Localized and asynchronous patterns via canards in coupled calcium oscillators

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February 8, 2005

Abstract

In this paper we consider the mechanism for localized behavior in coupled calcium oscillators described by the canonical two-pool model. Localization occurs when the individual cells oscillate with amplitudes of different orders of magnitude. Our analysis and computations show that a combination of diffusive coupling, heterogeneity, and the underlying canard structure of the oscillators all contribute to the localized behavior. Two key quantities characterize the different states of the system by representing the effects of both the autonomous and the non-autonomous terms which are due to the coupling. By highlighting the influence of the canard phenomenon, these quantities identify stabilizing and destabilizing effects of the coupling on the localized behavior. We compare our analysis with computations, describing multi-mode states and asynchronized large oscillations in addition to the localized states.

1 Introduction

Patterns in which different cells oscillate with amplitudes of different orders of magnitude have been observed in chemical, biological and optical systems [1, 2, 3, 4, 5]. This phenomenon, known as localization, can occur by various mechanisms according to the nature of the uncoupled oscillators and the type of coupling. For oscillations governed by underlying limit cycles rather than conservative oscillations, the mechanism of localization is typically controlled by effective parameters in critical regimes, for example, near bifurcations or transitions in qualitative behavior [5, 6, 7]. It is useful to relate these parameters to the bifurcation or control parameters of the single oscillators or to the coupling terms which can be local [5] or global [6, 7].

Our focus here is on different mechanisms that produce localization in a biochemical model of diffusively coupled calcium oscillations. In a localized pattern one oscillator has large amplitude oscillations (LAO) and a second oscillator exhibits small amplitude oscillations (SAO), which are an order of magnitude smaller than the LAO. Two important ingredients in the mechanisms described here are the relatively small coupling and heterogeneity in the population of oscillators. A third key factor is the canard phenomenon [8, 9, 10, 11, 12]. In two-dimensional relaxation oscillators undergoing a
Hopf bifurcation, this phenomenon appears as a sudden transition from a SAO regime to a LAO regime which may occur due to small changes in some of the parameters of the model. In the context of globally coupled relaxation oscillators studied in [6, 7], this feature of the canard phenomenon played a critical role in the localization, and we expect it to be significant in systems with other types of coupling.

The specific calcium oscillators studied in this paper are described by the canonical two pool model [13]. Calcium oscillations depend on a parameter IP$_3$ (inositol (1,4,5)-triphosphate) which controls calcium release and are well documented for the single cell model (see Appendix A). Since the single oscillator is well understood, this model is an ideal candidate for developing new methods for studying localized oscillations due to the interaction of coupling and the canard phenomenon, which in the two-pool model is related to variation in the parameter representing IP$_3$.

The analysis of [6, 7] explained the mechanism for spatially localized oscillations in models of the globally coupled Belousov-Zhabotinsky (BZ) reaction [1, 2, 3] and globally coupled FitzHugh-Nagumo (FHN) models. However, the mechanism for localization in the present model is different from that in [6, 7]. There the individual oscillators are identical, and heterogeneity in the cluster (set of oscillators in the same amplitude regime) size is created through global inhibitory coupling, while localization in the two-pool model is due to heterogeneity in the individual oscillators and a competing influence from diffusive coupling. This is surprising since, intuitively, diffusion tends to homogenize the system. In fact, we find that relatively small diffusive coupling has a non-trivial influence on localized states, supporting and stabilizing them in unexpected regimes.

The diffusively coupled two-pool system also exhibits localized states of mixed-mode type [14, 15, 16], where one oscillator is always in a SAO regime while the other alternates over time between LAO and SAO regimes. This phenomenon is again a consequence of the interaction of coupling, heterogeneity and the canard phenomenon. Some insight into the different types of localized phenomena can be found by comparing related chemical and biological systems, in which sudden explosions of limit cycles and mixed-mode oscillations are often found [6, 7, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28]. In a single two-dimensional oscillator undergoing a canard explosion there is an exponentially small range of the parameter governing the transition between SAO to LAO regimes where the system is “in between” regimes. Then the limit cycles with the largest SAO’s occur for parameters near this transition regime, and they are typically sensitive to parameter perturbations. The solution of a two-dimensional relaxation oscillator can be either in a SAO or a LAO regime, but not in both; that is, one cannot find mixed-mode oscillatory solutions. In a three-dimensional system with at least two slow and one fast equations, the range of parameter values for which the system is in between regimes is large as compared to the two dimensional case. As a consequence, oscillations in the SAO regime are often less sensitive to parameter perturbations [14, 29], so that mixed-mode oscillations can be found. In a coupled system, which is by definition higher dimensional, this reduced sensitivity allows for the more complex dynamics studied in this paper.

We give some historical context for the study of the canard phenomenon, summa-
rizing those results related to our analysis and observations. The canard phenomenon was discovered by Benoit et al. [10] for the van der Pol (VDP) oscillator. Using non-standard analysis techniques, they showed the existence of a canard critical value, denoted $\lambda_c$ in the following sections, which marks the transition between SAO and LAO behavior. Eckhaus [9] and Baer et al. [30, 31] used asymptotic techniques to study the canard phenomenon and to find expressions for the canard critical value $\lambda_c$ for VDP- and FitzHugh-Nagumo- (FHN) type equations. Dumortier and Roussarie [8] and Krupa and Szmolyan [11, 12] used geometric singular perturbation theory and blow-up techniques to study the canard phenomenon and to give an expression for $\lambda_c$ for two-dimensional relaxation oscillators. We follow the latter authors in our approach.

The canard phenomenon and related mixed-mode oscillations in higher dimensional relaxation oscillators (autonomous and non-autonomous) have been studied analytically and numerically [14, 29, 32, 33, 34]. In some cases, the maximum number of subthreshold oscillations alternating with a large amplitude oscillation can be estimated [14]. However, global predictions are not always possible; that is, determining whether the system displays subthreshold oscillations and, if they do, how many of them are present in a mixed mode state depends on initial conditions or the reset value after a large amplitude oscillation. Several approaches have been developed to deal with this type of problem by studying them as reduced two-dimensional systems evolving in time [15, 16, 35].

1.1 The model and strategy

In this paper we present a new asymptotic technique for understanding the canard phenomenon for diffusively coupled relaxation oscillators. Our goal is to obtain analytical expressions and reduced systems which can be used to understand the mechanistic aspects of localized patterns in diffusively coupled relaxation oscillators and to make predictions about them in terms of the model parameters. We focus primarily on the coupling parameters and the bifurcation (control) parameter (related to IP$_3$ in the original application). The method does not depend on the particular model that we have used; therefore we expect that it can be valuable for the analysis of other coupled relaxation oscillations.

Our starting point is the system of diffusively coupled calcium oscillators described by the two-pool model in a dimensionless form [36].

\[
\begin{align*}
V'_k &= \mu_k - V_k - \gamma/\epsilon F(V_k, W_k) + D_v (V_j - V_k), \\
W'_k &= \frac{1}{\epsilon} F(V_k, W_k) + D_w (W_j - W_k),
\end{align*}
\]

for $k = 1, 2$ where

\[
F(V, W) = \beta \left( \frac{V^n}{V^n + 1} \right) - \left( \frac{W^m}{W^m + 1} \right) \left( \frac{V^p}{V^p + \alpha^p} \right) - \delta W.
\]

A more detailed description of the dimensional model as well as the nondimensionalization is given in the Appendix A. In (1) $V_k$ and $W_k$ are the concentrations of calcium.
in the cytoplasm and the calcium sensitive store or pool, respectively. The parameters $D_v$ and $D_w$ give intercellular coupling. The parameter $\epsilon$ is very small indicating that the rate at which calcium is released from the $\text{Ca}^{2+}$-sensitive pool is very large. The parameter $\mu_k$ is the bifurcation or control parameter related to IP$_3$; oscillations are stable or unstable depending on different parameter regimes of $\mu_k$. By making a change of variables, the single cell two-pool model can be transformed into a FHN-type system [36, 37]. Therefore it is not unexpected that we can find localized behavior in the coupled system, given the previous results from [6, 7], as discussed above.

