Localized and asynchronous patterns via canards in coupled calcium oscillators

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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

Localized oscillatory patterns are characterized by one group of cells displaying large amplitude oscillations (LAO) and the remaining cells exhibiting small amplitude oscillations (SAO), an order of magnitude smaller in amplitude than the LAOs. Localization has been observed in chemical, biological and optical systems [1, 2, 3, 4, 5] and 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, 7, 8]. 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 [7, 8].

Our focus here is on different mechanisms that produce localization in a simple biochemical model of diffusively coupled calcium oscillations, also relevant for other systems of relaxation oscillators. Two important ingredients here are the relatively small coupling and heterogeneity in the population of oscillators. A third key factor is the canard phenomenon [9, 10, 11, 12, 13]. In two-dimensional (2D) relaxation oscillators undergoing a Hopf bifurcation, this phenomenon is sometimes referred to as the canard explosion, appearing as a sudden transition between the SAO and LAO regimes as a parameter passes through its canard critical value. In the context of the coupled system we compute both an effective canard critical value and an effective bifurcation parameter for each cell. The effective bifurcation parameters change over time, and for the individual cells it can be compared to the effective critical value to illustrate whether that cell engages in SAO or LAO activity, or a combination of the two.

The specific calcium oscillators considered in this paper are described by the canonical two pool model [14]. Although this model is too simple to reproduce the calcium dynamics in all its complexity, it has served as a basic prototypical model which captures the main features of calcium oscillations, well documented for the single cell model [15] (see Appendix A). The oscillatory dynamics depend on a control parameter IP$_3$ (inositol (1,4,5)-triphosphate) which regulates calcium release and controls the oscillations amplitude, thus playing the role of the bifurcation parameter for the canard phenomenon in the 2D single cell model. The canard structure is just one of a number of this model’s features found also in more general types of limit cycle-type oscillators. Then the relatively simple two-pool model is an ideal candidate for developing new methods for studying the interaction of coupling and the canard phenomenon. Through a new asymptotic technique we obtain analytical expressions and reduced systems which can be used to understand the mechanistic aspects of localized patterns and to make predictions about them. The approach does not depend on the particular model; we expect that it is valuable for the analysis of other diffusively coupled relaxation oscillators, since it is based primarily on the interaction of the bifurcation (control) parameter (related to IP$_3$ in the original application) and on the coupling parameters. In order to capture the broad range of effects which may occur in these systems, we have introduced a general diffusive coupling; the physiologically relevant one for calcium oscillators corresponds to a specific case within this general coupling.

The analysis of [7, 8] explained the mechanism for spatially localized oscillations for globally coupled Belousov-Zhabotinsky (BZ) reaction [1, 2, 3] and FitzHugh-Nagumo (FHN) models, where the canard phenomenon also played a critical role. In both models 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. In contrast, 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.

We summarize the historical context for the canard phenomenon, mentioning those results closely related to this study. The canard phenomenon in 2D was discovered by Benoit et al. [11] for the van der Pol (VDP) oscillator. It has been studied various different techniques: non-standard analysis [11], asymptotic [10, 16, 17], and geometric singular perturbation theory and blow-up [9, 12, 13]. 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. We follow Krupa and Szmolyan [12, 13] in our approach and in the calculation of the canard critical value, denoted by $\lambda_c$, which marks the sudden transition between the SAO and LAO regimes.

The canard phenomenon in 3D (or higher dimensions) is more generic than in 2D. While 2D systems can display SAO or LAO but not both for a fixed set of parameters, 3D systems can display mixed-mode oscillations (MMO) that alternate over time between SAO and LAO [18, 19, 20, 21, 22]. The diffusively coupled two-pool system studied here, a 4D system, is able to exhibit a more complex pattern: localized states of mixed-mode type (localized mixed-mode oscillations) where one oscillator is always in a SAO regime while the other alternates over time between LAO and SAO regimes. As we show in this manuscript, this pattern, which cannot be obtained for 2D and 3D systems, can nevertheless be explained by decomposing the 4D diffusively coupled two-pool model into two 2D forced (effectively 3D) subsystems, similarly to the analysis of localized patterns obtained in the globally coupled BZ reaction [7, 8].

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 MMOs are often found [7, 8, 19, 20, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34]. MMOs have been studied both analytically and numerically [18, 35, 36, 37, 38, 21], and in some cases the maximum number of subthreshold oscillations alternating with a large amplitude oscillation can be estimated [18]. However, global predictions are not always possible; the appearance and prevalence of subthreshold oscillations in a mixed mode state depends on initial conditions or the reset value after a large amplitude oscillation. Several approaches have been developed in some of the references mentioned above to deal with this type of problem by studying them as reduced two-dimensional systems evolving in time.
1.1 The model and strategy

Our starting point is the system of diffusively coupled calcium oscillators described by the two-pool model in a dimensionless form [15].

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

(1)

for \( j, k = 1, 2, j \neq k \), where

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

(2)

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 parameter \( \epsilon \) is very small indicating that the rate at which calcium flows from the \( IP_3 \) to the \( Ca^{2+} \) sensitive pools is very large. The parameter \( \mu_k \) is the bifurcation or control parameter related to \( IP_3 \), defining parameter regimes where oscillations are stable or unstable. The parameters \( D_v \) and \( D_w \) give diffusive coupling between individual cells. This choice of coupling, while not physiologically realistic, provides a simple first step in understanding the interaction of coupling, heterogeneity, and the canard phenomenon on localization. In particular the coupling term in the second equation in (2) is not realistic since the calcium pools in two different cells are not diffusively connected. However, this general form allows development of principles for the influences of coupling, which then can be applied to more complex models. 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.

