Sub-Hopf/fold-cycle bursting and its relation to (quasi-)periodic oscillations

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Abstract. We investigate the emergence of bursting oscillations and their relation to (quasi-)periodic behaviour in two different model systems, a pH oscillator and a calcium oscillator. Both systems are described by 3-dimensional ODE systems and follow different ‘routes’ to bursting oscillations as parameters are varied. In the first part, we exploit the slow-fast structure of the 3-dimensional ODE systems to show that the bursting oscillations are of sub-Hopf/fold-cycle type over a wide range of parameters. For this purpose, a slow variable is used as a quasi-static bifurcation parameter for the remaining 2-dimensional fast subsystem. For the pH oscillator, a subsequent two-parameter continuation reveals a transition in the bursting behaviour from sub-Hopf/fold-cycle to fold/sub-Hopf type. In the second part, we argue that the particular constellation of a subcritical Hopf bifurcation together with a saddle-node bifurcation of a periodic orbit (fold-cycle) may not only account for the bursting oscillations, but also allows for (quasi-)periodic oscillations on a 2-torus suggesting a common origin for both types of dynamics.

1. Introduction

Bursting or mixed-mode oscillations are frequently observed as asymptotic states in spatially homogeneous chemical [1, 2, 3, 4] and biological [5, 6, 7, 8, 9, 10, 11, 12] reaction systems where they are of potential relevance for signal transduction processes [13, 14]. Biological signal transduction networks frequently involve so-called second messengers, i.e. small and unspecific molecules, for instance calcium ions, which are able to transport different information contents. In such cases information is coded in the geometric outline of the concentration oscillations of the second messenger [15], while the intensity of a stimulus is stored in the frequency of the oscillations [16]. Bursting oscillations are periodic patterns consisting of \(L\) large amplitude (spiking) oscillations and \(S\) small amplitude oscillations per oscillation period for which the nomenclature \(L^S\) has prevailed. Such oscillations are highly suitable for the encoding of different information contents, and, in fact, bursting oscillations are often observed to occur in signal transduction processes.

Alternatively, bursting behaviour can be classified by a slow-fast analysis introduced by Rinzel and Ermentrout [17]. Systems exhibiting bursting oscillations typically involve a fast oscillatory subsystem which is coupled to at least one slow variable which then acts as a quasi-static
Figure 1. Time series obtained from a numerical simulation of the bursting pH oscillations in the hemin system (left image): 4 large amplitude oscillations alternate with 19 small ones. The rectangular region is magnified in the right image showing the small amplitude oscillations.

bifurcation parameter for the fast subsystem. Subsequently, Izhikevich [18] has extended this approach to classify the bursting behaviour according to the type of bifurcations occurring in the fast subsystem that lead to the emergence and disappearance of the small amplitude oscillations.

Recently, the hemin – hydrogen peroxide – sulfite reaction system (henceforth called ‘hemin system’) has been introduced as a biocompatible enzyme model system [19, 20] that exhibits bursting oscillations in the pH value of the reaction medium (Figure 1). It belongs to a larger family of so-called pH oscillators [24, 25, 26, 27, 28] that induce periodic changes in the pH value of the corresponding reaction medium which may affect physiological parameters in the environment of the system, e.g. in the permeability of membranes or the activity of enzymes.

The dynamics of the hemin system were originally modelled by a 6-dimensional ODE system [29]. Recently, we have derived a 3-dimensional approximation to the 6-dimensional system using the method of quasi integrals [30] which preserved the local codimension two bifurcation structure of the original ODE system such that both systems are identical at this level. The method of quasi integrals comprises a rather general algorithmic procedure to search for slow invariant manifolds, particularly in higher dimensional reaction networks where analytical methods usually fail. Thus, it is not required that the different time scales of the individual reaction steps of a reaction mechanism are known in advance. On the contrary, the method identifies them. Once the different time scales (or the fast reactions) are known, it is more or less straightforward to apply singular perturbation techniques [32, 33, 34, 35] to obtain a lower dimensional approximation of the original dynamics on a slow manifold of the system which, in its simplest form, yields just a quasi-steady-state approximation [36, 37]. On the other hand, since the method of quasi integrals leads to the identification of the fast reactions of a given system, it can be used as a supplement to existing methods that rely on an a priori grouping of the individual reaction steps into fast and slow ones before singular perturbation techniques may successfully be applied.

In the present article we investigate the emergence of bursting oscillations and their relation to oscillations on a 2-torus in two different model systems, the hemin system and a calcium oscillator model [38]. Since oscillations on a 2-torus can be either periodic or quasiperiodic, we shall refer to this kind of behaviour collectively as (quasi-)periodic. The dynamics of both models are well described by 3-dimensional ODE systems on which a slow-fast analysis is performed to
characterize the bursting behaviour of the systems.

The basic ideas underlying a slow-fast analysis are introduced in section 2. The following section is devoted to a detailed study of the bursting oscillations in the hemin system. It will be shown that they are of sub-Hopf/fold-cycle type over a wide range of parameters. A subsequent two-parameter continuation reveals a transition in the bursting behaviour from sub-Hopf/fold-cycle to fold/sub-Hopf type which can be attributed to a codimension two bifurcation (saddle-node separatrix-loop) in the fast subsystem. The relation between (quasi-)periodic and bursting oscillations is analyzed in section 4 where we will demonstrate that the bifurcations in the fast subsystem leading to sub-Hopf/fold-cycle bursting may equally lead to (quasi-) periodic oscillations on a 2-torus. For the calcium oscillator model we will see that the bursting oscillations arise as a 2-torus continuously deforms. In contrast, the bursting oscillations in the hemin system appear as periodic orbits in narrow parameter windows in a chaotic domain far away from the parameter region where (quasi-)periodic behaviour is observed. The final section summarizes the results and discusses some of their consequences.

2. Slow-fast analysis: The method

The slow-fast analysis has been introduced by Rinzel and Ermentrout to describe the bursting behaviour of neural systems [17]. Slow-fast bursters typically involve a fast oscillatory subsystem (generating spiking oscillations) and a slow subsystem which triggers the emergence of small amplitude oscillations as the trajectory of the full system passes certain codimension one bifurcation points in the fast subsystem. Therefore, the fast subsystem must be at least 2-dimensional whereas the slow subsystem may comprise only a single degree of freedom. In the following, we will consider only slow-fast bursters with a 2-dimensional fast and a 1-dimensional slow subsystem of the form

\[
\begin{align*}
\dot{x} &= f(x, y, p) \\
\dot{y} &= g(x, y, p) \\
\dot{p} &= \varepsilon h(x, y, p)
\end{align*}
\] (1)

where \(\varepsilon\) is a small parameter indicating that \(p\) evolves on a longer time scale than the fast \(x-y\) subsystem.

Consider Figure 2 where the slow-fast structure of the 3-dimensional hemin system is illustrated in a cartoon. For the time being, let us consider the limit \(\varepsilon \to 0\) in (1) which corresponds to the assumption that \(p\) is not a dynamical variable, but a parameter for the 2-dimensional fast \(x-y\) subsystem. Then, for each fixed parameter value \(p_0\), there exist certain invariant sets in the 2-dimensional fast subsystem. In Figure 2, for example, three invariant sets coexist in the plane \(F_{p_0}\): A stable limit cycle (black circle), an unstable limit cycle (red circle) and a stable fixed point (black dot).

At the next step, the dynamical nature of \(p\) is taken into account. For this purpose, we again consider the dynamics of the ODE system (1), but this time for small nonzero \(\varepsilon\). As \(p\) slowly evolves in time according to the third equation in (1), the type and stability of the invariant sets of the fast \(x-y\) subsystem will also change. In this sense, \(p\) now acts as a quasi-static bifurcation parameter for the fast subsystem. For example, as \(p\) moves to the left, the stable and the unstable limit cycle merge in a saddle-node bifurcation (SNP) and disappear leaving the stable stationary state (thin black line) as the only invariant set. On the other hand, as \(p\) moves to the right, the unstable limit cycle shrinks and vanishes in a subcritical Hopf bifurcation (SH). Henceforth, a large amplitude limit cycle coexists with a saddle point. Eventually, a saddle-node bifurcation (SN\(_1\)) occurs on the large amplitude limit cycle to form a saddle-node homoclinic orbit by which the periodic solution of the fast subsystem ceases to exist.

The basic assumption underlying the slow-fast analysis is that the time scale separation between the fast and the slow subsystems is such that the stationary and oscillatory states,
which exist in the fast subsystem at a particular value of $p$, extend along the $p$ direction to quasi-stationary manifolds in the 3-dimensional phase space (cf. Fig. 2). Thus, the stationary states become line-like quasi-stationary manifolds ($\mathcal{L}$) while the oscillatory states form cylinder-like manifolds ($\mathcal{C}$). This means that the flow of the full 3-dimensional ODE system always remains in the neighbourhood of the stable invariant sets of the fast subsystem. For example, the large amplitude (spiking) oscillations in Figure 1 occur close to the cylinder-like manifold $\mathcal{C}$ of Figure 2 while the small amplitude (bursting) oscillations occur along the line-like manifold ($\mathcal{L}$). Note that the cylinder-like manifold is terminated at the left side by a saddle-node bifurcation (SNP) and at the right side by a saddle-node homoclinic orbit such that large amplitude oscillations are only possible in a finite region of the phase space.

3. Bursting oscillations in the hemin system

3.1. The hemin system

The bursting oscillations observed experimentally [19, 20] are qualitatively well reproduced by a 6-dimensional ODE system [29]. Recently, we derived a 3-dimensional approximation to the 6-dimensional ODE system using quasi integrals [30]. It was shown that the local codimension two bifurcation diagrams of both systems are virtually identical. However, to analyze the slow-fast structure of the 3-dimensional ODE system, it was convenient to perform a suitable change of coordinates [31]. The resulting 3-dimensional ODE system will be used as the starting point for the slow-fast analysis of the bursting oscillations in subsection 3.2. It reads

\begin{align*}
\dot{x} &= k_0 x_2^0 - x \left\{ k_0 + k_1 s(x, y) + (k_2 + k_3 (a - x - y + s(x, y))) \left( x_1^0 - x_2^0 + x - s(x, y) \right) \right\} \\
\dot{y} &= - (k_6 + k_0) y + k_7 (p - y) (a - x - y + s(x, y)) \\
\dot{p} &= k_0 (p^0 - p) - k_8 (p - y).
\end{align*}

(2)
Table 1. Parameter set for the hemin system (2).

| Parameter  | Value                                    |
|------------|------------------------------------------|
| $k_1$      | $0.2 \text{ M}^{-1}\text{s}^{-1}$        |
| $k_2$      | $1.5 \text{ M}^{-1}\text{s}^{-1}$        |
| $k_3$      | $8.5 \cdot 10^6 \text{ M}^{-2}\text{s}^{-1}$ |
| $k_4$      | $1000 \text{ s}^{-1}$                    |
| $k_5$      | $10^{10} \text{ M}^{-1}\text{s}^{-1}$    |
| $k_6$      | $0.011 \text{ s}^{-1}$                   |
| $k_7$      | $2.5 \cdot 10^4 \text{ M}^{-1}\text{s}^{-1}$ |
| $k_8$      | $2.5 \cdot 10^{-4} \text{ s}^{-1}$      |
| $x_1^0$    | $0.025 \text{ M}$                        |
| $x_2^0$    | $0.045 \text{ M}$                        |
| $x_4^0$    | $2.2 \cdot 10^{-4} \text{ M}$            |
| $p_0$      | $3 \cdot 10^{-4} \text{ M}$              |
| $a$        | $x_4^0 - x_1^0 + x_2^0$                  |
| $k_0$      | $[1, 5] \cdot 10^{-4} \text{ s}^{-1}$   |

Figure 3. One-parameter bifurcation diagram for the ODE system (2). Black and red circles denote minima and maxima of stable and unstable oscillations, respectively.

where $s(x, y)$ stands for the slow manifold of the 6-dimensional ODE system given by

$$s = \frac{1}{2}(x + y - a - \frac{k_4}{k_5}) + \frac{1}{2} \sqrt{(x + y - a + \frac{k_4}{k_5})^2 + 4 \frac{k_4}{k_5}(x_1^0 - y)}.$$  \hspace{1cm} (3)

In (2) all parameters but $k_0$ are fixed. Their dimensional numerical values are compiled in Table 1. Similar to the experimental situation, the flow rate $k_0$ is the principal control parameter for the system. The higher the flow rate, the higher is the matter flow through the system. Thus, the flow rate is a suitable parameter to drive the system away from equilibrium.

As the flow rate is increased, one observes successively the following asymptotic states (cf. Fig. 3)$^1$: A stable stationary state (black line) becomes unstable at $k_0 = 1.6461$ via a subcritical Hopf bifurcation (Fig. 3, inset) giving rise to an unstable limit cycle (red circles).

$^1$ Variables in the Figures and in the text are rescaled according to $x \rightarrow 10^2\text{M}^{-1}x$, $y \rightarrow 10^4\text{M}^{-1}y$, $p \rightarrow 10^4\text{M}^{-1}p$ and $k_0 \rightarrow 10^4 s k_0$. 


This unstable cycle merges with a second one in a saddle-node bifurcation SNP (inset, open triangle) at \( k_0 = 1.6438 \). However, stable oscillations (black circles) arise by an inverse Neimark-Sacker bifurcation NS (inset, filled square) at \( k_0 = 1.6519 \) where a 2-torus bifurcates towards lower values of \( k_0 \) where it coexists with a saddle point (corresponding to the red dashed line in the inset of Fig. 3) in a very narrow parameter interval before it becomes homoclinic to the saddle and vanishes.

The simple periodic oscillations are stable up to \( k_0 = 2.5169 \) where the first of a whole cascade of period doubling bifurcations PD occurs and the primary periodic orbit (red circles) becomes unstable (cf. Fig. 3). For increasing \( k_0 \) a chaotic attractor is formed where the bursting oscillations appear as embedded periodic orbits. As the flow rate \( k_0 \) is increased beyond the period doubling bifurcation point PD, one observes periodic-chaotic progressions of bursting oscillations and chaotic behaviour, i.e. the large parameter interval \( k_0 \in (2.517, 3.858) \) (bounded by the dotted lines in Fig. 3) is interspersed with smaller intervals where bursting oscillations arise as stable periodic orbits which differ in the number of large and small amplitude oscillations (for details, see [31]).

3.2. SubHopf/fold-cycle bursting

In the following, we shall investigate the type of bursting of the hemin system at a fixed value of the bifurcation parameter \( k_0 = 2.8 \) which is chosen such that it lies within one of the periodic windows described in the last subsection (cf. Fig. 3) where a \( 4^{19} \) state is stable (Fig. 4). Here, the trajectory performs 4 large amplitude oscillations which are followed by 19 small amplitude oscillations. We perform a slow-fast analysis by treating the variable \( p \) as a (quasi-static) bifurcation parameter for the 2-dimensional fast subsystem

\[
\begin{align*}
\dot{x} &= k_0 x_2^0 - x \left( k_0 + k_1 s(x,y) + \left( k_2 + k_3 (a - x - y + s(x,y)) \right) (x_1^0 - x_2^0 + x - s(x,y)) \right) \\
\dot{y} &= -(k_6 + k_0) y + k_7 (p - y) (a - x - y + s(x,y)).
\end{align*}
\tag{4}
\]

Note that this fast subsystem is simply obtained by omitting the third equation

\[
\dot{p} = -(k_0 + k_8) p + k_8 y + k_0 p^0
\tag{5}
\]

of the 3-dimensional ODE system (2). The justification of this procedure is provided by inspection of dimensionless variables. After scaling the variables \( \tilde{x} = 10^2 M^{-1} x, \tilde{y} = 10^4 M^{-1} y \) and \( \tilde{p} = 10^4 M^{-1} p \) according to their inflow concentrations \( x_2^0 \) and \( p^0 \), cf. Table 1), these new variables are \( O(1) \). With the additional scalings \( \tilde{s} = 10^2 M^{-1} s \) and \( \tilde{a} = 10^2 M^{-1} a \) we also get \( O(\tilde{s}) = O(1) \) and \( O(\tilde{a}) = O(1) \). Therefore the right hand sides of \( \tilde{x} \) and \( \tilde{y} \) will be at least of order \( O(10^2 s^{-1}) \) whereas the one of \( \tilde{p} \) will turn out to be of order \( O(10^{-4} s^{-1}) \).

The one-parameter bifurcation diagram of the fast subsystem (4) is shown in Figure 5 which, clearly, is topologically equivalent to the cartoon in Figure 2 in the region close to the subcritical Hopf bifurcation SH. In particular, there is a stable quasi-stationary line-like manifold (black line) that is composed of stable fixed points of the fast subsystem. This manifold becomes unstable (red dashed line) via a subcritical Hopf bifurcation SH where an unstable limit cycle (red circles) bifurcates towards lower values of \( p \). The cylinder-like manifold is created by a saddle-node bifurcation of periodic orbits SNP from which a stable (black circles) and an unstable limit cycle bifurcate towards higher values of \( p \).

In order to determine the nature of the bursting behaviour of the hemin ODE system at \( k_0 = 2.8 \), we overlay the bifurcation diagram of the fast subsystem (Fig. 5) with a projection of the \( 4^{19} \) orbit (Fig. 4) onto the \( p-x \) plane as shown in Figure 6. Note that the (blue) trajectory always remains in the neighbourhood of the quasi-stationary manifolds of the fast subsystem. More precisely, the large amplitude oscillations occur close to the cylinder-like manifold while...
Figure 4. 3-dimensional phase portrait of a $4^{th}$ bursting state at $k_0 = 2.8$.

Figure 5. One-parameter bifurcation diagram of the fast subsystem (4).

the small amplitude oscillations occur along the line-like manifold. This can be seen in Figure 7 which shows a magnification of the dashed rectangular region of Figure 6.

In Figure 6 we will describe one revolution of the trajectory in detail: The blue arrow indicates
Figure 6. Overlay of the one-parameter bifurcation diagram of the fast subsystem (Fig. 5) with a projection of the $4^{19}$ orbit (Fig. 4) onto the $p$-$x$ plane.

the direction of the flow. To the left of the SNP point, the line-like quasi-stationary manifold is the only attractor. Since the eigenvalues along this manifold are complex, the trajectory performs damped oscillations as it approaches the subcritical Hopf bifurcation point SH. Beyond that point, the quasi-stationary manifold becomes unstable causing the subsequent oscillations to increase until the orbit is finally attracted by the cylinder-like manifold (near the stable limit cycle solutions (black circles) of the fast subsystem). Then 4 large amplitude oscillations are performed in the vicinity of the cylinder-like manifold (Fig. 6). When the trajectory passes the saddle-node bifurcation point SNP the orbit ‘jumps back’ to the line-like manifold to begin the next revolution.

According to the classification scheme of bursting mechanisms given in [18], which is based on the nature of the bifurcations in the fast subsystem delimiting the domain of bursting oscillations, the hemin system is a sub-Hopf/fold-cycle burster at $k_0 = 2.8$ since the large amplitude (spiking) oscillations terminate at a fold-cycle bifurcation (which is also called as saddle-node bifurcation of periodic orbits, SNP) while the small amplitude (bursting) oscillations disappear via a subcritical Hopf bifurcation (SH).

In general, a $L^S$ state found in a periodic window of the chaotic domain described in subsection 3.1 wraps around the cylinder-like manifold $L$ times and oscillates $S$ times along the line-like manifold before the next period begins.

3.3. A transition between sub-Hopf/fold-cycle and fold/sub-Hopf bursting
In the last subsection, we studied the bursting type of the ODE system (2) at one particular value of the control parameter $k_0$. However, it can be presumed that the quasi-stationary manifolds of the fast subsystem (4) somehow deform as the bifurcation parameter $k_0$ is varied which, in turn, may cause changes in the bursting behaviour. In this sense, one can consider the flow rate $k_0$ as an external bifurcation parameter for the fast subsystem while the slow variable $p$ acts as an internal parameter since it cannot be tuned externally, but instead evolves dynamically according to (5). Hence, we are led to consider the two-parameter bifurcation diagram shown
Figure 7. Magnification of the dashed rectangular region in Figure 6.

in Figure 8 where the external parameter $k_0$ and the slow variable $p$ are used as the relevant parameters in order to detect changes in the bursting behaviour of the hemin system.

The blue dashed line marks the section $k_0 = 2.8$ along which the one-parameter bifurcation diagram of Figure 5 has been calculated. The subcritical Hopf bifurcation SH and the saddle-node bifurcation of periodic orbits SNP, shown there, have now become curves in the two-parameter plane (SH – red, dashed; SNP – black, dash-dot) which emanate from a codimension two bifurcation point, the generalized Hopf (GH, open triangle) or Bautin bifurcation [39]. Note that these two curves remain close together over a wide range of values of the flow rate parameter $k_0$ which is, in fact, a prerequisite for sub-Hopf/fold-cycle bursting to occur. In addition, there is a second curve of subcritical Hopf bifurcations SH$_2$ and a second curve of saddle-node bifurcations (not shown) at higher values of the slow variable which emanate from GH$_2$. However, they occur in a different region of phase space and thus have no direct impact on the actual dynamics of the 3-dimensional system. Whether the actual dynamics are (quasi-)periodic (for $k_0 \in (1.6461, 16519)$), simple periodic (for $k_0 \in (1.6519, 2.5169)$), or of bursting type (for $k_0 \in (2.5169, 3.8580)$) is eventually determined by the interplay between the fast and slow subsystem and therefore cannot be decided exclusively from the bifurcation structure of the fast subsystem.

However, the two-parameter bifurcation diagram shown in Figure 8 can be used to identify transitions in the bursting behaviour of the ODE system (2). For this purpose, consider the intersection point $(p, k_0) = (2.211, 3.773)$, marked with the red arrow, where the curve of subcritical Hopf bifurcations SH and the curve of saddle-node bifurcations of stationary points SN$_1$ cross each other. This opens the possibility that in a neighbourhood of the intersection point the (unstable) oscillatory states emanating from the subcritical Hopf bifurcation interact with the branch of (unstable) stationary states that originate in the saddle-node bifurcation. In order to show that this does indeed lead to a transition in the bursting behaviour, we compare the bifurcation diagrams of the fast subsystem for two neighbouring values of the flow rate $k_0$ corresponding to the two blue dotted lines in Figure 8.
Figure 8. Two-parameter bifurcation diagram of the fast subsystem (4). SH – subcritical Hopf bifurcation, H – supercritical Hopf bifurcation, SNP – saddle-node bifurcation of periodic orbits, BT – Bogdanov-Takens point, CP – cusp singularity, GH – generalized Hopf bifurcation, SN – saddle-node bifurcation of fixed points.

Figure 9 shows an overlay of the codimension one bifurcation diagrams of the fast subsystem with the trajectories (blue lines) for $k_0 = 3.6$ (Fig. 9a) and $k_0 = 3.8$ (Fig. 9b), respectively. These diagrams are similar to the one presented in Figure 5, but now for the variable $y$ instead of $x$. Note, however, that the range of the axis of the slow variable has been increased to visualize the global aspects of the bifurcation structure of the fast subsystem before and after the transition in the bursting behaviour. At $k_0 = 3.6$, the cylinder-like manifold (Fig. 9a, black circles) is bounded by the saddle-node bifurcation SNP at the left side and the saddle-node homoclinic orbit SNHC at the right side (at $p \approx 2.7$) where the saddle-node bifurcation SN1 occurs on the large amplitude limit cycle. The two saddle-node bifurcations SN1 and SN2 are the same as those found at the intersections of the blue dotted lines with the black solid lines SN1 and SN2 in Figure 8.

As the flow rate $k_0$ increases from 3.6 to 3.8, the saddle-node homoclinic orbit as well as the two saddle-node bifurcation points SN1 and SN2 move towards lower values of $p$ until the first of them (SN1) collides with the unstable limit cycle (red circles) at approximately $k_0 \sim 3.778$ (not shown). This leads to a codimension two bifurcation in the fast subsystem, a so-called saddle-node separatrix-loop bifurcation [40], where the saddle-node homoclinic orbit turns into a saddle homoclinic orbit (SCH) and, in addition, the saddle-node bifurcation SNP disappears (Fig. 9b). The SNHC is an orbit homoclinic to a non-hyperbolic equilibrium whereas the SCH is an orbit homoclinic to a hyperbolic equilibrium. After the codimension two bifurcation has occurred ($k_0 > 3.778$), the cylinder-like manifold disappears and the fast subsystem becomes...
bistable. Henceforth, the bursting behaviour of the hemin system is of fold/sub-Hopf type since the upper stationary state disappears via the subcritical Hopf bifurcation SH while the lower stationary state undergoes a fold bifurcation at SN\textsubscript{1}. A typical trajectory (blue line, Fig. 9b) jumps back and forth between the two quasi-stationary states causing a strong relaxational character to the oscillations.

4. Sub-Hopf/fold-cycle bursting and (quasi-)periodic oscillations on a 2-torus
In this section we wish to investigate the relation between bursting oscillations of sub-Hopf/fold-cycle type and (quasi-)periodic oscillations on a 2-torus. Therefore, we consider two model systems: The hemin system and, in addition, a recently introduced model for a Ca\textsuperscript{2+} oscillator system [38]. The latter also exhibits bursting oscillations of sub-Hopf/fold-cycle type. Again using the slow-fast method described in section 2, it will be shown that in both systems the (quasi-)periodic oscillations are associated with the same bifurcations of the fast subsystem that also account for the emergence of bursting oscillations.

4.1. The hemin system
As described in subsection 3.1 the hemin system has a Neimark-Sacker point NS at \(k_0 = 1.6519\) (cf. inset Fig. 3) where a smooth 2-torus bifurcates towards lower values of \(k_0\) (Figs. 10a,c). As the flow rate \(k_0\) is slightly decreased, the torus rapidly deforms (Figs. 10b,d) and approaches the saddle point S (open triangle) which emerges after the subcritical Hopf bifurcation SH corresponding to the red dashed line in the inset of Figure 3. The saddle point acts as an organizing center for the torus (Fig. 10b). The flow approaches the ‘outer part’ of the torus along the 2-dimensional unstable manifold of the saddle point. Then it moves to the left (i.e. towards lower \(p\) values) until it changes direction and returns along the 1-dimensional stable manifold of the saddle. Note that in Figures 10(a,b) the numerical integration was stopped before the trajectory made a full revolution on the torus in order to reveal a portion of the flow along the ‘inner part’ of the torus.

The reason for the trajectory to change its direction in Figures 10(a,b) can be grasped from the slow-fast analysis of (4). For this purpose, we superimpose the orbits shown in Figures 10(a,b) on the bifurcation diagram of the fast subsystem (4). Note that the bifurcation structure is the
Figure 10. Transition from a smooth torus at $k_0 = 1.65189$ (a,c) to a distorted one at $k_0 = 1.65180$ (b,d). Blue arrows denote the direction of the flow. ‘S’ marks a saddle point.

same as the one generating bursting oscillations. From Figure 11a it becomes apparent that the trajectory (blue line) on the smooth torus sweeps back and forth the saddle-node bifurcation point SNP of the fast subsystem. This suggests that the SNP point acts as a trap for the flow as long as the torus remains sufficiently small, i.e. as long as $k_0$ is close to the Neimark-Sacker bifurcation point $k_0 = 1.6519$. However, as the flow rate becomes smaller, the torus increases in size until the flow gets near the stable manifold of the saddle point S. When this happens the smooth torus almost instantaneously deforms into the torus shown in Figure 11b.

The flow on the deformed torus also closely follows the invariant sets of the fast subsystem. The large amplitude oscillations occur in the vicinity of the cylinder-like manifold (bold black lines) until the saddle-node bifurcation point SNP is passed to the left and the trajectory gets attracted by the line-like manifold (black solid line) along which the orbit returns to the neighbourhood of the saddle point S to begin the next revolution.

4.2. A calcium oscillator model
Recently, a calcium oscillator model was proposed which describes the coupling between Ca$^{2+}$ transport from the cytoplasm into the endoplasmic reticulum due to Ca$^{2+}$-ATPases (SERCA pumps) and intracellular energy-generation processes delivering ATP for the active transport [38]. The dynamics of the system were modeled using a 3-dimensional ODE system of the form

$$\frac{d}{dt}[Ca^{2+}] = \nu_0 - \Phi([Ca^{2+}],[ATP])$$

$$\frac{d}{dt}[ATP] = q\Psi([GLC],\Phi) - \Phi([Ca^{2+}],[ATP]) - k[ATP]$$

(6)
Figure 11. Overlay of the smooth torus (a) at $k_0 = 1.65189$ and the distorted torus (b) at $k_0 = 1.65180$ with the bifurcation diagram of the fast subsystem (4). Bold black/red lines denote stable/unstable limit cycles.

Figure 12. One-parameter bifurcation diagram of the calcium oscillator model (6).

\[
\frac{d}{dt} [GLC] = \nu_1 - \Psi([GLC], \Phi)
\]

where $\Phi$ and $\Psi$ are nonlinear functions describing the rate of $\text{Ca}^{2+}$ transport and the ATP-generation rate, respectively. $[GLC]$ denotes the glucose concentration in the system. The two main control parameters are the $\text{Ca}^{2+}$ influx rate $\nu_0$ and the ATP-degradation rate $k$. (For details, see [38]).

A one-parameter bifurcation diagram of the 3-dimensional ODE system (6) is displayed in Figure 12. As the ATP-degradation rate $k$ is increased from $3s^{-1}$ to $4s^{-1}$, the system undergoes...
a supercritical Hopf bifurcation \( H \) at \( k = 3.163 s^{-1} \) which is followed by a supercritical Neimark-Sacker bifurcation \( NS \) at \( k = 3.199 s^{-1} \) where the primary periodic orbit (black circles) becomes unstable (red circles) and a stable 2-torus is created (Fig. 13). As \( k \) is increased from the NS point, the torus continuously deforms (a,b) and eventually bursting oscillations arise (c,d). Figures 13(e,f,g,h) show the corresponding time series.

The flow on the torus in Figure 13a and the bursting oscillations in Figure 13d are strongly reminiscent of their corresponding counterparts in the hemin system (Fig. 10a and Fig. 6) which suggests that the ODE system (6) exhibits a slow-fast structure similar to that of the hemin system (2) where the glucose concentration \([GLC]\) now plays the role of the slow variable \( p \) of the hemin system. In order to test this hypothesis, we calculated the bifurcation diagram of the fast subsystem

\[
\begin{align*}
\frac{d}{dt}[Ca^{2+}] &= \nu_0 - \Phi([Ca^{2+}],[ATP]) \\
\frac{d}{dt}[ATP] &= q\Psi([GLC],\Phi) - \Phi([Ca^{2+}],[ATP]) - k[ATP]
\end{align*}
\]

by treating the glucose concentration \([GLC]\) as a quasi-static bifurcation parameter. The result is shown in Figure 14 where the bifurcation diagrams are superimposed on the phase portraits displayed in Figures 13(a-d).

Unlike the torus in the hemin system, the torus close to the Neimark-Sacker point in Figure 14a is now located near the subcritical Hopf bifurcation \( SH \). As long as the torus is small, i.e. for \( k \) close to \( k_{NS} = 3.199 s^{-1} \), it remains in the neighbourhood of the SH point and the flow can be described as follows (Fig. 14b, blue arrow): The trajectory (blue line) oscillates back and forth around the SH point. It approaches the SH point with decreasing amplitude along the stable part of the line-like quasi-stationary manifold (black solid line) in an oscillatory manner. Beyond the subcritical Hopf point the line-like manifold becomes unstable and the amplitude of the oscillations increases while the trajectory re-enters the basin of attraction of the stable part of the line-like manifold. Consequently, it changes direction and completes one revolution along the torus.

As the ATP-degradation rate \( k \) is increased, the torus continuously grows in size until the trajectory reaches the basin of attraction of the cylinder-like manifold near the large amplitude limit cycles (black circles) of the fast subsystem. When this happens, bursting oscillations become possible (Figs. 14c,d) which are of sub-Hopf/fold-cycle type since the bifurcation structure of the fast subsystem is identical to that of the hemin system shown in Figure 5. In contrast to the oscillations on the 2-torus shown in Figures 14(a,b), the large and small amplitude oscillations of the bursting oscillations have different frequencies.

5. Summary and Discussion

We have investigated the bursting oscillations in two model systems, the hemin system and a \( Ca^{2+} \) oscillator system, both of which exhibit sub-Hopf/fold-cycle bursting over a wide range of parameters. The dynamics of these two systems are described by 3-dimensional ODE systems (eqs. 2 and 6) with a slow-fast substructure, i.e. each of them comprises a 2-dimensional fast and a 1-dimensional slow subsystem where the slow variable acts as a quasi-static bifurcation parameter for the fast subsystem. The merit of such a decomposition is that it can be used to classify the bursting behaviour of the full 3-dimensional system according to the bifurcations occurring in the fast subsystem that lead to the emergence and disappearance of the bursting oscillations.

A prerequisite for sub-Hopf/fold-cycle bursting is that a subcritical Hopf bifurcation and a saddle-node bifurcation of a periodic orbit take place at nearby values of the slow variable in the fast subsystem, as is the case if the fast subsystem is close to a generalized Hopf bifurcation.
Figure 13. Deformation of the 2-torus: (Quasi-)periodic oscillations close to the Neimark-Sacker point at $k = 3.1991 \text{s}^{-1}$ (a,e) and $k = 3.2 \text{s}^{-1}$ (b,f) and the transition to bursting oscillations at $k = 3.23 \text{s}^{-1}$ (c,g) and $k = 4 \text{s}^{-1}$ (d,h).
For the hemin system, we explicitly verified that this condition is fulfilled over a wide range of the external control parameter $k_0$. For this purpose, a two-parameter continuation was performed using the flow rate $k_0$ and the slow variable $p$ (Fig. 8).

We further argued that the two-parameter bifurcation diagram can be useful to detect qualitative changes in the bursting behaviour of the system. For the hemin system, we found a transition in the bursting behaviour from sub-Hopf/fold-cycle to fold/sub-Hopf type which is caused by a codimension two bifurcation in the fast subsystem. As a result of the bifurcation, the non-hyperbolic homoclinic orbit SNHC becomes hyperbolic (SHC) and the invariant cylinder-like manifold is destroyed (Fig. 9). Henceforth, the fast subsystem is bistable and leads to relaxational oscillations.

A further issue that has been addressed is the relation between bursting oscillations of sub-Hopf/fold-cycle type and (quasi-)periodic oscillations. In both of the model systems investigated we observed tori with special flows (cf. Fig. 11 and Figures 14a,b) suggesting an explanation in terms of the slow-fast structure of the corresponding ODE systems. Clearly, the flow on these tori is such that a typical trajectory oscillates faster in the direction perpendicular to the slow variable. If we consider a 2-torus as a direct product of two circles with different radii (Fig. 15), then the angular velocity $\omega_L$ along the circle with the larger radius is much larger than that of the circle with the smaller radius (Fig. 15a). In other words, the ‘unusual’ phase flow in...
Figure 15. Sketch of the flow on 2-tori with different ratios of angular velocities: \( \omega_L > \omega_S \) (‘unusual’) (a) and \( \omega_L < \omega_S \) (‘usual’) (b).

Figure 11 and Figure 14 is a result of the time scale separation in the ODE systems (2) and (6).

A subsequent slow-fast analysis of the flow on the tori supports this picture. In particular, we observed the same bifurcation structure in the fast subsystem as for the bursting oscillations. Thus, the particular constellation of a subcritical Hopf bifurcation and a saddle-node bifurcation of a periodic orbit also allows for (quasi-)periodic oscillations on a 2-torus. While this holds true for both systems, there is, however, an important difference: The (quasi-)periodic oscillations in the hemin system emerge near the saddle-node bifurcation point (SNP, Fig. 11a) which leads to the blow-up effect, i.e. the torus rapidly increases in size in a very narrow parameter interval as the flow rate \( k_0 \) is decreased below the Neimark-Sacker point (cf. Fig. 11b). In contrast, the torus in the calcium oscillator model is generated near the subcritical Hopf bifurcation (Fig. 14a) which leads to a continuous deformation into bursting oscillations as the torus increases in size (Fig. 13). Thus, the two model systems follow different ‘routes’ to bursting oscillations. While the bursting oscillations in the hemin system arise as periodic orbits in narrow parameter windows of a chaotic domain far away from the region in parameter space where (quasi-)periodic behaviour is observed, the bursting oscillations in the calcium oscillator model emerge as a 2-torus continuously deforms. Both of these routes are well-known. However, our analysis suggests that the quasi-periodic route to bursting oscillations is followed if the corresponding torus is created near the subcritical Hopf bifurcation of the fast subsystem.

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