.1), (3.2) with \(n = 2\) has a stable synchronized oscillation, then the same is true for any \(n\). If the system with \(n = 2\) is studied by numerical simulation and observed to display synchronization, then we are assured that the synchronized oscillation will be stable for the system with arbitrarily large \(n\). The caveat must be made here that since the notion of stability is a local one, it is possible that for \(n = 2\) the synchronized oscillation will be globally stable, but for some larger \(n\) the synchronized oscillation will only be locally stable. Finding criteria for global stability of the synchronized oscillation of system (3.1), (3.2) is an interesting question for further research.

Theorem 4.1 provides an understanding of synchronization in the case of weak coupling (\(|\beta|\) small). It is shown that synchronization can occur for
arbitrarily weak coupling, provided it is of the ‘right’ sign, as determined by the integral $\sigma$. It is to be noted that in many cases only a positive value for $\beta$ makes physical sense, as in the case of coupled cells where $\beta$ is given by (1.3), in which case the condition for synchronization is $\sigma < 0$. This criterion can be used for a systematic studies of synchronization in the weak-coupling regime, in dependence on various parameters. An example of such a study was given in section 6 for $\lambda - \omega$ oscillators. In this case calculations are particularly simple, because the periodic solution in the uncoupled case is available in closed form. More generally such a study can be performed with the aid of numerical computation. Suppose that the coupling function $h$ in (3.2) depends on some parameters $\alpha = (\alpha_1, \ldots, \alpha_m)$, and we want to determine the subset in the space of parameters $\alpha$ that will lead to synchronization for small $\beta > 0$. We first compute the periodic solution $\bar{x}(t)$ of (1.2), for example by direct numerical simulation. We then substitute $\bar{x}(t)$ into the formula (4.7) for $\sigma$. The dependence of $\sigma$ on $\alpha$ follows from $\alpha$-dependence of $h$, and the function $\sigma(\alpha)$ can be computed by a numerical integration. The surface $\sigma(\alpha) = 0$ will separate the parameter space into synchronizing and non-synchronizing regions in the small parameter case.

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