A change of variables transforms the single cell two-pool model into a FHN-type system [15, 39], so although the coupling we use here is not global as in [7, 8], it is not unexpected that we can find localized behavior in the coupled system as in [7, 8]. An example of this behavior for (1) is shown in Figure 1 in terms of the convenient parameter \( \lambda_k \), which is just \(-\mu_k + \) a constant (see (3)). In the top graphs we show the oscillations for uncoupled non-identical oscillators, \( D_v = D_w = 0 \) and \( \lambda_1 \neq \lambda_2 \) (\( \mu_1 \neq \mu_2 \)). A key quantity for predicting SAO or LAO in each single relaxation oscillator is the canard critical value \( \lambda_c \), which delineates the parameter ranges for which the oscillator is in a SAO regime (\( \lambda_k < \lambda_c \)) and a LAO regime (\( \lambda_k > \lambda_c \)). For the uncoupled system shown in the top of Figure 1, both \( \lambda_1 > \lambda_c \) and \( \lambda_2 > \lambda_c \), consistent with the observation of LAO for each single oscillator. The value of \( \lambda_c \) can be estimated as a function of the parameters of the model using a geometric [12] or asymptotic [10] approach, as we show in Section 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. In our analysis we extend the idea of a canard critical value to the coupled system.

When there is coupling in (1) each oscillator is composed of two contributions, the autonomous and non-autonomous parts labeled with “$k$” and “$j$” respectively. As in [7,8] each member in the system (1) can be thought of as an autonomous oscillator forced by the non-autonomous part. The patterns studied here are the result of contributions from both parts, so that a simple yet important step is the transformation which allows these two contributions to be transparently identified. Then we can define two quantities which capture their effects on localized, MMO, and asynchronous LAO states:

- **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 autonomous part of a single oscillator, modified from the uncoupled case by those terms appearing in the coupled system as additional autonomous contributions. This quantity $\lambda_c(D_v,D_w)$, obtained by an extension of [7], plays a role similar to that of the canard critical value $\lambda_c$ for a single oscillator and reduces to it in the uncoupled case $D_v = D_w = 0$. Here we use the theory developed in [13].

- **The effective bifurcation parameters**, $\lambda_k^{\text{eff}}(D_v,D_w,V_j,W_j)$ for $k = 1, 2$ ($j \neq k$). 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 understand and predict (de-)stabilization of localization and other phenomena. The effect of forcing on relaxation type oscillators has been found to result in richer patterns both experimentally and theoretically [38, 40]. A forcing viewpoint has been used also in [7, 8] to study localized patterns in the BZ reaction. A related important aspect can be the timing of the variation of $\lambda_c(D_v,D_w)$ compared with the position of $V_k$ and $W_k$ in the phase plane, which we outline for specific cases.

In [6], a comparison of synaptic input strength to a time-dependent threshold at a key moment was used to determine whether a neuron is recruited into an active population or not. In the system with study in this paper, the comparison is between a dynamic variable and a time-independent threshold. This threshold still carries information about the coupling through its dependence on the diffusion coefficients.

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 [7, 13]. 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 form in which each uncoupled oscillator is of VDP-type: each uncoupled oscillator has activator and inhibitor variables whose nullclines are a cubic-like curve and a vertical line, respectively. The transformation we use here is different from the one used in [15] (see Appendix A) where the transformation resulted in a system of FHN-type rather than VDP-type; for the FHN-type the inhibitor nullcline is linear, non-vertical and non-constant. The form we use here is more suitable for identifying the autonomous and nonautonomous contributions. For each value of $k$ the coordinate change for the full transformation is given by

$$v_k = -\frac{V_k}{\gamma} - v_{\text{min}}, \quad w_k = \gamma W_k + V_k - w_{\text{min}}, \quad \lambda_k = - (\mu_k + \gamma v_{\text{min}}). \quad (3)$$

The transformation of variables, applied to the uncoupled oscillators, is a “rotation” of the nullclines followed by a translation which places the local minimum of the resulting cubic-like nullcline, $(v_{\text{min}}, w_{\text{min}})$, at the origin. Then we define

$$f(v, w) = F(-\gamma(v + v_{\text{min}}), v + v_{\text{min}} + (w + w_{\text{min}})/\gamma), \quad (4)$$

and by rescaling time, $t \rightarrow \epsilon t$, and substituting (3) and (4) into (1) we get

$$\begin{cases} v'_k = f(v_k, w_k) - \epsilon / \gamma \left[ -\lambda_k + \gamma (1 + D_v) v_k \right] + \epsilon D_v v_j, \\ w'_k = \epsilon \left[ -\lambda_k + \gamma (1 + D_v - D_w) v_k - D_w w_k + \gamma (D_w - D_v) v_j + D_w w_j \right], \quad (5) \end{cases}$$

for $k = 1, 2$.

For the parameters used in this paper, we find that $v_{\text{min}} \approx -0.3570$ and $w_{\text{min}} = 1.5503$. Note that for $D_w = 0$ (even for values of $D_v > 0$), system (5) is a VDP-type oscillator. This property is lost if $D_w > 0$. However, the form of (5) 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.