As an example of localized behavior for (1), we consider Figure 1. As shown in the following sections, it is convenient to give the results in terms of the parameter $\lambda_k$, which is just $-\mu_k$ plus a constant (see (3)). In the top graphs we show the oscillations in the uncoupled case $D_v = D_w = 0$. Then both oscillators are in the LAO regime. Note that the oscillations of the two systems are not identical, since $\lambda_1 \neq \lambda_2$ ($\mu_1 \neq \mu_2$).

In the bottom graphs, we show the behavior for the same values of $\lambda_k$, but with a small coupling coefficient $D_w = 0.01$ and $D_v = 0$. The first oscillator has LAO while the second has SAO, corresponding to localized oscillations. Clearly these localized oscillations have been induced by the diffusive coupling.

A key quantity for predicting SAO or LAO in a single relaxation oscillator is the canard critical value $\lambda_c$. Roughly speaking, for each one of the oscillators in the uncoupled system (1) ($D_v = D_w = 0$), $\lambda_c$ delineates the parameter ranges for which the oscillator is in a SAO regime ($\lambda_k < \lambda_c$) and a LAO regime ($\lambda_k > \lambda_c$). The value of $\lambda_c$ can be estimated as a function of the parameters of the model using a geometric [11] or asymptotic [9] approach, as we show in Section 2. For the uncoupled system shown in the top of Fig. 1, both $\lambda_1 > \lambda_c$ and $\lambda_2 > \lambda_c$, which is consistent with the observation of LAO for each single oscillator. In our analysis we extend the idea of a canard critical value to the coupled system.

For the coupled system (1) we observe that each oscillator is composed of two contributions, one from the autonomous part and a second from the non-autonomous part, labeled with “$k$” and “$j$” respectively. As in [6, 7] each member in the system (1) can be thought of an autonomous oscillator forced by the non-autonomous part. The patterns studied here are the result of a combination of both the contribution of the autonomous and nonautonomous parts, and we examine two quantities which summarize these effects. These quantities and their application to the study of localized patterns are discussed in detail in Sections 2.2 and 2.3.

- **The canard critical value**, $\lambda_c(D_v, D_w)$. We derive an analytical expression which gives an approximation to the threshold for LAO or SAO for the single oscillator models, modified from the uncoupled case by those terms which appear in the coupled system as additional autonomous contributions. Then $\lambda_c(D_v, D_w)$ plays a role similar to that of the canard critical value for a single oscillator, and reduces to this value in the uncoupled case $D_v = D_w = 0$, generalizing [6]. Here we use the theory developed in [12].

- **The effective bifurcation parameters**, $\lambda_k^{\text{eff}}(D_v, D_w, V_j, W_j)$ for $k = 1, 2$. This quantity can be viewed as a generalization of the bifurcation parameter, combining $\lambda_k$.
\(-\mu_k + \text{a constant}\) with non-autonomous contributions from the coupling which vary with time through \((V_j, W_j)\). Thus it is a dynamical quantity, as forced through the coupling with the other oscillator. It can be compared to the threshold value \(\lambda_c(D_v, D_w)\), common to both oscillators, to predict (de-)stabilization of localization and other phenomena.

The main focus of our analysis is on the localized solutions, but there are also other interesting and non-trivial phenomena that are observed. In Section 4 we show asynchronous oscillations where both components demonstrate either LAO or mixed-mode states (see Figures 15 and 16). In many of these cases we use the expressions for \(\lambda_c\) and \(\lambda_{k}^{\text{eff}}\) to explain the phenomena, even though a phase plane analysis may be required for a detailed description. Throughout the paper we consider the effect of varying the coupling coefficients \(D_v, D_w, \) and \(\mu_k\) while keeping the other parameters fixed, as given in Appendix A.

The paper is organized as follows. In Section 2 we give a reduction of the model which gives a convenient viewpoint for the canard phenomenon. We also provide a canard analysis and derive the expressions for \(\lambda_c(D_v, D_w)\) and \(\lambda_{k}^{\text{eff}}\), generalizing [6, 12]. In Section 3 we use these two quantities to explain and predict localized phenomena in the coupled case, and compare to numerical simulations. In Section 4 we discuss other asynchronous oscillations in the coupled case, and show how they are related to the canard analysis.

## 2 The canard phenomenon: background and development of mechanistic tools

First we transform system (1) to a more suitable form in which, when uncoupled, describes 2 VDP oscillators. This transformation is different from the one used in [36] (see Appendix A), but relevant and useful for analysis of the canard phenomenon. We change coordinates

\[
v_k = -\frac{V_k}{\gamma} - v_m, \quad w_k = \gamma W_k + V_k - w_m, \quad \lambda_k = -(\mu_k + \gamma v_m),
\]

and substitute these into (1) to get

\[
\begin{aligned}
v'_k &= f(v_k, w_k) - \epsilon / \gamma [-\lambda_k + \gamma (1 + D_v) v_k] + \epsilon D_v v_j, \\
w'_k &= \epsilon [-\lambda_k + \gamma (1 + D_v - D_w) v_k - D_w w_k + \gamma (D_w - D_v) v_j + D_w w_j],
\end{aligned}
\]

where

\[
f(v, w) = F(-\gamma(v + v_m), v + v_m + (w + w_m) / \gamma).
\]

for \(k = 1, 2\), where \((v_m, w_m)\) are the coordinates of the local minimum of \(F(-\gamma v, v + w / \gamma)\) that we consider in the canard analysis below. For the parameters in this paper, we find that \(v_m \approx -0.3570\) and \(w_m = 1.5503\). The form of (4) allows a valuable
perspective on the pair of equations for each $k$; below we show that the corresponding nullclines can be viewed as those from the uncoupled case perturbed by diffusive coupling and forcing by the other oscillator. System (4) is a coupled system of FHN oscillators. When $D_w = 0$ (no diffusive coupling in the original $W$ variable), (4) becomes a coupled system of VDP oscillators. In the remainder of this section we give the analysis involving the canard phenomenon for the uncoupled case and derive the expressions for the canard critical value $\lambda_c$ and the effective bifurcation parameters $\lambda_{\text{eff}}$.

For the cases $D_v > 0$ and/or $D_w > 0$ system (4) can be seen as two forced autonomous oscillators; that is, two autonomous oscillators, each forced by the other one. In order to understand the dynamics of system (4) it is useful to decompose each one of these oscillators into its autonomous and non-autonomous parts. The autonomous part for (4) is

$$
\begin{align*}
\dot{v}_k &= f(v_k, w_k) - \epsilon / \gamma \left[-\lambda_k + \gamma (1 + D_v) v_k\right], \\
\dot{w}_k &= \epsilon \left[-\lambda_k + \gamma (1 + D_v - D_w) v_k - D_w w_k\right].
\end{align*}
$$

and clearly, the remaining terms give the non-autonomous part. Note that the diffusion coefficients $D_v$ and $D_w$ appear also in the autonomous part of each oscillator.

## 2.1 Canard phenomenon for the uncoupled case

First we review the canard phenomenon, referring the reader to [8, 9, 11, 12] for a more thorough introduction. In this section we discuss the general dynamical structure that is the basis for analyzing our model. Consider the following system:

$$
\begin{align*}
\dot{v} &= \hat{F}(v, w), \\
\dot{w} &= \epsilon \hat{G}(v, w; \lambda),
\end{align*}
$$

where $0 < \epsilon \ll 1$. The function $\hat{F}$ is such that its zero level curve is a cubic-like function, which can be written as $w = \hat{f}(v)$, taking its local minimum as $(0,0)$ without loss of generality. The function $\hat{G}$ is a non-increasing function of $w$ such that the zero level curve $\hat{G}(v, w; \lambda) = 0$ is an increasing function of $v$ for every $\lambda$ in a given neighborhood of $\lambda = 0$, and is also a decreasing function of $\lambda$ for all $v$ in a neighborhood of $v = 0$. In the uncoupled case of system (4), $\hat{G}$ does not depend on $w$ so that the null-cline is simply $v = \lambda / \gamma$, but in the general case this curve is written as $w = \hat{g}(v; \lambda)$. We further assume that $\hat{F} = 0$ and $\hat{G} = 0$ intersect at $(v_0, w_0)$ with $v_0 = 0$ when $\lambda = 0$, and that $(v_0, w_0)$ is an unstable fixed point lying on the central branch of $\hat{f}$ when $\lambda > 0$. We illustrate this in Figure 2. As we explain later the autonomous part (6) of system (4) satisfies the above conditions.

The nullclines for the uncoupled model studied in this manuscript are presented in Figure 3 for two different values of $\lambda$. Keeping all other parameters fixed, the dynamics of system (7) depends on the value of $\lambda$, which determines the relative position of the
w-nullcline with respect to the v-nullcline. For some value \( \lambda = \lambda_H = \mathcal{O}(\epsilon) > 0 \), system (7) undergoes a Hopf bifurcation in a neighborhood of \((0,0)\). Then it has a stable fixed point for values of \( \lambda < \lambda_H \) and a limit cycle for values of \( \lambda > \lambda_H \) (see [6, 12] for more details). For the parameters of the model studied in this manuscript, \( \lambda > \lambda_H \) and the Hopf bifurcation is supercritical, so that the limit cycle created is stable. As \( \lambda \) increases, the amplitude of the limit cycle created at the Hopf bifurcation increases slowly for small enough values of \( \lambda \); for these values, part of the trajectory is very close to the unstable middle (unstable) branch of the \( v \) nullcline for a while, then crosses the unstable branch and moves toward the left branch of the \( v \) nullcline, as illustrated in Figure 3-a. At some critical value \( \lambda_c > \lambda_H \) the trajectory moves toward the right branch of the \( v \)-nullcline instead of moving toward the left branch. Then for increasing \( \lambda \) the limit cycle expands rapidly (over an exponentially small range of the parameter \( \lambda \)), becoming a relaxation oscillator [38, 39, 40, 41], as seen in the transition from Figure 3-a to 3-b, together with the corresponding time series for \( v \) and \( w \) presented in Figure 4. After that, the amplitude of the limit cycle either increases slowly or remains constant as \( \lambda \) is increased, until the oscillator becomes a full relaxation oscillator. This rapid change from a “small” amplitude limit cycle to a “large” amplitude limit cycle is known as the canard phenomenon [8, 9, 10, 11, 12, 42].

In this case the canard phenomenon has been induced by changes in the value of \( \lambda \), which shifts both the \( v \)- and \( w \)-nullclines. As seen in eqs. 4, the shift in the \( v \)-nullcline is an order of magnitude smaller due to a factor of \( \epsilon \). The different effect on the \( w \)- and \( v \)-nullclines means that their relative position can change significantly as we vary \( \lambda \). By symmetry, for larger values of \( \lambda \) the \( w \)-nullcline is placed near the local maximum of \( w = f(v) \) and a similar effect is seen. In the following we concentrate on the canard phenomenon near the minimum \( v = 0 \).

2.2 Calculation of the canard critical value \( \lambda_c(D_v, D_w) \)

For a single oscillator of the form (7) satisfying the canard conditions (see [11, 12]), Krupa et al. gave an approximate expression for \( \lambda_c \), the critical value of \( \lambda \) dividing between the SAO and LAO regimes [12]. For values of \( D_v \) and \( D_w \) in the range considered in this paper the canard conditions are satisfied for the autonomous part of the system (6). So, following the results in [12], the canard critical value can be generalized to \( \lambda_c(D_v, D_w) \). Note that \( \lambda_c \) for an uncoupled oscillator becomes \( \lambda_c(0,0) \) in this notation.

In the coupled case of (4), the autonomous part resulting from the diffusion in (6) may change the canard critical value in each oscillator to a value \( \lambda_c(D_v, D_w) \). Then this quantity can be used to test for the influence of the coupling on localization. For example, suppose that \( \lambda_1 < \lambda_c(D_v, D_w) \) and \( \lambda_c(D_v, D_w) < \lambda_2 < \lambda_c(0,0) \) in the absence of any other contribution such as non-autonomous forcing effects. Then the first oscillator is in a SAO regime while the second one is still in a LAO regime, even though \( \lambda_2 < \lambda_c(0,0) \); that is, the system exhibits a localized state due to diffusion.

In Appendix B we derive an approximate expression (27) for the canard critical
value corresponding to (6)

\[ \lambda_c(D_v, D_w) = -\gamma (1 + D_v - D_w) / (2 f_{vv}^3) \left[ \gamma (1 + D_v - D_w) f_{vw} f_{vv} + \gamma (1 + D_v - D_w) f_{wv} - 2 (1 + D_v) f_{vv}^2 \right] \epsilon + O(\epsilon^{3/2}) \].  

(8)

For the parameters used in our simulations, we obtain an analytical approximation \( \lambda_c(0,0) \approx 0.014 \) which is within the \( O(\epsilon^{3/2}) \) correction in (8) of the numerical results of Figures 4. In the following we use the numerically obtained value of \( \lambda_c(0,0) = 0.0155 \) for the parameters used in this study.

In Figure 5 we show the graphs of the analytical prediction of \( \lambda_c(D_v, D_w) \) as a function of \( D_v \) and \( D_w \). In general, \( \lambda_c(D_v, D_w) \) increases with \( D_v \) and decreases with \( D_w \). This value is useful in predicting localized behavior, when the non-autonomous part of the equation consists of SAO which can be neglected to leading order.

2.3 The effective bifurcation parameters: \( \lambda_k^{\text{eff}} \)

As noted above, the coupling in the oscillators influences the dynamics through two aspects, namely, the autonomous and non-autonomous parts of the oscillator. The non-autonomous part can be viewed as the forcing exerted to each oscillator by the other one which moves the nullclines in a dynamic fashion, thus effectively transforming the value of \( \lambda_k \) to a periodic function depending not only on the diffusion coefficients but on the dynamic variables of the forcing oscillator. We denote it by \( \lambda_k^{\text{eff}}(D_v, D_w, V_j, W_j) \). This dynamical quantity, rather than a constant value, has to be compared against the canard critical value \( \lambda_c(D_v, D_w) \) at some specific times in order to understand the nature of localized solutions. Specifically, in Sections 3 and 4 we show a number of cases in which fluctuations in \( \lambda_k^{\text{eff}} \) above or below \( \lambda_c(D_v, D_w) \) lead to LAO or SAO, respectively. Then this quantity lends a viewpoint complementary to the canard critical value, \( \lambda_c(D_v, D_w) \).

The effect of forcing on relaxation type oscillators has been found to result in richer patterns both experimentally and theoretically [34, 43]. A forcing approach has been also used in [6, 7] to study localized patterns in the Belousov-Zhabotinsky reaction.

We define

\[ \lambda_k^{\text{eff}}(D_v, D_w, v_j, w_j) = \lambda_k + \gamma (D_v - D_w) v_j - D_w w_j. \]

(9)

Substituting the value \( \lambda_k^{\text{eff}} \) in Eq. (4) we get

\[
\begin{align*}
v'_k &= f(v_k, w_k) - \frac{\epsilon}{\gamma}[ -\lambda_k^{\text{eff}}(D_v, 0, v_j, w_j) + \gamma (1 + D_v) v_k ], \\
w'_k &= \epsilon[ -\lambda_k^{\text{eff}}(D_v, D_w, v_j, w_j) + \gamma (1 + D_v - D_w) v_k - D_w w_k].
\end{align*}
\]

(10)

Note that (10) has the same form as (6) with \( \lambda_k^{\text{eff}} \) replacing \( \lambda_k \). From (9) it is clear that \( \lambda_k^{\text{eff}} \) is time-dependent through \( v_j \) and \( w_j \) for \( j \neq k \). The definition of \( \lambda_k^{\text{eff}} \) is based on perturbations to the value of \( \lambda_k \) in the \( w_k \) equation, since it is clear from (4) that...
a shift in $\lambda_k$ translates directly into a shift in the $w$-nullcline with the same order of magnitude. As discussed in Section 2.1, small variations in the $w$-nullcline can result in $O(1)$ transitions between SAO and LAO. Perturbations to $\lambda$ in the $v_k$ equation do not in general trigger the canard explosion, since these changes have a coefficient of $O(\epsilon)$ and are in practice higher order corrections to the nullcline.

3 Analysis for localized solutions

In this section we analyze several mechanisms by which localized solutions are created as a consequence of diffusive coupling. By looking at the expressions for $\lambda_c(D_v, D_w)$ and $\lambda_k^{\text{eff}}$, we explain how the coupling coefficients affect the dynamics of the oscillators. For example, when $D_v > 0$ or $D_w > 0$ there can be a shift in the canard critical value $\lambda_c(D_v, D_w)$ which effectively places $\lambda_1$ or $\lambda_2$ in different oscillatory regimes (LAO or SAO) as compared to the uncoupled case. In addition, there can be a dynamic variation in $\lambda_k^{\text{eff}}$ relative to $\lambda_c(D_v, D_w)$ and/or relative to the location of oscillator $k$ in the phase plane, which plays a role similar to selecting parameter regimes for SAO or LAO. We relate these effects to stabilization and destabilization of certain dynamics by the coupling coefficients $D_w$ and $D_v$.

3.1 Destabilization of SAO by $D_w$

In Figure 6 we consider subthreshold values of $\lambda_k < \lambda_c(0, 0)$ ($\lambda_2 = .01$, and $\lambda_1 = .015$) so that without coupling, the oscillators would exhibit only SAO. The presence of the coupling ($D_v = 0$ and $D_w = .05$) decreases the canard critical value, $\lambda_c(D_v, D_w)$, which plays an important role in the resulting localized state. The key features of this case are:

i) $\lambda_1$ is close to $\lambda_c(0, 0)$, so that for $D_w \neq 0$ the critical value $\lambda_c(D_v, D_w) < \lambda_1$,

ii) $\lambda_2$ is less than both $\lambda_c(0, 0)$ and $\lambda_c(D_v, D_w)$

iii) $\lambda_2$ is sufficiently small so that fluctuations in $\lambda_2^{\text{eff}}$ do not drive $v_2$ and $w_2$ to LAO.

Conditions ii) and iii) maintain the SAO in the second oscillator, and i) causes LAO in the first oscillator, thus yielding the localized state. Note that the combination of the three conditions is important: since $v_2$ and $w_2$ remain small they can be neglected in predicting the behavior of $v_1$ and $w_1$. Then, the threshold for LAO in oscillator 1 is given by $\lambda_c(D_v, D_w) < 0.015$, so that $\lambda_1 > \lambda_c(D_v, D_w)$.

The localization considered in Figure 6 above holds for a range of values of $\lambda_1 > \lambda_c$ ?, holding $\lambda_2$ fixed. However, for larger values of $\lambda_2$, keeping all other parameters fixed, the localized oscillation is lost to an asynchronous LAO pattern as shown in Figure 13 (Section 4.1). There condition iii) is violated, leading to transitions from localization to LAO. If both $D_w$ and $D_v$ are nonzero, one can observe localized oscillations over a larger range of $\lambda_2$ and $\lambda_1$, as we show next.
3.2 Stabilization of SAO by $D_v$ and $D_w$

We explore two types of localized behavior which result from a stabilization of SAO by the coupling. In the first case, the coupling limits the variation due to non-autonomous effects, while in the second case a key ingredient is the communication of the non-autonomous effects through the coupling.

**Controlled variation in $\lambda_k^{\text{eff}}$**

In Figure 7 we show localized behavior for $\lambda_1, \lambda_2 > \lambda_c(0, 0)$ ($\lambda_1 = .02$ and $\lambda_2 = .016$) and $D_w = D_v = .05$. In the absence of coupling, both oscillators are in the LAO regime.

The key factors for this localized phenomenon are:

i) $\lambda_1 > \lambda_c(D_v, D_w)$

ii) $\lambda_2 < \lambda_c(D_v, D_w)$

iii) The fluctuations in $\lambda_2^{\text{eff}}$ are not sufficient to drive $v_2$ and $w_2$ to LAO.

In the absence of non-autonomous effects, conditions i) and ii) would be sufficient to guarantee a localized state, with oscillator 1 in LAO and oscillator 2 in SAO. However, as mentioned in Section 3.1 and shown in Section 4.1, the fluctuations in $\lambda_2^{\text{eff}}$ may exceed $\lambda_c(D_v, D_w)$, providing a possibility for a shift to LAO for oscillator 2. So we consider the range of $\lambda_2^{\text{eff}}$ to verify that oscillator 2 remains in SAO. Then fluctuations in $\lambda_2^{\text{eff}}$ are negligible, so that i) implies that oscillator 1 has LAO.

The range of $\lambda_2^{\text{eff}}$ can be approximated by substituting the range of $v_1$ and $w_1$ for LAO into (9). Then the approximate range of $\lambda_2^{\text{eff}}$ is $\lambda_c - D_w \max(w_j), \lambda_c - D_w \min(w_j)$, neglecting $v_2$ and $w_2$ for SAO. Since $w_j > 0$ for all but a very small time interval, effectively $\lambda_2^{\text{eff}} < \lambda_c(0.05, 0.05)$. Note also that $D_v = D_w$ in (9) so that the variation in $\lambda_2^{\text{eff}}$ is decreased compare with the case $D_v = 0$ and $D_w > 0$, so that $D_v$ has a stabilizing effect on the localized state.

This phenomenon is also observed for smaller values of $\lambda_2$, in particular, for values of $D_v$ and $D_w$ for which $\lambda_2^{\text{eff}} < \lambda_c(D_v, D_w)$ as in Figure 6. By increasing $\lambda_2$ above .017, we observe numerically a transition to asynchronous LAO for both oscillators, as expected for $\lambda_2 > \lambda_c(0.05, 0.05) \approx .017$.

**Increased variation in $\lambda_k^{\text{eff}}$**

Figure 1 shows a second example of stabilized localized oscillations, with $\lambda_1 = .023, \lambda_2 = .016, D_v = 0$ and very small $D_w = .01$. In this case the mechanism for localized oscillations is different than above, owing primarily to four factors:

i) $\lambda_2$ slightly larger than $\lambda_c(D_v, D_w)$

ii) $\lambda_1$ significantly larger than $\lambda_c(D_v, D_w)$

iii) Significant variation in $\lambda_2^{\text{eff}}$, driven by $v_1$ and $w_1$.

iv) The coupling is very small, so that $\lambda_c(D_v, D_w) \approx \lambda_c(0, 0)$.
Condition ii) gives large enough oscillations in $v_1$ and $w_1$ which causes iii). Due to i), we observe that $\lambda_2^{\text{eff}}$ falls below $\lambda_c$ for significant time intervals, driving the second oscillator to SAO. Then the fluctuations in $\lambda_1^{\text{eff}}$ are negligible, so ii) implies that the first oscillator remain in LAO.

Condition iv) guarantees that the forcing of the second oscillator by the first is not too large, even though $v_1$ and $w_1$ exhibit LAO. In contrast, as $D_w$ increases, $\lambda_c(D_v, D_w)$ is shifted and the fluctuations in $\lambda_k^{\text{eff}}$ increase for both $k = 1, 2$, eventually reaching the state where the interactions between the oscillators is strong enough to destabilize the localized oscillations to anti-phased LAO’s, discussed in Section 4.

### 3.3 Destabilization of localized solutions to SAO by $D_v$

In Figure 8 we demonstrate how parameters in a localized regime can be destabilized by increasing $D_v$. There we take $\lambda_1 = 0.02$, $\lambda_2 = 0.012$. For very small coupling, we obtain localized solutions; this is not surprising since $\lambda_1$ is in the LAO regime and $\lambda_2$ is in the SAO regime. When we increase the coupling to $D_v = .1$ with $D_w = 0$, we find that the localized oscillations lose stability to SAO for both oscillators. (There is typically a long transient of mixed mode oscillations (see Section 4.2) before both oscillators reach SAO.) Here the key factors are:

1. $\lambda_c(D_v, D_w)$ increases with $D_v$
2. $\lambda_1^{\text{eff}}(D_v, D_w) < \lambda_c(.1, 0)$ for part of the trajectory
3. $v_1$ increases through zero when $\lambda_1^{\text{eff}}(D_v, D_w) < \lambda_c(.1, 0)$
4. $\lambda_2$ is well below $\lambda_c(.1, 0)$

Condition i) would be enough to cause SAO in the first oscillator for values of $\lambda_1$ closer to $\lambda_c(0, 0)$. For larger values of $\lambda_1$ as in Figure 8 a complete description can only be obtained by considering the phase plane and $\lambda_1^{\text{eff}}$, as described by conditions ii) and iii). As shown in Figure 8-b, $\lambda_1^{\text{eff}}$ is subthreshold ($\lambda_1^{\text{eff}} < \lambda_c(D_v, D_w)$) for the part of the trajectory on which the oscillations either return to the left branch of the $v-$nullcline (SAO), or follow the LAO cycle (see Figure 3-a). The subthreshold value of $\lambda_1^{\text{eff}}$ determines that the system takes the SAO route. Due to condition iv) $(v_2, w_2)$ is also in SAO so that the localized state is lost.

These patterns can also be sensitive to parameters changes (or noise). In Section 4, we show how mixed mode asynchronous patterns can be obtained with slight variations in $\lambda_k$, $D_v$ and $D_w$.

### 3.4 Mixed-mode localized solutions

In these patterns one of the oscillators remains in the SAO regime, while the second alternates between periods of SAO and LAO. The dynamics are sensitive to small parameter changes, but they can be observed for different values of the coupling and the bifurcation parameters. Synchronized mixed-mode oscillations have been found in strongly diffusively coupled neural models [16]. To our knowledge, localized mixed-mode oscillations of the type shown here have not yet been reported.
Regular mixed-mode localization

In Figures 9 and 10 we show two types of regular mixed-mode localized solutions, where there is a fixed number of SAO and LAO in each period. In both cases $\lambda_1 = .0168$ and $\lambda_2 = .0135$, but different solutions are observed by varying $D_v$ and $D_w$. Recall that these coupling coefficients compete in the destabilizing and stabilizing effects on SAO.

In Figure 9 we consider $D_v = .1$, $D_w = .05$. In this case there is an interplay between the fluctuations in $\lambda_1^{\text{eff}}$ and the location of the oscillators in the phase plane. The main features of these solutions are:

i) $\lambda_1 \neq \lambda_2$, resulting in phase differences when both oscillators have SAO,
ii) $\lambda_1 > \lambda_c(1,.05)$, but $\lambda_1$ is close to $\lambda_c(1,.05)$.
iii) $\lambda_2 < \lambda_c(1,.05)$, with $\lambda_2$ a significant distance from $\lambda_c(1,.05)$.
iv) $v_1$ increases through zero when $\lambda_1^{\text{eff}}(D_v,D_w) < \lambda_c(1,.05)$

Condition iii) allows $(v_2,w_2)$ to remain in SAO, as long as the coupling is not large. The mixed-mode behavior in the first oscillator can then be seen from a combination of the other conditions. We begin by considering the system when both oscillators exhibit SAO. Points i) and ii) imply that $\lambda_1^{\text{eff}}$ fluctuates about $\lambda_c(1,.05)$, with a net effect of $\lambda_1^{\text{eff}} > \lambda_c(1,.05)$. Then the SAO of oscillator 1 gradually grow in amplitude, with an eventual transition to LAO due to condition ii). To complete the mixed-mode cycle points ii) and iv) combine to drive the first oscillator back to SAO. The forcing of $(v_1,w_1)$ through the coupling with $(v_2,w_2)$ is large enough to cause fluctuations in $\lambda_1^{\text{eff}}$, so that it drops sufficiently below $\lambda_c(1,.05)$ as $v_1$ increases through zero (see Figure 9b). As in Section 3.3, this forces the system back to the left branch of the $v$-nullcline and back into the SAO regime. Then the cycle repeats.

Another mechanism for regular mixed mode oscillations is shown in Fig. 10 for $D_v = .05$ and $D_w = .1$, with $\lambda_1$ and $\lambda_2$ as above. Since the canard critical value is reduced as compared to the previous case, that is, $\lambda_c(0.05,.1) < \lambda_c(1,.05)$ the key conditions are similar, but the variations in $\lambda_1^{\text{eff}}$ and $\lambda_2^{\text{eff}}$ have different effects.

i) $\lambda_1 \neq \lambda_2$, resulting in phase differences when both oscillators have SAO,
ii) $\lambda_1 > \lambda_c(0.05,.1)$, but $\lambda_1$ is close to $\lambda_c(0.05,.1)$.
iii) $\lambda_2 < \lambda_c(0.05,.1)$, with $\lambda_2$ closer to $\lambda_c(0.05,.1)$ as compared with the previous case.
iv) Comparison with phase plane

As above, an analysis of $\lambda_2^{\text{eff}}$ can give a partial description of the phenomenon, without studying the full phase plane dynamics. Again we begin by considering the initial state where both oscillators exhibit SAO. Conditions i) and ii) again yield gradual growth in these SAO for $(v_1,w_1)$. The difference as compared with the regular mixed mode oscillations discussed above is condition iii). In this case it allows increasing oscillations in $(v_1,w_1)$ to drive $\lambda_2^{\text{eff}}$ sufficiently above $\lambda_c(0.05,.1)$, so that $(v_2,w_2)$ exhibits one LAO per cycle. This LAO in $(v_2,w_2)$ forces $\lambda_1^{\text{eff}}$ well below $\lambda_c(0.05,.1)$, so that $(v_1,w_1)$ remains in SAO. The feedback through fluctuations in $\lambda_2^{\text{eff}}$ is also sufficient to
force the second oscillator back to the SAO, and the cycle repeats.

**Irregular mixed-mode localization**

In Figures 11 and 12 we show irregular mixed-mode localized oscillations. In Fig. 11 the values of $\lambda_1$, $\lambda_2$ and $D_v$ are as in Fig. 9 (for which regular mixed-mode oscillations are observed) and $D_w = 0.072$. In Fig. 12 $\lambda_1$ is slightly smaller than in Fig. 9. The difference in the number of SAO and LAO can be explained through secondary bifurcations in canards in systems with more than two degrees of freedom, with the number of SAO’s and LAO’s dependent on initial conditions and reset values following LAO’s [14]. However, a detailed analysis of this phenomenon is outside the scope of this work.

4 **Asynchronous LAO patterns**

In this Section we demonstrate a number of patterns in which both oscillators exhibit LAO. For most of these phenomena, a careful phase plane analysis is required to completely describe the behavior. Nevertheless, we outline some cases in which the expressions for $\lambda_c$ and $\lambda_k^{\text{eff}}$ can lend some insight into the dynamics.

4.1 **Destabilization of localization and SAO by $D_w$**

Localized solutions shown in Figure 6 shift to LAO antiphased pattern as $\lambda_2$ increases. In Figure 13 we show the case for $\lambda_1 = .015$, $\lambda_2 = .012$, $D_w = .05$, $D_v = 0$. Note that the parameter values are the same as in Figure 6, with the exception of an increase in $\lambda_2$. Then the SAO are increased, so that the fluctuations in $\lambda_k^{\text{eff}}$, together with the new relative position of $v_2$ to its nullcline, force the system to asynchronous LAO. Therefore a phase plane analysis is required to predict this transition.

One can also obtain anti-phased LAO for $\lambda_1 = \lambda_2$, as shown in Figure 14 for $\lambda_1 = \lambda_2 = .01$, $D_v = 0$, and $D_w = .1$. Even though both $\lambda_k$’s are well within the SAO regime for the uncoupled system, the coupling is sufficient to drive the system to LAO. Here the main factors are:

i) Break of symmetry in the initial condition. (Here we have used $v_1(0) = .03$, $w_1(0) = .01$, $v_2(0) = -.3$, and $w_2(0) = -.1$)

ii) $\lambda_k^{\text{eff}} > \lambda_c(0, .1)$ for sufficiently large values of $|\gamma v_k + w_k|$ in (9)

iii) $\lambda_k^{\text{eff}} > \lambda_c(0, .1)$ when $v_k$ increases through 0.

The asymmetric initial conditions lead to anti-phased oscillations, which are necessary for Condition ii). Then $\lambda_k^{\text{eff}} > \lambda_c(0, .1)$ for the crucial part of the dynamics, pushing the oscillator onto the trajectory of LAO. Given condition (iii), these LAO are then sustained.

In contrast, if we consider identical, in-phase oscillations with $\lambda_1 = \lambda_2 < \lambda_c$ as in Figure 14, or if the initial conditions are similar for the two oscillators, then from (9)
we find that $\lambda_k^{\text{eff}} \sim \lambda_k$ and conditions ii) and iii) are not satisfied. Then in-phase LAO can not be sustained, and the system moves to SAO.

### 4.2 Mixed mode patterns and irregular LAO

Here we show some of the mixed mode patterns, composed of periods of both SAO and LAO and irregular LAO. In the previous section we noted that localized oscillations can destabilize to SAO, or to these mixed mode patterns. Although a detailed study of the phase plane is necessary to completely predict these patterns, the behavior of $\lambda_k^{\text{eff}}$ suggests conditions under which these patterns are observed.

#### Mixed mode patterns

In this section we show both coherent and incoherent mixed mode states. As in Section 3.4, mixed-mode refers to behavior that alternates between SAO and LAO. By coherent mixed mode states, we mean that the oscillators show phase locked behavior when in the LAO part of the cycle, while an incoherent mixed mode state is one where the LAO part of the cycle is not phase locked. These different types of mixed mode oscillations have qualitatively similar interactions between the oscillators. Both types depend on three common key factors:

i) One oscillator is above threshold, for example, $\lambda_1 > \lambda_c(D_v, D_w)$,

ii) $\lambda_1$ is close to $\lambda_c(D_v, D_w)$, so that fluctuations in $\lambda_1^{\text{eff}}$ may cause transitions in behavior.

iii) $\lambda_2$ is well below the critical value $\lambda_c(D_v, D_w)$

Factors i) and ii) influence the length of the alternating periods of SAO and LAO, driven by oscillator 1. As discussed in Section 3.4, these factors have a net effect of $\lambda_1^{\text{eff}} > \lambda_c(D_v, D_w)$, so that if oscillator 1 is initially in the SAO regime, the amplitude of its oscillations grows until it eventually makes the transition to LAO due to condition ii). From factor iii) we see that $\lambda_2^{\text{eff}} < \lambda_c$, so that the second oscillator maintains SAO until the first oscillator is in LAO. For smaller values of $\lambda_2$ the transition of the second oscillator to LAO is slaved to the first oscillator, so that LAO in the second oscillator immediately follows the first. The proximity of $\lambda_k$ to $\lambda_c(D_v, D_w)$ influences fluctuations in $\lambda_k^{\text{eff}}$ for both $k = 1, 2$, which in turn influences the length of the LAO part of the cycle, as we discuss in particular cases below.

In Figure 15 we show coherent mixed mode patterns for $\lambda_1 = .017, \lambda_2 = .01, D_v = .1, D_w = 0$, where a single LAO follows a fixed period of SAO. Then the LAO in the second oscillator, slaved to the first, creates a significant variation in $\lambda_1^{\text{eff}}$. Here $\lambda_2$ is sufficiently small so that the second oscillator returns to SAO following the first and the cycle repeats.

Next we see how variations in $\lambda_k$ for $k = 1, 2$ can change these mixed mode oscillations. Figure 16 shows incoherent mixed mode oscillations, where the behavior of the LAO is no longer phase locked, for $\lambda_1 = .02, \lambda_2 = .012, D_v = .1, D_w = 0$. Here the increased values of $\lambda_1$ and $\lambda_2$ play a crucial role in the difference between the coherent and incoherent mixed modes states shown in Figures 15 and 16, respectively. In
Figure 16 the fluctuations in $\lambda_1^{\text{eff}}$ drop below $\lambda_c(D_v, D_w)$ less frequently, so that the first oscillator has a stronger preference for the LAO state than in Figure 15. Similarly, fluctuations in $\lambda_2^{\text{eff}}$ make LAO more likely in the second oscillator in Figure 16. Then the LAO’s of the two are no longer phase locked, and the second oscillator enters LAO before the first. Thus we observe the incoherent mixed mode oscillations, since condition iii) plays a weaker role in the dynamics of the LAO for increased values of $\lambda_2$.

A fourth crucial element in maintaining this pattern is:

iv) (De)stabilizing effects on LAO and SAO related to the magnitude of $D_v$ and $D_w$

As seen in Section 3, increasing $D_v$ and decreasing $D_w$ favors SAO. Then in Figure 15, conditions iii) and iv) lead to LAO in oscillator 2 which are slaved to oscillator 1. Increasing $D_v$ while fixing the other parameters as in Figure 15, we observe that the mixed mode solutions shown there destabilize to SAO for both oscillators. Decreasing $D_v$ and increasing $D_w$ destabilizes the mixed-mode state to LAO for both oscillators.

Irregular LAO
We show irregular LAO in Figure 17 for $\lambda_1 = .017 = \lambda_2$, $D_v = .2$, $D_w = .1$. This phenomenon can be observed by starting with initial conditions such as the mixed-mode oscillations in Figure 15, and increasing the values of $\lambda_2$, $D_v$, and $D_w$ accordingly. Several aspects of the parameter values contribute to this phenomenon:

i) $\lambda_k$ is near $\lambda_c(D_v, D_w)$ for both $k = 1, 2$,
ii) Moderate values of coupling $D_v$ and $D_w$
iii) $D_v > D_w$

Condition i) allows fluctuations in $\lambda_k^{\text{eff}}$ that cause occasional excursions to the SAO regime. From the computations we observe that this aspect is crucial for the irregularity; for larger values of $\lambda_1 = \lambda_2$ these oscillations synchronize to regular LAO. Factor ii) refers to the range of the coupling coefficients $D_v$ and $D_w$ which are large enough to destabilize localization, as seen in previous sections, but not large enough to encourage synchronization, as in [16]. Condition iii) balances the competitive effects of $D_v$ and $D_w$: increasing $D_w$ alone contributes to asynchronized LAO, as shown in Figures 13 and 14, while increasing $D_v$ destabilizes LAO, as in Figure 8 and the mixed-mode oscillations in Figures 15 and 16. Thus, for these intermediate values of the coupling, while keeping $\lambda_k$ near $\lambda_c$, fluctuations in $\lambda_k^{\text{eff}}$ play a significant role in the irregularity.

5 Discussion
In this study we demonstrate and analyze the mechanisms of various types of localized patterns in a diffusively coupled model of calcium (relaxation) oscillators. In addition to the classical localized patterns with each oscillator displaying either LAO or SAO but not both, we found MMO localized patterns in which one oscillator displays SAOs and
the other alternate between LAOs and SAOs either in a regular or irregular manner. We demonstrate that the patterns presented here can be explained in a self-consistent manner by extending concepts developed for the analysis of the canard phenomenon in two dimensions [9, 11]. Two key quantities, the perturbed canard critical value and the effective bifurcation parameter, capture the autonomous and non-autonomous effects introduced through the coupling. These quantities are valuable diagnostics for explaining and predicting the pattern dynamics, particularly for the localized patterns, since these states appear by a variety of mechanisms.

The coupling, heterogeneity, and the canard phenomenon combine to support localization and MMOs in a number of regimes. In some cases, by increasing $D_w$, SAOs can be destabilized in only one oscillator in a system where the uncoupled oscillators both display SAOs. In other cases, by increasing both $D_v$ and $D_w$, SAOs can be stabilized in only one oscillator in a system where the uncoupled oscillators both display LAOs. Both mechanisms have the common feature that the localized patterns appear when the two oscillators are in different states, displaying either LAOs or SAOs but not both. A different type of mechanism is responsible for the generation of mixed-mode oscillatory patterns. There, when uncoupled, the oscillators display either SAOs or LAOs but not both. By increasing both $D_v$ and $D_w$, the LAO regime is partially destabilized and the corresponding oscillator enters a MMO regime.

The key contributing factors for localization are different from other prototypical examples, such as the localized patterns observed both experimentally [1, 2] and theoretically [3, 6, 7] in the globally coupled Belousov-Zhabotinsky reaction. These patterns, with each oscillator stabilized in a different amplitude regime, are obtained for values of the global feedback parameter that are neither too large nor too small. In that setting localization is a consequence of the inhibitory global coupling rather than diffusive (local) coupling. Localized patterns have been also obtained in non-relaxation oscillatory systems as well [4, 5].

The MMO patterns presented here are an additional consequence of the coupling. Single two-dimensional relaxation oscillators undergoing a supercritical Hopf bifurcation display either LAO or SAO but not both. The possibility of obtaining oscillatory patterns in which both LAO and SAO are present requires a higher dimensional system with at least one fast and two slow equations. Note that the present coupled system has two fast and two slow variables. Three dimensional systems of this type produce mixed-mode oscillations (MMO) in which SAOs alternate with LAOs either in a regular or irregular way [19, 23, 24, 25, 26, 27, 44] (see also references therein). Quasi-synchronized MMO have also been obtained in a system of strongly diffusively coupled two-dimensional relaxation oscillators with two fast and two slow variables [16]. There both oscillators alternate between LAOs and SAOs and were almost synchronized as a consequence of the strong coupling. The MMO’s observed in the present study are different from the ones found in [16]; when one operates away from the strong coupling limit, a richer variety of patterns appear, including localized and asynchronous MMOs. The experimental and theoretical irregular (in amplitude and frequency) patterns observed in experiments and simulations of the BZ reaction [1, 2, 3] are a higher dimensional manifestation of irregular MMO patterns that have been observed in globally coupled relaxation oscillators. A detailed analysis of these patterns in higher dimen-
sional systems is outside the scope of this study. For some insight into the techniques used to analyze MMOs in three dimensional systems we refer to [14, 16, 23, 29].

Among the non-localized but still interesting patterns we found are LAO antiphase patterns for parameter values for which both uncoupled oscillators are in a SAO regime. Furthermore, moderate increases in the coupling can also partially destabilize SAO, leading to an antiphased MMO regime. LAO antiphase patterns have been previously found for the coupled van der Pol oscillator [32] and the globally coupled Belousov-Zhabotinsky reaction [3].

Acknowledgments

The authors want to thank Nancy Kopel for reading an earlier version of this manuscript, and Martin Wechselberger and Martin Krupa for useful discussions. This work was partially supported by the Burroughs Wellcome Fund (HGR), NSF-DMS 0072311 (RK) and a NSERC discovery grant (RK).

References


A The two-pool model

We give a brief summary of the two-pool model and a common transformation used to analyze the oscillations. We follow [36]. The two-pool model derives its name from the original assumption of two distinct internal Ca$^{2+}$ stores in the cell, one sensitive to IP$_3$ (inositol (1,4,5)- triphosphate) and the other sensitive to Ca$^{2+}$, with concentrations denoted $c$ and $c_s$, respectively. The equations describe the interaction of $c$ and $c_s$, which have the dimensional form as summarized in Keener and Sneyd [36],

$$\frac{dc}{dt} = r - kc - \mathcal{F}(c, c_s) \quad \frac{dc_s}{dt} = \mathcal{F}(c, c_s)$$

Here $\tau$ is time, $r$ is the influx of Ca$^{2+}$ due to IP$_3$, and Ca$^{2+}$ is pumped out at a rate $kc$. Since $r$ is constant for constant IP$_3$, by varying $r$ one can study variations in the behavior of the system due to IP$_3$. The function $\mathcal{F}$ describes the flux from the IP$_3$-sensitive pool to the Ca$^{2+}$-sensitive pool, and it is a combination of uptake, release, and leakage with rate $-k_fc_s$. In particular

$$\mathcal{F}(c, c_s) = \mathcal{J}_{\text{uptake}} - \mathcal{J}_{\text{release}} - k_fc_s$$

$$= \frac{U_1c^n}{K_1^n + c^n} - \frac{U_2c_s^m}{K_1^m + c_s^m} \frac{c^\rho}{K_3^\rho + c^\rho} - k_fc_s.$$

The positive feedback of Ca$^{2+}$ release is evidenced by the dependence of $\mathcal{J}_{\text{release}}$ on $c$. The system is non-dimensionalized using

$$V_k = c/K_1, \quad W_k = c_s/K_2, \quad t = \tau k, \quad \epsilon = kK_2/U_2,$$

$$\mu = r/(kK_1), \quad \alpha = K_3/K_1, \quad \beta = U_1/U_2, \quad \gamma = U_1/U_2, \quad \delta = k_fK_2/U_2, (13)$$

to obtain (1) with $D_w = D_v = 0$.

In [36] the following reduction for a single oscillator was proposed, substituting

$$\tilde{v}_k = W_k, \quad \tilde{w}_k = V_k + \gamma W_k$$

into the non-dimensionalized equations for a single oscillator,

$$\tilde{F}(\tilde{v}, \tilde{w}) = F(\tilde{w} - \gamma \tilde{v}, \tilde{v})$$

(15)

to get

$$\left\{ \begin{array}{l}
\tilde{v}'_k = \frac{1}{\mu} \tilde{F}(\tilde{v}_k, \tilde{w}_k), \\
\tilde{w}'_k = [\mu_k + \gamma \tilde{v}_k - \tilde{w}_k].
\end{array} \right.$$ (16)

for $k = 1, 2$. Then this system describes a FHN oscillator, with the $\tilde{v}$ and $\tilde{w}$-nullclines significantly different from the $v$- and $w$-nullclines of the system (4). The form of the nullclines in (16) are not convenient for the canard analysis used in this paper. Therefore we use the transformation (3) instead This transformation is ours, which can also be viewed as a linear transformation of (14). Throughout the paper we use the parameter values as in [36] $\alpha = .9, \beta = .13, \gamma = 2, \delta = .004$ and $\epsilon = .01$.
B The canard critical value for the canonical form

We follow [6] and extend our result to the case studied in this manuscript. The calculations are similar to those in [6]. We consider a system of the form
\[
\begin{cases}
  v' = F(v, w) + \epsilon \Psi(v, w, \lambda, \epsilon), \\
  w' = \epsilon G(v, w, \lambda)
\end{cases}
\]
where \( \Psi(v, w, \lambda, \epsilon) = \mathcal{O}(v, w, \lambda, \epsilon) \). We make the same assumptions as in Krupa et al [11, 12]. The canonical form is given by
\[
\begin{cases}
  v' = -w + v^2 - w h_1(v, w) + v^2 h_2(v, w) + \epsilon h_6(v, w, \lambda, \epsilon), \\
  w' = \epsilon \left[ v - \lambda + v h_3(v, w, \lambda) - \lambda h_4(v, w, \lambda) + w h_5(v, w, \lambda) \right],
\end{cases}
\]
where
\[
\begin{align*}
  h_1(v, w) &= \frac{2 G_v^{1/2} F_{vw}}{|F_w|^{1/2} F_{vv}} v + \mathcal{O}(w), \\
  h_2(v, w) &= \frac{2 G_v^{1/2} |F_w|^{1/2} F_{vvv}}{3 F_{vv}^2} v + \mathcal{O}(w), \\
  h_3(v, w, \lambda) &= \frac{|F_w|^{1/2} G_{vv}}{G_v^{1/2} F_{vv}} v + \mathcal{O}(w, \lambda), \\
  h_4(v, w, \lambda) &= -\frac{2 G_v^{1/2} |F_w|^{1/2} G_{v\lambda}}{F_{vv} |G_{\lambda}|} v + \mathcal{O}(w, \lambda), \\
  h_5(v, w, \lambda) &= \frac{G_w}{G_v^{1/2} |F_w|^{1/2}} v + \mathcal{O}(v, w, \lambda), \\
  h_6(v, w, \lambda) &= \frac{2 \Psi_v}{F_{vv}} v + \mathcal{O}(v^2, w, \lambda, \epsilon)
\end{align*}
\]
and all the function are evaluated at \((v, w, \lambda, \epsilon) = 0\).

Following [6] and [12] the following expression for \( \lambda_c \) can be calculated
\[
\lambda_c = L \frac{a_1 - 3 a_2 + 2 a_3 - 2 a_5 - 4 a_6}{8} \epsilon + \mathcal{O}(\epsilon^{3/2}),
\]
where
\[
\begin{align*}
  L &= \frac{2 G_v^{3/2} |F_{vv}|^{1/2}}{4 F_{vv} |G_{\lambda}|}, & a_1 &= \frac{\partial h_1}{\partial \hat{v}} = -\frac{2 G_v^{1/2} F_{vv}}{|F_w|^{1/2} F_{vv}}, & a_2 &= \frac{\partial h_2}{\partial \hat{v}} = \frac{2 G_v^{1/2} |F_w|^{1/2} F_{vvv}}{3 F_{vv}^2}, \\
  a_3 &= \frac{\partial h_4}{\partial \hat{v}} = \frac{|F_w|^{1/2} G_{vv}}{G_v^{1/2} F_{vv}}, & a_5 &= h_5 = \frac{G_w}{G_v^{1/2} |F_w|^{1/2}}, & a_6 &= \frac{\partial h_6}{\partial \hat{v}} = 2 \Psi_v F_{vv}^2.
\end{align*}
\]
where all the functions are evaluated at 0.

Substituting into (25) we get

$$
\lambda_{\epsilon} (\sqrt{\epsilon}) = - \frac{G_v^{3/2} |F_w|^{1/2}}{4 F_{vv} |G_\lambda|} \left[-a_1 + 3 a_2 - 2 a_3 + 2 a_5 + 4 a_6\right] \epsilon + \mathcal{O}(\epsilon^{3/2}) =
$$

$$
= - \frac{G_v}{2 F_{vv} |G_\lambda|} \left[ G_v F_{vvv} F_{vv} + G_v |F_w| F_{vvv} - |F_w| G_{vvv} F_{vv} + G_{vv} F_{vvv}^2 + 2 \Psi_v F_{WW}^2 \right] \epsilon + \mathcal{O}(\epsilon^{3/2}).
$$

(27)

where all the functions are calculated at 0.
Captions

Figure 1: Localized solution induced by diffusive coupling in a diffusively coupled two-pool model. (a) uncoupled case: both oscillators are in a LAO regime. (b) coupled case: one oscillator is in a LAO while the other is in a SAO regime.

Figure 2: Schematic representation of phase planes for system (7) for different values of $\lambda$. The nullclines of (7) are given by $w = f(v)$ and $w = g(v, \lambda)$ which are the solutions of $\bar{F}(v, w) = \bar{G}(v, w; \lambda) = 0$.

Figure 3: Phase plane for a single two-pool oscillator. (a) $\lambda < \lambda_c$: the system is in a SAO regime. (b) $\lambda > \lambda_c$: the system is in a LAO regime.

Figure 4: $v$ and $w$ traces for a single two-pool oscillator. (a) $\lambda < \lambda_c$: the system is in a SAO regime. (b) $\lambda > \lambda_c$: the system is in a LAO regime.

Figure 5: $\lambda_c(D_v, D_w)$ as a function of $D_v$ for different values of $D_w$. $\lambda_c(D_v, D_w)$ is given by eq. (8).

Figure 6: Localized solutions for a diffusively coupled two-pool model. ($v_1, w_1$) is in a SAO regime and ($v_2, w_2$) is in a LAO regime.

Figure 7: Localized solutions for a diffusively coupled two-pool model. ($v_1, w_1$) is in a SAO regime and ($v_2, w_2$) is in a LAO regime.

Figure 8: SAO solutions for a diffusively coupled two-pool model. (a) Both ($v_1, w_1$) and ($v_2, w_2$) are in a SAO regime. (b) Evolution of $\lambda_k^{\text{eff}}$ for $k = 1, 2$, compared with $\lambda_c(D_v, D_w)$ and with the dynamics of $v_1$ and $v_2$.

Figure 9: Regular mixed-mode localized solutions for the diffusively coupled two-pool model. ($v_1, w_1$) is in a SAO regime and ($v_2, w_2$) is in a mixed-mode oscillation regime with alternating single LAO and single SAO. (b) Evolution of $\lambda_k^{\text{eff}}$ for $k = 1, 2$, compared with $\lambda_c(D_v, D_w)$ and with the dynamics of $v_1$ and $v_2$.

Figure 10: Regular mixed-mode localized solutions for the diffusively coupled two-pool model. ($v_1, w_1$) is in a SAO regime and ($v_2, w_2$) is in a mixed-mode oscillation regime with one LAO alternating with three SAOs.

Figure 11: Irregular Mixed-mode localized solutions for a diffusively coupled two-pool model. ($v_2, w_2$) is in a SAO regime and ($v_1, w_1$) is in a mixed-mode oscillation regime with a single LAO alternating with 1-4 SAOs.

Figure 12: Irregular Mixed-mode localized solutions for a diffusively coupled two-pool model. ($v_1, w_1$) is in a SAO regime and ($v_2, w_2$) is in a mixed-mode amplitude regime with a single LAO alternating with 2-3 SAOs on average.

Figure 13: Antiphased LAO regime for the diffusively coupled two-pool model with $\lambda_1 > \lambda_c(D_v, D_w)$ and $\lambda_2 < \lambda_c(D_v, D_w)$. 
**Figure 14:** Antiphased LAO regime for the diffusively coupled two-pool model with \( \lambda_1 = \lambda_2 < \lambda_c(D_v, D_w) \).

**Figure 15:** Coherent mixed-mode oscillations for the diffusively coupled two-pool model, with \( \lambda_2 \) sufficiently below \( \lambda_c(D_v, D_w) \).

**Figure 16:** Incoherent mixed-mode oscillations for the diffusively coupled two-pool model.

**Figure 17:** Irregular oscillations for the diffusively coupled two-pool model with moderate values of the coupling.
Figure 1:
Figure 2:

Figure 3:
Figure 4:
Figure 5:

Figure 6:
Figure 7:
Figure 9:
Figure 10:

\[ \lambda_1 = 0.0168 \quad \lambda_2 = 0.0135 \quad D_v = 0.05 \quad D_w = 0.1 \]

Figure 11:

\[ \lambda_1 = 0.0168 \quad \lambda_2 = 0.0135 \quad D_v = 0.1 \quad D_w = 0.072 \]
Figure 12:

Figure 13:
Figure 14:

Figure 15:
Figure 16:

Figure 17: