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Asymmetry of synchronisation tongue in persistent sodium plus potassium neuron model

I. A. Khovanov*, S. Perry, N. A. Khovanova

School of Engineering, University of Warwick, Coventry, CV4 7AL, United Kingdom

Abstract

In recent experimental studies, cardio-respiratory synchronisation was observed when the respiration rate was higher than the resting heart rate. Under this condition, there is a strong asymmetry in the synchronisation tongue towards frequencies higher than that of an unperturbed self-oscillator. These experimental results are compelling because they support a novel hypothesis about the interaction of cardiac and respiratory centres in the brain. This hypothesis, however, required further validation; we aimed to observe the key experimental features in related dynamical models. A number of simple self-oscillatory systems under an external driving force have been considered in this work, and a persistent sodium plus potassium neuron model was found to display the strong asymmetry, which is the key feature of the experimental observations. Bifurcations and other changes in the model’s state space were considered by varying the amplitude and frequency of the external force. It was shown that the strong asymmetry in the synchronisation tongue is linked to a non-uniformity of the surface of the non-synchronous invariant torus, and, within a certain range of parameters, to the additional saddle-node bifurcations of cycles. Then, it was demonstrated that the torus non-uniformity leads to changes in the shape of the phase difference potential as the amplitude increases. To illustrate the latter effect, a numerical approach for estimating the one dimensional phase difference profile and providing the corresponding explicit analytical expression is developed. Also, a discrepancy in synchronisation boundaries obtained by two different approaches, one based on bifurcational analysis and the other on a time series technique, was observed. The latter observation stresses the necessity of considering the standard deviation of instantaneous frequency alongside the mean value for the non-ambiguous identification of synchronisation in periodically driven systems.

Keywords: phase synchronisation, cardio-respiratory interaction, neuron model, dynamical system, bifurcations, saddle-node bifurcation, period-doubling bifurcation, manifolds of saddle cycle, statistics of instantaneous frequency, phase coupling function

*Corresponding author

Email address: i.khovanov@warwick.ac.uk (I. A. Khovanov)

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1. Introduction

In the majority of research publications, [1, 2] the phenomenon of cardio-respiratory synchronisation is examined at spontaneous respiration rates. Such considerations concluded that cardio-respiratory synchronisation is an elusive phenomenon of an intermittent nature [3]. In some other works, i.e. by Pokrovskii et al. (see [4, 5] and references in therein), it is suggested that at respiratory rates slightly higher than the resting heart rate, cardio-respiratory synchronisation manifests itself as a robust phenomenon with a distinct mechanism involving a strong coupling between the respiratory and cardiac neuronal regulatory centres. Subsequently [6, 7], respiratory rates corresponding to the boundaries of synchronisation regions have been identified. However, recent experimental research [8] has cast some doubt on the conclusions derived by Pokrovskii et al [6, 7]. In particular, it has been demonstrated [8] that natural variability (fluctuations) in the controlled breathing rate is significant and comparable with the width of synchronisation regions reported in works [6, 7]. Moreover, a significantly longer duration of experiments than in studies [6, 7] allowed observation of long transient periods before the heart rate is stabilised [8]. These periods were found to be comparable with the total length of experiments to observe synchronisation reported previously [6, 7]. These observations [8] concluded that careful consideration is required for the boundaries of synchronisation regions to be identified reliably.

Allowing longer measurements [8], cardio-respiratory synchronisation has been observed for breathing rates higher than the resting heart rate, in agreement with the original idea [4]. Note that the synchronisation is more pronounced for the athletes [9]: people regularly perform rhythmically breathing exercises. This fact presumably means that the action of respiration on the heart rhythm is stronger in this people group. The summary of the experimental results is shown in Fig. 1. Synchronisation was observed when the breathing rate was approximately 10% larger than the resting heart rate, and there was no synchronisation if the rate was close to the resting heart rate or less than it. This result demonstrates a strong asymmetry towards high frequencies in the synchronisation region. Note that the asymmetry was an essential component in the original hypothesis [4], where the condition that the respiratory rate is higher than the resting heart rate was associated with the existence of specific neural links between heart and respiratory centres in the medulla. Although presented without a solid mathematical basis, some supporting evidence [4] of the existence of these neural links has been reported in animals (but not in humans). Under this theory [4], the neural respiratory centre is considered as a driving force acting unidirectionally on the neural heart centre and locking the heart rate. The cardio-respiratory interaction can therefore be modelled as a self-oscillatory system (generator), corresponding to the heart centre, under the action of an external periodic force, corresponding to the respiratory centre. Such models are widely used to describe synchronisation phenomena and synchronisation regions in a variety of dynamical systems [10, 11, 12, 13].

These synchronisation regions shown on a parametric plane of frequency-amplitude of the external force are known as Arnold tongues [10, 11]. For a weak force, the tongues on the plane are symmetrical with respect to the natural frequency of the self-oscillator. A stronger force may lead to a distortion of the tongue’s symmetry and overlapping the tongues for different frequencies ratios, for example, for ratio 1:1 and ratio 2:1. An example of such distorted asymmetric tongues was reported by Glass and Mackey in work [14] which is one of the first papers describing synchronisation in biological systems. Similarly, distorted tongues were reported in many other works (see books [10, 11, 13] and references therein) for a large amplitude force or strong mutual coupling.
In contrast, a widely used phase description \[12, 13, 16\] typically assumes a small force or weak coupling between systems. This assumption means that the external perturbation or coupling does not change the system’s state space. Many phase reduction techniques were developed \[17\]. For weak coupling, they lead to differential equations for systems’ phases with a small parameter representing the amplitude of the external force or the strength of systems’ coupling. This parameter is an expansion factor for a phase coupling function, which is a phase potential for a system under an external force. As a result, the shape of the phase potential does not depend on the amplitude of the external forcing or coupling strength. So, such an approach is not able to describe the tongues’ distortion. Note that the phase reduction techniques \[17\] provide a simplified description that can be applied for analysing oscillators’ interaction beyond the phase synchronisation. The phase reduction shows to be particularly fruitful for analysing the large oscillatory networks \[15, 16, 18, 19, 20, 21\].

Recently, the phase reduction beyond the assumption of weak force (coupling) approximation was suggested \[22, 23\]. A numerical approach \[22\] allows one to reconstruct a phase coupling function for arbitrary parameters outside the synchronisation regions. This approach is helpful for the more generic task of characterising the system’s interaction. A theoretical technique \[23\] was developed as a perturbation theory around an unperturbed self-oscillatory solution. It was shown \[23\] that the consideration of high order coupling terms leads to changes in the shape of the phase potential. Note that the approach \[23\] was applied to coupled identical systems and its applicability to a more generic situation, in particular, to a system under external force, is unclear.

So, distorted asymmetrical Arnold tongues were observed with the increase of the external forcing amplitude or the strong coupling between systems. However, it is unclear could the asymmetry be described in the framework of the phase description. Consequently, the links between the asymmetry and changes in the phase potential remain unexplored. More generally, it is unclear what system’s properties for observing the strong asymmetry in the synchronisation regions are. The answers to these questions form the subject of this manuscript.

Intrigued by the fact that cardio-respiratory synchronisation for high respiratory rates has a strong asymmetry in the synchronisation tongue towards higher frequencies, we considered many dynamic models to identify those that could describe this feature. Note that we were not able to identify a suitable model in the reported synchronisation studies. We found that the persistent sodium plus potassium \((I_{\text{Na,p}} + I_K)\) neuron model \[24\] demonstrates the described asymmetry in Arnold tongues for a weak additive force acting on the model. In this manuscript, we analyse the strongly asymmetrical Arnold tongue in the \(I_{\text{Na,p}} + I_K\)-model. In particular, first, bifurcations associated with the asymmetry are considered together with the robustness of the asymmetry observations for variations in the model’s parameters. Also, the changes in the model’s state space are analysed. Second, for linking the asymmetry with the phase description, the numerical approach for estimating the phase potential is introduced and applied for characterising the tongue’s asymmetry. The approach is based on early ideas \[25\] of representing phase as a slow variable with respect to the system’s frequency. Considering a simpler (than typically discussed \[17, 22, 23\]) problem: a single system under an external periodic force, allows us to write down an analytical expression for the phase potential in the synchronisation regions. In such a way, the essential ingredients for the strong tongue’s asymmetry are identified. Additionally, our research aims to verify and explain the experimental results \[4, 5, 8\] and the hypothesis of coupling between respiratory and cardiac higher neural centres \[4\] through a modelling approach.
The structure of the manuscript is as follows. In the next section, the synchronisation tongue and related bifurcation in an archetypical self-oscillatory Van der Pol model are discussed. Then the asymmetric tongue in the $I_{Na,p} + I_K$-model is discussed alongside bifurcations, changes in the model's state space and evolution of the phase potential. Further, some pitfalls in identification of the phase synchronisation using experimental time-series are illustrated. Also, the robustness of the observed asymmetry with respect to parameters' variation is analysed. Finally, conclusions are made and open problems are outlined.

2. Typical synchronisation Arnold tongue for an external force of small amplitude

In previous works which considered the cardio-respiratory synchronisation at high guided breathing rates [4, 8], it was noted that the heart rate does not influence the breathing rate. This implies that breathing can be considered as an external driving force acting on the heart rate, which is in agreement with Pokrovskii's hypothesis [4]. In our earlier experiments [8], the strength of the coupling between the breathing and heart centres was not controlled and was unknown. Recently [9], however, it has been shown that the strength of this coupling varies for different people and is more pronounced in athletes. Another experimental observation [8] is that there is a strong noise background resulting from breathing and heart rate variation, which can be considered as fluctuations. The presence of such fluctuations explains the absence of synchronisation for large parts of the guided breathing interval, implying that the coupling strength is relatively weak (since fluctuations can destroy the synchronisation). The experimental observations [8, 9] thus conclude that the amplitude of the external force acting on the self-oscillator, which represents the heart centre, should be small.

In this section, it is assumed that both breathing and heart centres generate periodic signals in the absence of coupling, and that the stochastic components of rates observed in the experiments [8] are not taken into account. We assume unidirectional coupling between the breathing
and heart centres: the breathing centre is considered as an external periodic signal with a particular amplitude and frequency. It acts additively on the heart centre, which is represented as a self-oscillator. The basic synchronisation mechanisms in such a setting are well-studied [10, 11, 12]. In experiments [8], an instantaneous phase was used to detect synchronisation and address variability of rates. An instantaneous phase is often used to describe the synchronisation of periodic self-oscillators [10, 11, 12]. Let \( \phi(t) \) and \( \varphi = \omega t \) be the instantaneous phases of a self-oscillator and external force respectively. Synchronisation is observed when the difference \( \psi(t) = \phi(t) - \varphi(t) \) is limited and does not grow in time: \( \psi(t) < 2\pi \). For a weak external force, the dynamics of the phase difference are described by the following equation [10, 12]:

\[
\frac{d\psi}{dt} = -\delta + \epsilon \sin \psi,
\]

where \( \delta = \omega - \Omega_0 \) is the frequency detuning parameter; \( \Omega_0 \) is the frequency of the autonomous self-oscillator and \( \omega \) is the external signal’s frequency. Parameter \( \epsilon \) is proportional to the amplitude of the external force. The equilibrium points of the system (1) correspond to periodic motion (cycles), and the stable points correspond to synchronisation. The following condition defines the synchronisation region (tongue) [10, 12]:

\[
\epsilon = \pm \delta,
\]

Therefore the width of the tongue, which is proportional to \( \delta \), grows linearly with the amplitude of the external force. The positive and negative cases for \( \delta \) in (2) correspond to external frequencies lower and higher that the unperturbed frequency of the self-oscillator, respectively. The tongue demonstrates symmetry, and there is no preference for low or high frequencies. On the boundary of the tongue, saddle-node bifurcation of equilibrium points of the system (1) is observed. After this bifurcation, there are no equilibrium points in (1) and the phase difference \( \psi \) changes monotonically in time, which corresponds to non-synchronous motion. Note that other bifurcations on the boundary of the tongue are possible [10, 11, 12], but we limit our analysis to cases of saddle-node bifurcation only. In such cases, the phase description is valid, and the amplitude dynamics can be ignored [8]. Such a symmetrical tongue is a generic property of the majority of low-dimensional self-oscillatory systems studied under the action of a weak forcing [10, 11, 12].

As an example and illustration of the conclusion above, let us consider the synchronisation tongue for a Van der Pol self-oscillator:

\[
\ddot{x} + \dot{x}(x^2 - 1) + x = A \sin \omega t
\]

Here \( A \) and \( \omega \) are the amplitude and frequency of the external force, respectively. Let \( \Omega_0 \) be the frequency of the autonomous Van der Pol self-oscillator \( (A = 0) \), and \( \Omega \) be the mean frequency of the self-oscillator in the presence of force \( (A \neq 0) \). The values of \( \Omega_0 \) and \( \Omega \) can be found by considering the time series of coordinate \( x(t) \) and using the threshold crossing technique [12], a similar approach to that used in experiments [8]. To find the solutions for this system and all other systems below, the Runge-Kutta method of 4th order [26] was applied. Synchronisation with ratio 1:1 is observed when \( \Omega = \omega \). The Arnold tongue in Fig. 2(a) shows the region of synchronisation on the parameter plane. The width of the region grows with the amplitude \( A \). There is a relatively small asymmetry with respect to the linear relationship (2) - compare the solid and dashed lines in Fig. 2(a).
Figure 2: (a) The synchronisation tongue for Van der Pol self-oscillator (3) is shown on the parameter plane given by the frequency ratio \( \frac{\omega}{\Omega_0} \) (x-axis) and amplitude \( A \) (y-axis). The solid lines mark the boundary of the tongue obtained by numerical simulations of equation (3). The dashed lines indicate the symmetrical tongue which follows from condition (2). (b) The asymmetry coefficient \( C_A \) as a function of the normalised half-width \( \Delta_L \) for the tongue in figure (a).

Let \( \omega_L \) and \( \omega_H \) be the values of frequency \( \omega \) on the boundaries of the tongue; \( \omega_H > \omega_L \). The asymmetry coefficient \( C_A \) (Fig. 2(b)) can be calculated as follows

\[
C_A = \frac{\omega_H - \Omega_0}{\Omega_0} - \frac{\Omega_0 - \omega_L}{\Omega_0},
\]

and the normalised half-width for low frequencies is

\[
\Delta_L = \frac{\Omega_0 - \omega_L}{\Omega_0}
\]

Experimental results [8] show that \( (\omega_H - \Omega_0) \gg (\Omega_0 - \omega_L) \); consequently, to describe the experiment, \( C_A \) should be around 0.1 or 0.2, whereas \( \Delta_L \) should be close to zero. The dependence of \( C_A \) on \( \Delta_L \) shown in Fig. 2(b) for the Van der Pol self-oscillator (3) does not fit our experimental results at elevated respiratory frequencies, shown in Fig. 1; the asymmetry of the tongue is rather weak even for large values of amplitude \( A \).

Other models (the Rayleigh self-oscillator, and different versions of the FitzHugh-Nagumo neuron model), not presented here, were also considered, and demonstrated a similar behaviour to the Van der Pol oscillator, with a symmetrical synchronisation tongue. However, simulation of the \( I_{Na,p} + I_K \)-model with typical parameters [24] shows a strong tongue asymmetry, as described in the next section.

3. Synchronisation tongue and related bifurcation in \( I_{Na,p} + I_K \)-model

The \( I_{Na,p} + I_K \)-model is the two-dimensional version of the persistent sodium plus potassium neuronal model and is one of the fundamental models in computational neuroscience [24]. This is an example of the minimal neuron models demonstrating spiking behaviour and exhibiting periodic activity; it has the following form [24]

\[
C\dot{V} = I - g_L(V - E_L) - g_{Na}m_{\infty}(V)(V - E_{Na}) - g_Kn(V - E_K) + I_0 \sin(\omega t)
\]

\[
\dot{n} = (n_{\infty}(V) - n) / \tau
\]
where the activation functions $m_\infty$ and $n_\infty$ are

$$m_\infty(V) = \frac{1}{1 + \exp\left((V_{1/2,m} - V)/k_m\right)}, \quad n_\infty(V) = \frac{1}{1 + \exp\left((V_{1/2,n} - V)/k_n\right)}$$

In (6) the external force $I_0 \sin(\omega t)$ is a modulation force of the ionic current $I$. The parameters of the model are $C = 1 \, [\mu F/cm^2]$, $I = 40 \, [pA]$, $E_L = -78 \, [mV]$, $E_K = -90 \, [mV]$, $E_{Na} = 60 \, [mV]$, $g_L = 8 \, [S]$, $g_{Na} = 20 \, [S]$, $g_K = 10 \, [S]$. The dimensionless activation functions $n_\infty$ and $m_\infty$ have the following parameters: $V_{1/2,n} = -45$, $k_n = 5$ and $V_{1/2,m} = -20$, $k_m = 15$.

Numerical simulations of system (6) lead to the synchronisation tongue shown by marker □ in Fig. 3. In these simulations, the instantaneous frequency of coordinate $V(t)$ was determined using the threshold crossing technique [8, 12], which was followed by calculation of the mean value of the instantaneous frequency. The same approach was used in the experiments. Fig. 3 shows that the tongue becomes strongly asymmetric for the relatively small amplitude $I_0 > 1.1$. Such asymmetry fits the results of our experiments [8] perfectly. The synchronisation boundary for low frequencies deviates only weakly from the frequency ratio $\omega/\Omega_0 = 1$, whereas the boundary for high frequencies changes sharply with growing amplitude. It could be hypothesised that this behaviour is due to a bifurcation associated with the sharp change in the shape of the tongue.

![Figure 3](image-url)

Figure 3: The synchronisation tongue for neuron model (6) is shown on the parameter plane given by the frequency ratio $\frac{\omega}{\Omega_0}$ and amplitude $I_0$. The marker □ corresponds to the boundaries of synchronisation tongue obtained by numerical simulations of (6). The lines correspond to different bifurcations: the green solid line on the left to BL1, the red solid line on the right to BH2, the dashed magenta line to BH1 and the dash-dotted blue line to the period-doubling bifurcation. The marker × corresponds to the boundaries calculated using the reconstructed potential $U(\psi, I_0)$.

It is known that for a weak force, the boundaries of the synchronisation tongue are defined by the saddle-node bifurcation of cycles [10, 12]. Using custom software which implements known methods [27] for locating an unstable cycle and calculating its multipliers, we analysed...
bifurcations of cycles for different amplitudes $I_0$. At the saddle-node bifurcation, the collision and disappearance of two cycles occurs, with one of the multipliers equal to 1 at the bifurcation point (see [10, 11, 12] for further details). This bifurcation occurs on the boundary of the synchronisation tongue. Fig. 4 illustrates the changes in bifurcations as the amplitude $I_0$ increases, displaying the coordinate $V_i$ in the stroboscopic section $\omega t = 2\pi i$, where $i$ is an integer, alongside the largest cycle multiplier $\mu$. For amplitude $I_0 < 1.07$, there are two cycles within the synchronisation tongue: one of which, ST1, is stable; the other, SD1, is a saddle node. We denote the saddle-node bifurcations on the boundaries as BL1 and BH1 for low and high frequencies respectively: the index “1” in this notation corresponds to the stable cycle ST1. An example of the evolution of the cycles’ locations $V_i$ and the largest multiplier $\mu$ of the cycles is shown in Fig. 4(a) for a small amplitude $I_0 = 1.0$. Note that both bifurcations, BL1 and BH1, occur around particular values of $V_i$ which change only slightly with as amplitude $I_0$ increases (compare the black horizontal dashed lines in Figure 4(a)-(d) for bifurcation BH1). At these locations, the largest multiplier (dotted lines in Fig. 4(a)) of the stable ST1 and saddle SD1 cycles is equal to one. The inset in Fig. 4(a) shows a zoomed-in region around $\omega \Omega_0 \approx 1.008$. In this region, the largest multiplier of the saddle cycle SD1 has a minimum, which could be considered as a precursor of another saddle-node bifurcation occurring for parameters $I_0 \approx 1.061$ and $\omega \Omega_0 \approx 1.0093$. For larger amplitudes, $I_0 > 1.061$, there are four cycles in some region of the ratio $\frac{\omega}{\Omega_0}$, as shown in Fig. 4(b). For $I_0 = 1.1$, there are four saddle-node bifurcations: two bifurcations, BL1 and BH1, define the boundary of the synchronisation tongue, whereas the other two, BL2 and BH2, define the narrow region of the coexistence of two stable cycles ST1 and ST2 (Fig. 4(b)).

Up to amplitude $I_0 < 1.13$, bifurcation BH1 defines the synchronisation boundary for high frequencies - compare the dashed and solid lines in Fig. 3. However, the location of the bifurcation BH2 on the frequency axis changes significantly as $I_0$ increases, and for large amplitudes $I_0 > 1.13$, the boundary is instead defined by BH2 (Fig. 4(c, d) and the rightmost solid line in Fig. 3). Moreover, the synchronisation boundary increases shifts significantly towards higher frequencies, and this causes the asymmetry of the tongue in Fig. 3. Remarkably, the location of bifurcation BH1 on the frequency axis (see the dashed line in Fig. 3) changes only weakly with the increase of $I_0$, and this change is symmetrical with respect to the location of the bifurcation for low frequencies BL1. Thus, bifurcations BL1 and BH1 form a symmetric tongue, whereas the asymmetry appears due to the BH2 bifurcation (Fig. 3).

As the described bifurcations are local, in order to understand the changes in state space of system (6), the changes in location of stable and unstable cycles as well as changes in manifolds of saddle cycles need to be considered. The state space of system (6) in the stroboscopic section $\omega t = 2\pi n$ is shown in Fig. 5 for $I_0 = 1.5$ in three different cases: (a) before bifurcation BL2, (b) after BL2 but before BH1, and (c) after BH2. In the first case (Fig. 5(a)), there are three cycles in the state space: stable ST1, saddle SD1 and a repeller cycle RP. This is a well-described typical state space structure inside a synchronisation tongue [10, 11, 12]. The second case (Fig. 5(b)) corresponds to two coexistent stable cycles ST1 and ST2 ($I_0 = 1.5, \frac{\omega}{\Omega_0} = 1.015$). Two stable and two unstable cycles lie on a 1-dimensional curve which is formed by the one-dimensional unstable manifold of saddle cycles. This one-dimensional curve corresponds to an invariant torus, which represents unstable non-synchronised motion. Such a curve is observed outside the synchronisation tongue, but without the cycles. The unstable manifold does not play any significant role in changes in the state space: one branch of the unstable manifold of saddle cycles goes to the repeller cycle RP, and the other to infinity. The third case (Fig. 5(c))
shows the state space after bifurcation BH2, which leads to the disappearance of cycles ST1 and SD2; the remaining cycles ST2 and SD1 lie on an one-dimensional curve and the state space looks similar to the first case (Fig. 5(a)).
Figure 4: The coordinate $V_i$ of the stable cycles (solid lines) and saddle cycles (dashed lines) and their largest multipliers, $\mu$, (dotted lines) are shown as functions of the ratio $\frac{\omega}{\Omega_0}$ for different values of amplitude $I_0$: (a) $I_0 = 1$, (b) $I_0 = 1.1$, (c) $I_0 = 1.13$, (d) $I_0 = 1.5$. The insets show the behaviour of $\mu$ in a region around saddle-node bifurcations (b-d) and their precursor (a). Vertical grey lines indicate the values of $\frac{\omega}{\Omega_0}$ where the saddle-node bifurcation occurs. The dashed grey horizontal line shows the value of $V_i$ for the bifurcation BH1. The solid grey horizontal line shows the value of $\mu = 1$. Red and magenta colours correspond to stable cycles ST1 and ST2 respectively, and blue and green colours correspond to saddle cycle SD1 and SD2 respectively.

Fig. 5 demonstrates that the shape of the one-dimensional curve formed by the unstable
Figure 5: The state space of model (6) for different values of the ratio $\frac{\omega}{\Omega_0}$: (a) $\frac{\omega}{\Omega_0} = 0.995$, (b) $\frac{\omega}{\Omega_0} = 1.015$, and (c) $\frac{\omega}{\Omega_0} = 1.048$. The amplitude is $I_0 = 1.5$ and $\tau = 1$. Markers $\circ$ and $\Box$ correspond to stable cycles ST1 and ST2, respectively; markers $\times$ and $+$ correspond to saddle cycles SD1 and SD2, respectively. Marker $\Diamond$ corresponds to the repeller cycle RP. Solid and dashed lines represent unstable and stable manifolds, respectively. Arrows indicate the directions of motion on the manifolds. Figure (d) shows the reconstructed potential $U(\psi, I_0)$ for the following ratios: curve 1 (blue colour) $\frac{\omega}{\Omega_0} = 1$, curve 2 (red colour) $\frac{\omega}{\Omega_0} = 0.995$, curve 3 (black colour) $\frac{\omega}{\Omega_0} = 1.015$, and curve 4 (magenta colour) $\frac{\omega}{\Omega_0} = 1.048$. Stable and unstable states are denoted by the markers corresponding to the stable and saddle cycles in figures (a)-(c).

The saddle-node bifurcation has one-dimensional normal form [28] and is observed on a curve representing an invariant torus (Fig. 5). Therefore, a further insight in the asymmetry origin can be achieved by considering the phase difference $\psi(t)$ representing each point on the torus in one-dimensional space. The dynamics of $\psi(t)$ can be described by the following system:

$$\frac{d\psi}{dt} = -\delta + f(\psi, I_0).$$

This equation is similar to Eq. (1), but the external signal’s amplitude, $I_0$, can change the
form of the right-hand side of the equation. System (7) describes a motion of a particle in one-dimensional potential, \( U(\psi, I_0) \), defined by the following expression:

\[
U(\psi, I_0) = \delta \psi - \int f(\psi, I_0) d\psi.
\]  

(8)

Function \( f(\psi, I_0) \) and corresponding potential \( U(\psi, I_0) \) were reconstructed by the following procedure. First, an invariant torus curve was obtained by estimating the unstable manifolds of the saddle cycle (see Fig. 5(a)-(c)). In terms of phase difference \( \psi(t) \), each branch of the manifold is a trajectory connecting unstable and stable states. Since the phase difference \( \psi(t) \) in Eq. (7) is a slow varying function [25], the trajectory of \( \psi(t) \) was calculated via Hilbert transform of variable \( V(t) \) of Eq. (6) with averaging out fast oscillations. For averaging, a central moving average window of width \( 2\pi/\omega \) was applied three times. Then, the time derivative \( \dot{\psi}(t) \) was calculated by the central-difference scheme applied to \( \psi(t) \). The representation of the trajectory on the plane \( \dot{\psi}(t) \) versus \( \psi(t) \) gives the form of function \( f(\psi, I_0) \), which was represented using a high-order polynomial function. The potential \( U(\psi, I_0) \) was obtained via integration (8) and joining pieces of unstable manifold branches and taking into account that the potential is \( 2\pi \)-periodic function. The calculations were performed for \( \delta = 0 \) and a range of \( I_0 \) values. Note, similar calculations were performed for non-zero \( \delta \), and they confirmed the validity of Eq. (7) with an additive detuning term \( \delta \). The potentials reconstructed for \( \delta = 0 \) are discussed below.

Figure 6: (a) The reconstructed potentials \( U(\psi, I_0) \) for \( \delta = 0 \) and different values of amplitude: \( I_0 = 0.5 \) (solid red line), \( I_0 = 1.0 \) (dashed green line), and \( I_0 = 1.5 \) (dotted blue line). Insert in the figure shows the potentials without the bias and with the barrier heights normalised to be equal. (b) The potentials \( U(\psi, I_0) \) for \( I_0 = 0.5 \) and different values of frequency detuning parameter: \( \delta = 0 \) and \( \frac{\omega}{\Omega_0} = 1 \) (solid line), \( \delta = -0.0093 \) and \( \frac{\omega}{\Omega_0} = 0.9948 \) (dashed line with a negative slope), and \( \delta = 0.0090 \) and \( \frac{\omega}{\Omega_0} = 1.0052 \) (dashed line with a positive slope). The potentials shown with dashed lines correspond to the boundaries of the synchronisation tongue.

For small values of amplitude \( I_0 \), potential \( U(\psi, I_0) \) has a shape close to those described by system (1) (see Fig. 6(b) and Table I below). The changes in detuning parameter \( \delta \) rock the potential, leading to the saddle-node bifurcation of the equilibrium states in system (7). The potentials corresponding to the bifurcation are shown by dashed lines in Fig. 6(b). The increase of \( I_0 \) modifies the shape of \( U(\psi, I_0) \), leading to a flatter potential profile, larger barriers between the states and a negative bias in potentials (see Fig. 6(a)). An analysis shows that
the changes in the potential shape has the most significant impact on the synchronisation boundaries and, consequently, on the tongue’s asymmetry. The bifurcations of equilibrium states in the reduced phase model (7) fully correspond to cycles’ bifurcations in system (6). The saddle-node bifurcations within the synchronisation tongue can be linked to the complicated profile of potential \( U(\psi, I_0) \). The synchronisation boundaries (marker \( \times \) in Fig.

Further insight in the shape’s changes of \( U(\psi, I_0) \) can be provided by considering an analytical expression for the potential. Since potential \( U(\psi, I_0) \) is 2\( \pi \)-periodic function\[12, 15\], the potential can be written using Fourier series:

\[
U(\psi, I_0) = \delta \psi + C_0(I_0)\psi + \sum_{i=1}^{N} C_i(I_0) \cos [i\psi + 2\pi \theta_i(I_0)].
\] (9)

Coefficients \( C_i(I_0) \) and \( \theta_i(I_0) \) can be evaluated from the reconstructed potentials shown in Fig. 6(a). Table 1 provides values of \( C_i(I_0) \) that define potential (9) with the relative error less than 1%.

<table>
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<th>( I_0 = 0.5 )</th>
<th>( I_0 = 1.0 )</th>
<th>( I_0 = 1.5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_0 ) =</td>
<td>(-1.079 \cdot 10^{-5})</td>
<td>(-7.204 \cdot 10^{-5})</td>
<td>(-4.715 \cdot 10^{-4})</td>
</tr>
<tr>
<td>( C_1 ) =</td>
<td>(2.210 \cdot 10^{-4})</td>
<td>(4.431 \cdot 10^{-4})</td>
<td>(9.945 \cdot 10^{-4})</td>
</tr>
<tr>
<td>( \theta_1 ) =</td>
<td>(-0.209)</td>
<td>(-0.183)</td>
<td>(-0.072)</td>
</tr>
<tr>
<td>( C_2 ) =</td>
<td>(5.337 \cdot 10^{-6})</td>
<td>(3.806 \cdot 10^{-5})</td>
<td>(3.134 \cdot 10^{-4})</td>
</tr>
<tr>
<td>( \theta_2 ) =</td>
<td>(-0.179)</td>
<td>(-0.165)</td>
<td>(-0.166)</td>
</tr>
<tr>
<td>( C_3 ) =</td>
<td>(1.097 \cdot 10^{-5})</td>
<td>(1.291 \cdot 10^{-4})</td>
<td>(--)</td>
</tr>
<tr>
<td>( \theta_3 ) =</td>
<td>(--)</td>
<td>(-0.349)</td>
<td>(-0.372)</td>
</tr>
<tr>
<td>( C_4 ) =</td>
<td>(--)</td>
<td>(--)</td>
<td>(4.932 \cdot 10^{-5})</td>
</tr>
<tr>
<td>( \theta_4 ) =</td>
<td>(--)</td>
<td>(--)</td>
<td>(0.406)</td>
</tr>
</tbody>
</table>

Table 1: Coefficients in expression (9) obtained from the reconstructed potentials shown in Fig. 6(a) for \( \delta = 0 \). The central dot in values of \( C_i \) denotes the multiplication.

Values of \( C_i \) and \( \theta_i \) (see Table 1) highlight two main features. First, the increase of \( I_0 \) induces a stronger bias in potential \( U(\psi, I_0) \) that reflects in larger absolute values of coefficient \( C_0 \). Second, more harmonics in Fourier series in (9) are needed for describing the shape of \( U(\psi, I_0) \) for larger \( I_0 \). The additional harmonics change the potential shape. In comparison to small amplitude (\( I_0 = 0.5 \)), the barrier becomes sharper and the shape around an equilibrium state is more flat in potential \( U(\psi, I_0) \) for large amplitude (\( I_0 = 1.5 \)). The insert in Fig. 6(a) illustrates these changes in the potential shape. These changes contribute to the tongue’s asymmetry. So, for amplitude \( I_0 = 1.5 \), the tongue’ width is \( 0.077 \frac{\pi}{I_0} \) if all terms of the Fourier series (Table 1) are taking into account, and the width is reduced to \( 0.046 \frac{\pi}{I_0} \) if the first harmonic is used for evaluating \( U(\psi, I_0) \). Thus, the changes in the potential shape make a strong contribution to the tongue’s asymmetry.

As the amplitude \( I_0 \) grows further, cycle BH2 undergoes a period-doubling bifurcation. This bifurcation is characterised by the largest multiplier crossing -1, the cycle becoming a saddle and a new stable cycle of period 2 with respect to \( \omega \) appearing. The dash-dotted line in Fig. 3 denotes this bifurcation on the parameter plane. The appearance of a new cycle
with a doubled period should lead to 1:2 synchronisation. However, the mean frequency of the system oscillation, $\Omega$, is almost equal to the driving frequency $\omega$ in the region of the doubling bifurcation. Fig. 7 illustrates this observation. The cycle of period 2 is in the region indicated by the vertical dashed lines, as confirmed by the two values of $V_i$ in the stroboscopic section $\omega t = 2\pi i$. The frequency ratio $\frac{\Omega}{\omega}$ in this region is close to 1, and the values of the ratio in this region are indistinguishable from the values outside the region where the cycle of period 1 exists. Thus, the use of mean frequency $\Omega$ alone leads to an incorrect conclusion of the existence of 1:1 synchronisation. Additional calculation of the standard deviation $\sigma_\Omega$ of $\Omega$ (the solid line in Fig. 7(a)) indicates that there is no 1:1 synchronisation in this region. Therefore, simultaneous considerations of the first (mean) and second (standard deviation) moments of instantaneous frequency allow us to characterise the synchronisation correctly. The procedure of instantaneous frequency calculation in this study is similar to that widely used for experimental data [8]. A further increase in $I_0$ leads to the appearance of chaotic motion within the synchronisation tongue, but the mean frequency $\Omega$ is still very close to $\omega$ (Fig. 7(b)).

Figure 7: The figures illustrate weak sensitivity of the mean frequency $\Omega$ to the presence of bifurcations of cycles inside the synchronisation tongue. Red dots and solid blue line in the upper panel correspond to the values of mean frequency $\Omega$ and standard deviation $\sigma_\Omega$ of the instantaneous frequency of oscillation in model (6). The lower panel shows coordinate $V_i$ (black dots) of the steady state of (6) in the stroboscopic section $\omega t = 2\pi i$ as the ratio $\frac{\omega}{\Omega}$ varies. Dashed green vertical lines denote the period-doubling bifurcations of cycle ST2. $\sigma_\Omega$ is shown on a logarithmic scale and the non-zero value of $\sigma_\Omega$ for 1:1 synchronisation is explained by errors in numerical simulations of system (6). Figures (a) and (b) correspond to amplitudes $I_0 = 1.9$ and $I_0 = 2.9$, respectively; $\tau = 1.0$.

4. The role of scale separation

The previous section shows that model (6) demonstrates a strong asymmetry in synchronisation towards higher frequencies for parameter values adopted from book [24]. In this section we discuss how typical the asymmetry is for this model in a wider range of parameter values. Several parameters define nullclines of the model (6), and small variations in the shape of nullclines do not affect the asymmetry. The membrane capacity $C$ and the time constant $\tau$,
which characterises the transient potassium current, define the time scale separation between
the first and second equations of model (6). Both parameters vary for different neuron cells
and should be voltage-dependent quantities. Their variations are therefore relevant for this
neuron model. The structure of model (6) is such that parameters $C$ and $\tau$ are linked; it is
therefore sufficient to consider one of them, and we choose to consider varying $\tau$. Note that,
in experiments reported in the literature [24], the measured values of time constant $\tau$ vary in
a wide range: between 0.8 and 1.2.

To characterise the influence of parameter $\tau$ on the asymmetry of the tongue, the dependence
of coefficient $C_A$ on $\Delta_L$ for different values of $\tau$ was calculated and is shown in Figure 8. The
curve for $\tau = 1$ summarises the results presented in the previous section. For this value of $\tau$,
the coefficient $C_A$ reaches a value of 0.2 at $\Delta_L \approx 0.02$, and there is a sharp transition from
a symmetrical tongue to an asymmetrical one. An increase in $\tau$ leads to two effects. Firstly,
the transition becomes sharper, and it is observed at larger values of $\Delta_L$. Secondly, chaotic
motion manifests itself as soon as the tongue becomes asymmetrical. The latter effect leads to
the destruction of synchronisation with a 1:1 ratio. A reduction in $\tau$ from $\tau = 1$ suppresses
this chaotic behaviour. The asymmetry becomes more pronounced until $\tau \approx 0.97$, but after a
further decrease in $\tau$, the transition is again observed at larger values of $\Delta_L$. Thus the results
shown in Fig. 8 demonstrate that the asymmetry in the synchronisation tongue is sensitive to
time scale separation.

![Figure 8: The asymmetry coefficient $C_A$ as a function of the normalised half-width $\Delta_L$ for different values of parameter $\tau$: $\tau = 0.91$ (marker ○), $\tau = 0.93$ (marker □), $\tau = 0.97$ (marker ▽), $\tau = 1.0$ (marker +) and $\tau = 1.1$ (marker ×).](image)

Inside the synchronisation tongue, varying $\tau$ leads to a different influence on bifurcations.
For large values of $\tau$, the asymmetry is related to the saddle-node bifurcations discussed for
$\tau = 1$. Although these bifurcations are not observed for smaller values of $\tau$, however, the tongue
is still asymmetric. There is a 'fingerprint' of these bifurcations in the behaviour of the largest
multiplier of the stable cycle inside the synchronisation tongue. Figure 9(a) shows an example
of the evolution of the locations of the saddle and stable cycles and their largest multipliers
as the ratio $\frac{\nu}{\Omega_0}$ varies for $\tau = 0.98$ and $I_0 = 1$. The multiplier for the stable cycle has a
maximum around $\frac{\omega}{\Omega_0} \approx 1.01$ and the whole picture looks similar to that observed in the case of the presence of the saddle-node bifurcations (see Fig. 5(d)). Reconstructed potential $U(\psi, I_0)$ undergoes similar changes as those for $\tau = 1$ (compare Fig. 9(b) and Fig. 5(d)). These figures (Fig. 5 and Fig. 9) demonstrate that the asymmetry is related to the non-uniformity of the invariant torus formed by 1-dimensional manifolds of the saddle cycle and that the asymmetry can be associated with a particular shape of an equivalent potential for phase difference $\psi$.

![Figure 9: (a) The coordinate $V_i$ of the stable (solid lines) and saddle (dashed lines) cycles and their largest multipliers, $\mu$ (dotted lines), are shown as a function of the ratio $\frac{\omega}{\Omega_0}$ for $\tau = 0.98$ and $I_0 = 1.0$. Vertical grey lines indicate values of $\frac{\omega}{\Omega_0}$ where the saddle-node bifurcation occurs. The solid grey horizontal line shows the value of $\mu = 1$. Red and blue colours correspond to stable and saddle cycles, respectively. (b) Reconstructed potential $U(\psi, I_0)$ for $\tau = 0.98$, $I_0 = 1.0$ and different ratios: curve 1 (blue colour) $\frac{\omega}{\Omega_0} = 1$, curve 2 (red colour) $\frac{\omega}{\Omega_0} = 0.99$, curve 3 (black colour) $\frac{\omega}{\Omega_0} = 1.01$, and curve 4 (magenta colour) $\frac{\omega}{\Omega_0} = 1.04$. Stable and unstable states are denoted by markers $\circ$ and $\times$, respectively.

5. Conclusions

The $I_{Na_p} + I_K$-model shows a strong asymmetry towards higher frequencies in the synchronisation tongue for a range of parameters and in the presence of stochastic perturbations. This asymmetry is a robust effect connected to the non-uniformity of the invariant torus formed by the unstable manifolds of the saddle cycle(s) which exist within the tongue. For some parameters values, the asymmetry appears as a result of additional saddle-node bifurcations; however, the presence of such bifurcations is not in general required to observe the asymmetry. This effect is linked to the modification of the potential profile for phase difference. The profile becomes flatter around a stable state in the asymmetry region of the synchronisation tongue.

These results confirm that the asymmetry of the tongue is a feature of the model and can be used to explain the experimental results [8] summarised in Fig. 1. The $I_{Na_p} + I_K$-model [6] considered in this work is an example of a neuronal system which synchronises best when the frequency of the weak driving force is higher than the frequency of the unperturbed system. The existence of the neuronal system supports the original idea [4] that cardio-respiratory synchronisation occurs via direct interaction between neural centres in the medulla. The $I_{Na_p} + I_K$-model represents a single cell and can be seen as a model of excitable cells which initiate an excitation wave in a neural centre. Similarly to other, more complicated models of neural centres, e.g. the
network model for α-rhythm synchronisation, the $I_{NaP} + I_{K}$-model demonstrates chaotic behaviour, which has no direct relevance to cardio-respiratory synchronisation. However, the low-dimensional chaotic dynamics could be masked by the stochastic components (noise) observed in experiments due to variability in both breathing and heart rates.

The asymmetry in the $I_{NaP} + I_{K}$-model is observed within a relatively narrow range of parameters, indicating that this asymmetry is related to the structure of the mathematical model. The asymmetry is observed for weak force which does not change the model’s state space. The phase description is, therefore, valid and the phase potential (phase coupling function) can be used for characterising the asymmetry. The developed numerical approach allows us to reconstruct the phase potential that provides a pathway for describing and predicting the asymmetry. This approach could be useful for providing a reduced one dimensional model for the phase dynamics. Such models, often called as Kuramoto phase model, are widely used for analysing the synchronisation phenomena in network of self-oscillators. The suggested reconstruction procedure is straightforward for a single non-autonomous oscillator, and the extension of the procedure for describing coupled systems needs further research.

Some limitations of the threshold crossing technique widely used in experiments to determine the instantaneous frequency have been identified. In particular, since the external perturbation is regular (periodic rather than stochastic), the mean frequency should be sufficient to identify synchronisation. However, this is not the case for model (6). The mean frequency of the model remained extremely close to that of the external force even after the period-doubling bifurcation occurred and the synchronisation switched from a 1:1 to a 1:2 ratio. The additional use of the standard deviation of the instantaneous frequency made it possible to identify the presence of the bifurcation and the corresponding change in synchronisation ratio. This result shows the importance of using extended statistical measures beyond the mean value to describe and quantify synchronisation phenomena for experimental data.

The data that support the findings of this study are openly available in wrap.warwick.ac.uk, reference number 158974 with the URL http://wrap.warwick.ac.uk/158974/

References