For the cases $D_v > 0$ and/or $D_w > 0$ system (5) can be seen as two forced autonomous oscillators; that is, two autonomous oscillators (terms with the subscript $k$),
each forced by the other one (terms with subscript \( j \)). In order to understand the dynamics of system (5) it is useful to decompose each one of these oscillators into its autonomous and non-autonomous parts. The autonomous part for (5) is

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

and clearly, the remaining terms give the non-autonomous part. Note that system (6) is an uncoupled one but it incorporates diffusive effects. In this way, system (6) can be seen as an intermediate description between the fully uncoupled and the fully coupled ones, that partially captures the effects of diffusion.

### 2.1 Canard phenomenon for the uncoupled case

First we review the canard phenomenon for two-dimensional oscillators, referring the reader to [9, 10, 12, 13] for a more thorough introduction. Consider the following system:

\[
\begin{aligned}
v' &= \hat{F}(v, w), \\
w' &= \epsilon \hat{G}(v, w; \lambda),
\end{aligned}
\]

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) and such that its local maximum is to the right of \( v = 0 \). 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 VDP oscillator case, \( G \) does not depend on \( w \); it is a vertical line. In the more general case that includes FHN type oscillators, we assume \( G \) can be written \( w = \hat{g}(v; \lambda) \).

We further assume that the nullclines \( w = \hat{f}(v) \) and \( w = \hat{g}(v; \lambda) \) (\( \hat{F} = 0 \) and \( \hat{G} = 0 \)) intersect at \((v_0, w_0) = (0,0)\) when \( \lambda = 0 \), and that for \( \lambda > 0 \), \((v_0, w_0)\) lies on the central branch of \( \hat{f} \). Precise mathematical statements of the former assumptions are given in Appendix B. We schematically illustrate this in Figure 2. The autonomous part (6) of system (5) satisfies the above conditions. In the special case of \( D_w = 0 \) in (6), the nullcline \( \hat{G} = 0 \) is the vertical line \( v = \lambda \gamma^{-1} (1 + D_v)^{-1} \).

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 [7, 13] 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 the 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 the limit cycle expands sharply, becoming a relaxation oscillator \([41, 42, 43, 44]\), 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. The amplitude of the limit cycle either increases slowly or remains constant as \( \lambda \) is increased. The dramatic transition from a “small” amplitude limit cycle to a “large” amplitude limit cycle is known as the canard phenomenon \([9, 10, 11, 12, 13, 45]\), which occurs for an exponentially small (in \( \epsilon \)) interval of values of \( \lambda \) in a neighborhood of \( \lambda_c \). Following \([13]\) and \([7]\), we calculate in Appendix B an asymptotic expansion \( \lambda_c \) in powers of \( \epsilon^{1/2} \), obtaining an analytical approximation \( \lambda_c \approx 0.014 \) for the parameters used in this study. For the single uncoupled oscillators \((D_v = D_w = 0)\) this analytical approximation is within the \( O(\epsilon^{3/2}) \) correction in (8) of the numerically obtained value, \( \lambda_c \approx 0.015330 \approx 1.4\epsilon + O(\epsilon^{3/2}) \) (taking \( \epsilon = .01 \)). In Figures 3 and 4 we show results for \( \lambda < \lambda_c \) and \( \lambda > \lambda_c \), and in the following sections we use the numerically obtained value of \( \lambda_c \) for comparisons with the coupled case.

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. (5), 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 Appendix B and \([12, 13]\)), Krupa and Szmolyan gave an approximate expression for \( \lambda_c \), the critical value of \( \lambda \) dividing between the SAO and LAO regimes \([13]\).

For \( D_v \geq 0 \) or \( D_w \geq 0 \), the singularity and non-degeneracy assumptions listed in Appendix B are satisfied by system (6), the autonomous part of system (5). So one expects the existence of a canard critical value \( \lambda_c(D_v, D_w) \) such that for values of \( \lambda < \lambda_c(D_v, D_w) \) (\( \lambda > \lambda_c(D_v, D_w) \)), system (6) is in a SAO (LAO) regime.

In Appendix B we derive \( \lambda_c(D_v, D_w) \) following \([7, 12, 13]\) for a canonical system. System (6) is brought to the canonical form (17) by substituting
\( f(v, w) \) from (4) and \(-\lambda + \gamma (1 + D_v - D_w) v - D_w w\) into \( F(v, w) \) and \( G(v, w; \lambda) \) in (17), respectively. Then one gets the following expression for the canard critical value

\[
\lambda_c(D_v, D_w) = -\epsilon \gamma (1 + D_v - D_w) [\gamma (1 + D_v - D_w) f_{vw} f_{vv} + \\
\gamma (1 + D_v - D_w) |f_w| f_{vww} - D_w f_{vuv}^2 - 2 (1 + D_v) f_{vuv}^2]/(2 f_{vuv}^3) + O(\epsilon^{3/2}).
\]

Note that \( \lambda_c \) for an uncoupled oscillator becomes \( \lambda_c(0,0) \) in this notation. Note also that \( \lambda_c(D_v, D_w) \) is independent of \( \lambda \); although the two oscillators may be heterogeneous (\( \lambda_1 \) and \( \lambda_2 \) are not necessarily equal), they still have a common value for \( \lambda_c(D_v, D_w) \).

In the coupled case of (5), 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 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 increased \( D_w \). 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 bifurcation parameter to an oscillating function depending not only on the diffusion coefficients but also on the dynamic variables of the forcing oscillator. We denote this dynamical quantity as \( \lambda_k^{\text{eff}}(D_v, D_w, V_j, W_j) \) and compare it 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, \( \lambda_c(D_v, D_w) \).

We define

\[
\lambda_k^{\text{eff}}(D_v, D_w, v_j, w_j) \equiv \lambda_k + \gamma (D_v - D_w) v_j - D_w w_j. \tag{8}
\]

Substituting the value \( \lambda_k^{\text{eff}} \) in Eq. (5) we get
\[
\begin{aligned}
    v'_k &= f(v_k, w_k) - \epsilon \left[-\lambda_k^{\text{eff}}(D_v, 0, v_j, w_j) + \gamma (1 + D_v) v_k \right] / \gamma, \\
    w'_k &= \epsilon [-\lambda_k^{\text{eff}}(D_v, D_w, v_j, w_j) + \gamma (1 + D_v - D_w) v_k - D_w w_k].
\end{aligned}
\]  

Note that (9) has the same form as (6) with \(\lambda_k^{\text{eff}}\) replacing \(\lambda_k\). From (8) it is clear that \(\lambda_k^{\text{eff}}\) is time-dependent through \(v_j\) and \(w_j\) for \(j \neq k\). Since the model includes the more general form of diffusive coupling with both \(D_v\) and \(D_w\), the expression for \(\lambda_k^{\text{eff}}\) captures several general effects. Fluctuations in \(v_j\) can increase or decrease \(\lambda_k^{\text{eff}}\) depending on the difference \(D_v - D_w\). In contrast, \(D_w > 0\) also decreases \(\lambda_k^{\text{eff}}\) since the significant fluctuations in \(w_j\) are positive. In the following sections we illustrate the different influences of these coupling coefficients. For example, \(D_v\) alone provides positive feedback, contributing to localized and asynchronous MMO’s, as well as transitions to both LAO’s and SAO’s. Contributions from \(D_w\) can promote localization and anti-phased oscillations. Combinations of these contributions provide additional routes to localized oscillations and asynchronous LAO’s.

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 (5) 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. We relate the quantities \(\lambda_c(D_v, D_w)\) and \(\lambda_k^{\text{eff}}\) to stabilization and destabilization of certain dynamics by the coupling coefficients \(D_w\) and \(D_v\). 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.

3.1 Destabilization of SAO by \(D_w\)

In Figure 6 we consider values \(\lambda_1 = .015\) and \(\lambda_2 = .01\), \(D_v = 0\) and \(D_w = .05\). Since \(\lambda_k < \lambda_c(0, 0)\) for \(k = 1, 2\), the oscillators exhibit only SAO when uncoupled. The key features of this case are:

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

ii) \(\lambda_2 < \lambda_c(D_w, D_v)\),
Uncoupled Coupling Effect $\lambda_k$ near $\lambda_c(0,0)$ $\lambda^\text{eff}_k$ Fig. 

| SAO/SAO | $D_w \uparrow$ | S | 1 | - | 6 |
| LAO/SAO | $D_w \approx D_v$, both $\uparrow$ | S | 2 | - | 7 |
| LAO/SAO | $D_w \ll 1$ | S | 2 | - | 1 |
| LAO/SAO | $D_v \uparrow$ | D | - | 1 | 8 |
| LAO/SAO | $D_v \uparrow$ or $D_w \uparrow$ | S | 1 | 1,2 | 9-12 |

Table 1: Significant factors in the routes to and from localized states. Column 1 gives the state of system without coupling for oscillator 1 and 2. Column 2 indicates the element of coupling which plays a role in the transition, $\uparrow$ for increasing. Column 3 gives the coupling effect on the localized state, S or D for stabilizing/destabilizing. Column 4 gives the index $k$ for any $\lambda_k$ close to the critical canard value $\lambda_c(0,0)$ in the uncoupled case. Column 5 gives the index $k$ for variation in any $\lambda^\text{eff}_k$ which plays a significant role in the transition. Column 6 gives the number of the figure in which the behavior is shown.

iii) Fluctuations in $\lambda^\text{eff}_2$ do not drive $v_2$ and $w_2$ to LAO.

Conditions ii) and iii) maintain the SAO in the second oscillator, so that $v_2$ and $w_2$ can be neglected in predicting the behavior of $v_1$ and $w_1$. Then condition i) causes LAO in the first oscillator, thus yielding the localized state.

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 due to the violation of condition iii) (see Figure 13 in Section 4.1). 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. The difference between the two types is the variation in non-autonomous effects captured in $\lambda^\text{eff}_k$.

**Controlled variation in $\lambda^\text{eff}_k$**

In Figure 7 we show localized behavior for $\lambda_1 = .02$, $\lambda_2 = .016$, and $D_w = D_v = .05$. Since $\lambda_k > \lambda_c(0,0)$ for $k = 1,2$, 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 $\lambda^\text{eff}_2$ 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 $\lambda_k^{\text{eff}}$ may exceed $\lambda_c(D_v,D_w)$, providing a possibility for a shift to LAO for oscillator 2. To confirm condition (iii) the range of $\lambda_k^{\text{eff}}$ can be approximated by substituting the range of $v_1$ and $w_1$ for LAO into (8). Then the approximate range of $\lambda_k^{\text{eff}}$ is $(\lambda_c(D_v,D_w) - D_w \max(w_1), \lambda_c(D_v,D_w) - D_w \min(w_1))$, neglecting $v_2$ and $w_2$ for SAO. Since $w_1 > 0$ for all but a very small time interval, effectively $\lambda_k^{\text{eff}} < \lambda_c(D_v,D_w)$, confirming condition iii). Note also that $D_v = D_w$ in (8) so that the variation in $\lambda_k^{\text{eff}}$ is decreased compared 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 $\lambda_k^{\text{eff}} < \lambda_c(D_v,D_w)$ as in Figure 6. For $\lambda_2 \geq \lambda_c(D_v,D_w)$ there is a transition to asynchronous LAO for both oscillators, as expected.

**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 $D_w = .01$. The mechanism for localized oscillations is different from that 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 $\lambda_k^{\text{eff}}$, driven by $v_1$ and $w_1$,
iv) The coupling is very small, so that $\lambda_c(D_v,D_w) \approx \lambda_c(0,0)$.

Conditions i) and ii) imply that large enough oscillations in $v_1$ and $w_1$ cause iii), since $\lambda_k^{\text{eff}}$ falls below $\lambda_c$ for significant time intervals, driving the second oscillator to SAO. Then the fluctuations in $\lambda_k^{\text{eff}}$ are negligible, so that 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. For increased coupling $\lambda_c(D_v,D_w)$ is shifted and the fluctuations in $\lambda_k^{\text{eff}}$ increase for both $k = 1, 2$, destabilizing the localized oscillations to anti-phased LAO’s, discussed in Section 4.3.

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

In Figure 8 we demonstrate how a localized state for the uncoupled system, corresponding to $\lambda_1 > \lambda_c(0,0) > \lambda_2$, can be destabilized for $D_v > 0$. We take $\lambda_1 = .02$, $\lambda_2 = .012$ and $D_v = .1$, $D_w = 0$. 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:

i) $\lambda_c(D_v, D_w)$ increases with $D_v$,

ii) $\lambda_1^{\text{eff}} < \lambda_c(D_v, D_w)$ for part of the trajectory,

iii) $\nu_1$ increases through zero when $\lambda_1^{\text{eff}} < \lambda_c(D_v, D_w)$,

iv) $\lambda_2$ is well below $\lambda_c(D_v, D_w)$.

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 be obtained only 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) oscillator 2 is also in SAO so that the localized state is lost.

In Section 4, we show how the system in the regime $\lambda_1 > \lambda_c(0,0) > \lambda_2$ can be sensitive to parameter changes, exhibiting mixed mode asynchronous patterns for slight variations in $\lambda_1$, $D_v$ and $D_w$.

3.4 Mixed-mode localized solutions

In these patterns one of the oscillators remains in the SAO regime, while the second exhibits mixed mode oscillations (MMO), alternating 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 MMO have been found in strongly diffusively coupled neural models [20]. To our knowledge, localized MMO of the type shown here have not yet been reported.

Regular localized MMO

In Figures 9 and 10 we show two types of regular localized MMO, 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 show regular localized MMO for $D_v = .1$, $D_w = .05$. The main features are:

i) $\lambda_1 \neq \lambda_2$, resulting in phase differences when both oscillators have SAO,

ii) $\lambda_1 > \lambda_c(D_v, D_w)$, but $\lambda_1$ is close to $\lambda_c(D_v, D_w)$,

iii) $\lambda_2 < \lambda_c(D_v, D_w)$, with $\lambda_2$ a significant distance from $\lambda_c(D_v, D_w)$,

iv) $\nu_1$ increases through zero when $\lambda_1^{\text{eff}} < \lambda_c(D_v, D_w)$ following LAO.
We begin with the system in the state where both oscillators exhibit SAO. Conditions i) and ii) imply that $\lambda_1^{\text{eff}}$ fluctuates about $\lambda_c(D_v, D_w)$, with a net effect of $\lambda_1^{\text{eff}} > \lambda_c(D_v, D_w)$. Then the SAO of oscillator 1 gradually grows in amplitude, with an eventual transition to LAO due to condition ii). To complete the MMO cycle, conditions ii) and iv) combine to drive the first oscillator back to SAO: the forcing of $(v_1, w_1)$ via the coupling with $(v_2, w_2)$ is large enough to cause fluctuations in $\lambda_1^{\text{eff}}$, so that it drops sufficiently below $\lambda_c(D_v, D_w)$ as $v_1$ increases through zero following the LAO (see Figure 9b). As in Section 3.3, this forces $v_1$ back to the left branch of the $v$-nullcline and back into the SAO regime. Then the cycle repeats. Condition iii) allows $(v_2, w_2)$ to remain in SAO, as long as the coupling is not large. Similar localized MMO can be observed for $D_v \neq 0$ and $D_w = 0$, e.g. for $\lambda_1 = .0165, \lambda_2 = .011$ and $D_v = .046$.

Another mechanism for regular MMO is shown in Fig. 10 for $D_v = .05$ and $D_w = .1$, with $\lambda_1$ and $\lambda_2$ as above. The canard critical value is reduced as compared to the previous case (specifically,$\lambda_c(.05, .1) < \lambda_c(.1, .05)$), 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) $\lambda_1 > \lambda_c(D_v, D_w)$, but $\lambda_1$ is close to $\lambda_c(D_v, D_w)$,
iii) $\lambda_2 < \lambda_c(D_v, D_w)$, with $\lambda_2$ closer to $\lambda_c(D_v, D_w)$ as compared with the previous case.
iv) Following LAO, $v_2$ increases through zero when $\lambda_2^{\text{eff}} < \lambda_c(D_v, D_w)$

Again we begin with 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 MMO is condition iii) which allows increasing oscillations in $(v_1, w_1)$ to drive $\lambda_2^{\text{eff}}$ sufficiently above $\lambda_c(D_v, D_w)$. Then $(v_2, w_2)$ exhibits one LAO per cycle, which forces $\lambda_1^{\text{eff}}$ well below $\lambda_c(D_v, D_w)$ so that $(v_1, w_1)$ remains in SAO.

Condition (iv) shows that the feedback through fluctuations in $\lambda_2^{\text{eff}}$ is also sufficient to force the second oscillator back to SAO; as $v_2$ passes through zero it returns to the left branch of the nullcline since $\lambda_2^{\text{eff}} < \lambda_c(D_v, D_w)$, and the cycle repeats.

Irregular mixed-mode localization

In Figures 11 and 12 we show irregular localized MMO. In Fig. 11 the values are the same as in Fig. 9 (for which regular MMO are observed), except for $D_w = .072$. In Fig. 12, $\lambda_1$ is slightly smaller than in Fig. 9, with the other parameters the same. Transitions between LAO and SAO in the MMO can be observed for $\lambda_1^{\text{eff}} < \lambda_c(D_v, D_w)$ as $v_1$ increases through 0 (not shown), similar to conditions (iv) in the regular localized MMO of Figures 9b and 10b. 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 [18]. 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 \( \lambda_{ke} \) can lend some insight into the dynamics.

4.1 Destabilization of localization and SAO by \( D_w \)

In Figure 13 we show the case for \( \lambda_1 = .015, \lambda_2 = .012, D_w = .05, D_v = 0 \), that is, \( \lambda_1 > \lambda_c(D_w, D_v) > \lambda_2 \). Note that the parameter values are the same as in Figure 6, with the exception of an increase in \( \lambda_2 \), yielding a shift of the localized solutions shown in Figure 6 to a LAO antiphased pattern. The shift is due to a violation of condition iii) in Section 3.1; for increased \( \lambda_2 \) and \( v_1 < 0 \), \( \lambda_{ke} \) exceeds \( \lambda_c(D_v, D_w) \) as \( v_2 \) crosses through zero, forcing the system to asynchronous LAO. Therefore a phase plane analysis is required to completely predict this transition.

One can also obtain anti-phased LAO for \( \lambda_1 = \lambda_2 < \lambda_c(D_w, D_v) \), as shown in Figure 14 for \( \lambda_1 = \lambda_2 = .01, D_v = 0, \) and \( D_w = .1 \). 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) \( \lambda_{ke} > \lambda_c(D_v, D_w) \) for sufficiently large values of \( |\gamma v_k + w_k| \) in (8),

iii) \( \lambda_{ke} > \lambda_c(D_v, D_w) \) when \( v_k \) increases through 0.

The asymmetric initial conditions of condition i) lead to anti-phased oscillations, which are necessary for condition ii). Even though both \( \lambda_{ke} \)'s are well within the SAO regime for the uncoupled system, the coupling is sufficient to drive the system to LAO, via condition (iii) (See Figure 14b).

In contrast, if we consider identical, in-phase oscillations with \( \lambda_1 = \lambda_2 < \lambda_c(D_v, D_w) \)
as in Figure 14, or if the initial conditions are similar for the two oscillators, then from (8) we find that $\lambda_k^{\text{eff}} \sim \lambda_k$ and conditions ii) and iii) are not satisfied. Then in-phase LAO cannot be sustained, and the system moves to SAO.

### 4.2 Mixed mode patterns and irregular LAO

The behavior of $\lambda_k^{\text{eff}}$ suggests conditions under which MMO and irregular LAO are observed, complementing a detailed study of the phase plane necessary to completely predict these patterns.

#### Mixed mode patterns

In this section we show MMO of two types: coherent MMO, where the oscillators show phase locked behavior when in the LAO part of the cycle, and incoherent MMO, where the LAO part of the cycle is not phase locked. In Figure 15 we show coherent MMO for $\lambda_1 = .017, \lambda_2 = .01, D_v = .1, D_w = 0$, where a single LAO follows a fixed period of SAO. The three key factors in this case are:

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

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 $\lambda_c(D_v, D_w)$, so that $\lambda_2^{\text{eff}} < \lambda_c(D_v, D_w)$ when oscillator 1 exhibits SAO.

As also seen in Section 3.4, condition i) has 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). Condition iii) implies that the second oscillator maintains SAO until the first oscillator is in LAO. The LAO in the second oscillator is slaved to the first oscillator, immediately following LAO in oscillator 1. The LAO in the second oscillator creates a significant variation in $\lambda_1^{\text{eff}}$, so that oscillator 1 returns to SAO, as does the second oscillator due to condition iii), and the cycle repeats.

Figure 16 shows incoherent MMO, for $\lambda_1 = .02, \lambda_2 = .012, D_v = .1, D_w = 0$. Incoherent MMO have interactions that are qualitatively similar to that of coherent MMO, both depending on condition (i)-(ii) above. Condition (iii) above is modified for incoherent MMO,

(iii)* $\lambda_2$ is well below $\lambda_c(D_v, D_w)$, so that $\lambda_2^{\text{eff}}$ is below $\lambda_c(D_v, D_w)$ on average when oscillator 1 has SAO.

Here $\lambda_k$ are close to $\lambda_c(D_v, D_w)$, for both $k = 1, 2$, so that the influence of $\lambda_k^{\text{eff}}$ plays a crucial role in the difference between the coherent and incoherent MMO’s 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. Condition (iii)* implies that fluctuations in $\lambda_2^{\text{eff}}$
make LAO more likely in the second oscillator in Figure 16 than in Figure 15. Then the LAO’s of the two are no longer phase locked, and the second oscillator enters LAO before the first.

A fourth crucial element in maintaining both coherence and incoherence MMO:

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, as in Figure 15. Moderate values of $D_v$ together with conditions iii) and iv) lead to regular MMO where the LAO in oscillator 2 are slaved to oscillator 1. For larger $D_v$ with the other parameters fixed as in Figure 15, the MMO destabilize to SAO for both oscillators. Decreasing $D_v$ and increasing $D_w$ destabilizes the MMO 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 MMO state 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, which are 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 [20]. 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 MMO in Figures 15 and 16. Thus, for these intermediate values of the coupling, while keeping $\lambda_k$ near $\lambda_c(D_v, D_w)$, 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 alternates 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 [10, 12, 7, 8]. 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, 7, 8] 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 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 [25, 29, 30, 31, 32, 33, 46] (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 [20]. 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 [20]; 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 dimensional 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 [18, 20, 29, 35].

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 [36] and the globally coupled Belousov-Zhabotinsky reaction [3].

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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 [15]. 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 [15],

\[
\frac{dc}{d\tau} = r - kc - \mathcal{F}(c, c_s) \quad \frac{dc_s}{d\tau} = \mathcal{F}(c, c_s)
\]  

(10)

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 \(-k_f c_s\). In particular

\[
\mathcal{F}(c, c_s) = J_{\text{uptake}} - J_{\text{release}} - k_f c_s
\]

\[
= \frac{U_1 c^n}{K_1^n + c^n} - \frac{U_2 c_s^n}{K_3^n + c_s^n} - \frac{c^p}{K_3^p + c^p} - k_f c_s
\]

(11)

The positive feedback of Ca\(^{2+}\) release is evidenced by the dependence of \(J_{\text{release}}\) on \(c\). The system is non-dimensionalized using

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

\[
\mu = r/(k K_1), \quad \alpha = K_3/K_1, \quad \beta = U_1/U_2, \quad \gamma = U_1/U_2, \quad \delta = k_f K_2/U_2
\]

(12)

to obtain (1) with \(D_w = D_v = 0\)

\[
\begin{cases}
V_k' = \mu_k - V_k - \gamma/\epsilon F(V_k, W_k), \\
W_k' = \frac{1}{\epsilon} F(V_k, W_k),
\end{cases}
\]

(13)

for each \(k\). In [15] the following reduction for a single oscillator was proposed

\[
\bar{v}_k = W_k, \quad \bar{w}_k = V_k + \gamma W_k.
\]

(14)
Substituting (14) into (13) one gets
\[
\begin{align*}
\bar{v}'_k &= \frac{1}{\mu_k + \gamma} \bar{F}(\bar{v}_k, \bar{w}_k), \\
\bar{w}'_k &= [\mu_k + \gamma \bar{v}_k - \bar{w}_k]
\end{align*}
\]
for each value of \( k \).

System (15) describes an oscillator of FHN type, with the \( v \) and \( w \)-nullclines significantly different from the \( v \) and \( w \)-nullclines of system (5). However, the form of (16) is not the most convenient for the canard analysis we use in this paper. We propose a better and slightly different approach which is to transform system (13) into a van der Pol (VDP) type oscillator. (In a VDP type oscillator the \( \bar{w} \)-nullcline is a vertical line while in a FHN type oscillator it makes a positive angle with the \( \bar{v} \)-axis.) This is achieved by using transformation (3), which can also be viewed as a linear transformation of (14).

Throughout the paper we use the parameter values as in [15]: \( \alpha = .9, \beta = .13, \gamma = 2, \delta = .004, m = 2, n = 2, p = 4 \) and \( \epsilon = .01 \).

B The canard critical value for the canonical form

We follow [7] and extend our result to the case studied in this manuscript. The calculations are similar to those in [7]. We consider a system of the form
\[
\begin{align*}
v' &= F(v, w) + \epsilon \Psi(v, w, \lambda, \epsilon), \\
w' &= \epsilon G(v, w, \lambda)
\end{align*}
\]
where \( 0 < \epsilon \ll 1 \) and \( \Psi(v, w, \lambda, \epsilon) = O(v, w, \lambda, \epsilon) \). The functions \( F \) and \( G \) are as in Section 2.1. We make the following assumptions for \( \epsilon = 0 \):

- **Singularity:** \( F(0, 0) = 0 \) and \( \partial F/\partial v(0, 0) = 0 \), \( G(0, 0, 0) = 0 \).
- **Non-degeneracy assumptions defining the minimum:** \( \partial^2 F/\partial v^2(0, 0) > 0 \), \( \partial F/\partial w(0, 0) < 0 \).
- **Non-degeneracy assumptions defining a canard point:** \( \partial G/\partial v(0, 0, 0) > 0 \), \( \partial G/\partial w \leq 0 \), \( \partial G/\partial \lambda < 0 \).

With these assumptions system (17) satisfies the conditions stated in [12, 13]. The canonical form for system (17) is given by
\[
\begin{align*}
v' &= -w + v^2 - w h_1(v, w) + v^2 h_2(v, w) + \epsilon h_6(v, w, \lambda, \epsilon), \\
w' &= \epsilon [v - \lambda + v h_3(v, w, \lambda) - \lambda h_4(v, w, \lambda) + \lambda h_5(v, w, \lambda)],
\end{align*}
\]
where

\[ h_1(v, w) = \frac{2 G_v^{1/2} F_{vw}}{|F_w|^{1/2} F_{vv}} v + \mathcal{O}(w), \]  
(19)

\[ h_2(v, w) = \frac{2 G_v^{1/2} |F_w|^{1/2} F_{vvw}}{3 F_{vv}^2} v + \mathcal{O}(w), \]  
(20)

\[ h_3(v, w, \lambda) = \frac{|F_w|^{1/2} G_{vv}}{G_v^{1/2} F_{vv}} v + \mathcal{O}(w, \lambda), \]  
(21)

\[ h_4(v, w, \lambda) = -\frac{2 G_v^{1/2} |F_w|^{1/2} G_{vv\lambda}}{F_{vv} |G_\lambda|} v + \mathcal{O}(w, \lambda), \]  
(22)

\[ h_5(v, w, \lambda) = \frac{G_w}{G_v^{1/2} |F_w|^{1/2}} v + \mathcal{O}(v, w, \lambda), \]  
(23)

\[ h_6(v, w, \lambda) = \frac{2 \Psi_v}{F_{vv}} v + \mathcal{O}(v^2, w, \lambda, \epsilon) \]  
(24)

and all the function are evaluated at \((v, w, \lambda, \epsilon) = 0\).

Following [7] and [13] the following expression for \(\lambda_c\) can be calculated

\[ \lambda_c = L a_1 - 3 a_2 + 2 a_3 - 2 a_5 - 4 a_6 \frac{\epsilon + \mathcal{O}(\epsilon^{3/2})}{8}, \]  
(25)

where

\[ L = \frac{2 G_v^{3/2} |F_w|^{1/2}}{4 F_{vv} |G_\lambda|}, \quad a_1 = \frac{\partial h_1}{\partial \bar{v}} = -\frac{2 G_v^{1/2} F_{vw}}{|F_w|^{1/2} F_{vv}}, \quad a_2 = \frac{\partial h_2}{\partial \bar{v}} = \frac{2 G_v^{1/2} |F_w|^{1/2} F_{vvw}}{3 F_{vv}^2}, \]  

\[ a_3 = \frac{\partial h_4}{\partial \bar{v}} = \frac{|F_w|^{1/2} G_{vv}}{G_v^{1/2} F_{vv}}, \quad a_5 = h_5 = \frac{G_w}{G_v^{1/2} |F_w|^{1/2}}, \quad a_6 = \frac{\partial h_6}{\partial \bar{v}} = 2 \Psi_v F_{vv}^2, \]  
(26)

where all the functions are evaluated at \(0\).

Substituting into (25) we get

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

\[ = -\frac{G_v}{2 F_{vv}^3 |G_\lambda|} [G_v F_{vvw} F_{vw} + G_v |F_w| F_{vvw} - |F_w| G_{vw} F_{vv} + G_w F_{vv}^2 + 2 \Psi_v F_{vv}^2] \epsilon + \mathcal{O}(\epsilon^{3/2}). \]  
(27)

where all the functions are calculated at \(0\).
Table Captions

Table 1: Significant factors in the routes to and from localized states. Column 1 gives the state of system without coupling for oscillator 1 and 2. Column 2 indicates the element of coupling which plays a role in the transition, ↑ for increasing. Column 3 gives the coupling effect on the localized state, S or D for stabilizing/destabilizing. Column 4 gives the index $k$ for any $\lambda_k$ close to the critical canard value $\lambda_c(0,0)$ in the uncoupled case. Column 5 gives the index $k$ for variation in any $\lambda_k^{\text{eff}}$ which plays a significant role in the transition. Column 6 gives the number of the figure in which the behavior is shown.

Table 2: Significant factors in the routes to and from asynchronous LAO. Elements represented in each column are the same as in Table 1, with the exception of Column 3, which lists the stabilizing (S) or destabilizing (D) effect on asynchronous LAOs or MMOs. MMO(c) and MMO(i) refer to coherent and incoherent MMO, respectively.

Figure Captions

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 $\tilde{F}(v, w) = \tilde{G}(v, w; \lambda) = 0$.

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. $(v_2, w_2)$ is in a SAO regime and $(v_1, w_1)$ 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 SAO.

**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 $1 > \lambda_1(D_v, D_w)$ and $2 < \lambda_2(D_v, D_w)$.

**Figure 14:** Antiphased LAO regime for the diffusively coupled two-pool model with $1 = \lambda_1(D_v, D_w)$.

**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 7:
Figure 8:
Figure 9:
Figure 10:
Figure 13:
Figure 14:
Figure 15:
$\lambda_1 = 0.02 \quad \lambda_2 = 0.012 \quad D_v = 0.1 \quad D_w = 0.0$

$\lambda_{\text{eff}} = 0.02 \quad \lambda_{\text{eff}} = 0.012 \quad \lambda_c$

Figure 16:
Figure 17: