

## Phase and frequency locking in detailed neuron models

R. Stoop, J. Buchli, and M. Christen

Institute for Neuroinformatics ETHZ/UNIZH,  
Winterthurerstr. 190, 8057 Zürich, Switzerland  
E-mail: ruedi@ini.phys.ethz.ch

**Abstract**—Phase and frequency locking are generic phenomena among coupled limit cycles. As yet, it has been shown that simple models of the neurons (such as the Hodgkin-Huxley and Morris-Lecar) are on limit-cycle solutions. The same holds for in vitro pyramidal neurons, if they are driven by constant currents. It is, however, unknown whether this also holds for detailed neuronal compartment models. In this contribution we show computationally that locking holds and is measurable in these models as well, and can persist even under substantial changes of the driving. Thus, locking among neurons could provide a mechanism for cortical information processing, in the frequency as well as in the temporal coding paradigm.

### 1. Introduction: Detailed vs. generic neuron models

Both experiments and theoretical studies have shown the need to adopt a multi-level approach to understanding the brain, as molecular and genetic events can affect the entire central nervous system, and vice versa. At one extreme, there are the biophysical models of single neurons. These generally are based on one single concept, from which accurate neuron models can be constructed: Compartments, i.e., small cylindrical segments of the neuron, are modeled with their own complement of ion channels, computationally represented by an electrical circuit that takes into account membrane resistance, capacitance, and ionic conductances [1]. Within each compartment, ion currents are typically described as variable conductances in series with the ionic reversal potential. In the extended Hodgkin-Huxley formulation,  $Ca^{2+}$ -dependent voltage-gated channels generally require multiple state variables as well as Ca-concentration information. From the compartments, individual neurons can be constructed, and assembled towards full neural networks by means of synaptic conductive interconnections. On this level, synaptic currents are generally modelled as simple alpha-function responses to an action potential.

However: How much biological detail is needed for such a modeling? It is an open question as to whether a detailed numerical model can be more informative than a simplified analytical description of a cell. Neuronal geometry is a crucial determinant both of electrical properties and of neuronal connectivity. Every neuronal type has certain characteristic branching patterns, which are nevertheless unique from one cell to another. How does one represent the di-

versity of a subclass of neurons, while retaining the distinguishing features of this subclass?

To some extent, global information appears to provide a solution to this problem. But, how does one decide on the connectivity models on this level? Here, the plethora of answers is even larger. The generation of semi-global rhythms [2], e.g., could be one motivation for connectivity models, but there are certainly much more. This all indicates that analytical models might be very useful, if they are able to reflect "all" basic properties of the neuron. In this contribution, we shall focus on this issue in detail, by showing that detailed neuronal models – simulated by means of the NEURON environment [3] – are able to reflect the basic properties of limit cycles, which are phase and frequency locking.

### 2. Neuronal synchronization

In 1657, Christiaan Huygens [4] revolutionized the measurement of time by creating the first working pendulum clock. In early 1665, he discovered "... an odd kind of sympathy perceived by him in these watches [two pendulum clocks] suspended by the side of each other." The pendulum clocks swung with exactly the same frequency and 180 degrees out of phase; when the pendulums were disturbed, the antiphase state was restored within a half-hour and persisted indefinitely. Huygens deduced that the crucial interaction for this effect came from "imperceptible movements" of the common frame supporting the two clocks.

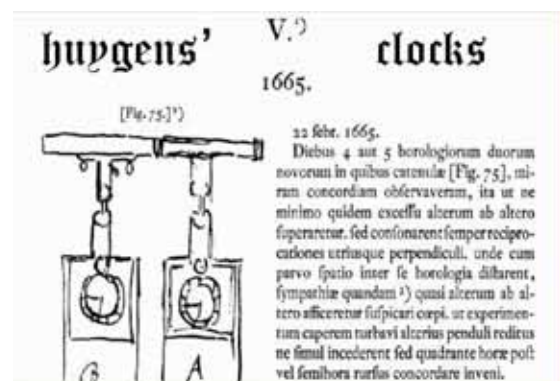


Figure 1: Huygens' clocks, jointly suspended from a common construction.

These observations are part of a set of properties that are generic for any (weakly) coupled limit-cycle systems: 1) Phase and frequency locking instead of exact temporal synchronization, 2) Farey-tree ordering of winding numbers, 3) devil's staircase structure of locked intervals [5]. These properties distinguish synchronization among limit cycles from synchronization among chaotic systems. In the latter case, the nonlinearity is usually maximally chosen, which implies chaotic individual systems. This then leads to the concept of a synchronization hyperplane for the symmetric solution, which is, upon the increase of the coupling, usually lost by means of a blow-out bifurcation [6]. In the coupling of the limit cycles, the systems that synchronize are generally not identical; when combined, this gives rise to higher-dimensional periodic solutions rather than to symmetric chaotic solutions. Here, an infinity of states of synchronization is due to the frequencies of the limit cycles, and not so much to the nonlinearity. The nonlinearity resides in the coupling, and can be chosen arbitrarily small.

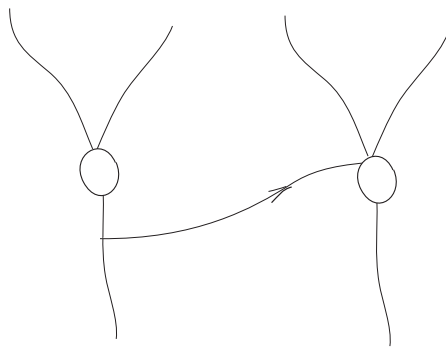


Figure 2: Uni-directionally connected neurons.

The question of whether neurons can be intrinsically (i.e., in itself) chaotic at all or not, has not been fully answered so far. Selverstone et al. [8] have found that somatogastric ganglion cells can behave chaotically. However, the questions of how realistic their experimental situation is and how significant these neurons are for cognition, are difficult to assess. We have shown that connected neurons in slice, when driven by constant though differing currents, engage in locking. For inhibitory pair-coupling, this response can become chaotic. This, however, only happens at very high interaction strengths on a small, though nonzero, part of the parameter set [7]. For this system, we have identified the Arnold tongues along which these lockings emerge (see Fig. 3, 4). This, on one hand, justifies the analytical modeling of pyramidal neurons by means of limit cycles, on the other hand it also yields insight into the way these neurons encode and process arriving information. One can, however, argue that during the slicing process, the neuronal processes and structures are so much affected that this experiment no longer mirrors the realistic biological behavior, and that the quasistatic conditions used in these experiments do not have relevance in terms

of the conditions of ever-varying currents in the (in vivo) brain. In this sense, neuronal locking could be an artifact of the preparation.

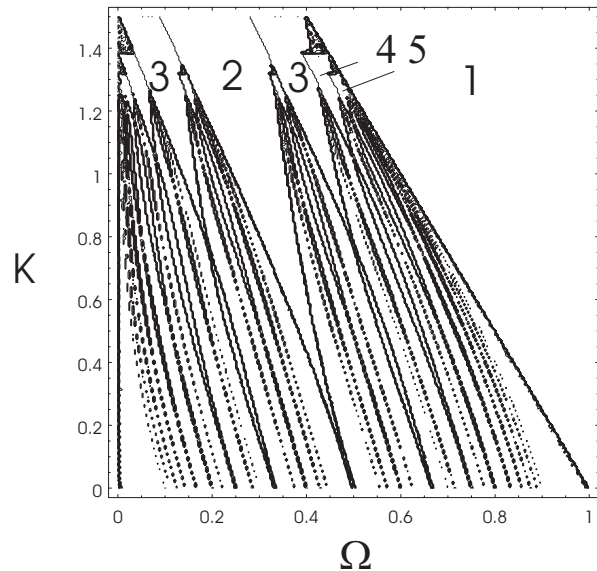


Figure 3: Arnold tongues from uni-directionally excitatorily connected pyramidal neurons (from in vitro experiments). The coupling constant  $K$  is in (macrobiologically) rescaled units.

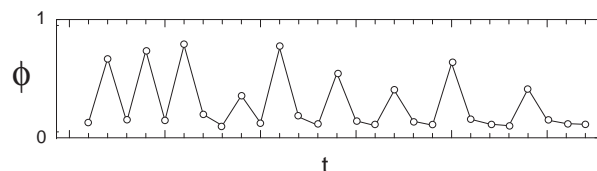


Figure 4: Typical phase-locking response for a sweep across the tongues, from the middle to right of Fig. 3, showing differing periodicities encoded (in vitro experiments). Depending on the velocity of the sweep, finer or just the basic periodicities are reported.

In fact, we have measured neuronal in vivo responses that were chaotic (of the sample,  $\sim 1/3$  was low-dimensional chaotic;  $\sim 1/3$  was high-dimensional with no real scaling properties, and  $\sim 1/3$  showed random spiking behavior many of them with long-tail distributions [2]). In our interpretation, however, this is a network-induced effect, either established by a chaotic modulation of the network input (combined with the networks's own ability to generate this effect), or by appropriate local interactions (leading to "noisy" neurons). The whole of this situation justifies the investigation of locking by means of detailed neuron simulations, to identify typical situations where synchronization of limit cycles holds, and where it fails.

### 3. Methods and materials: Detailed neuron models

The extent to which neurons synchronize is enhanced by uni-directional coupling, which is most often the case in biology. This will be the paradigm we use, see Fig. 2. Our detailed models of the neurons are based on a geometric structure comprising more than 100 compartments (see Mainen et al. [9]). However, also less detailed models were tested, yielding results that were quite close to the ones reported here. Detailed neurons were connected via one exponential synapse of the type provided by NEURON, based upon the relationship

$$i(t) = g(t)(v - e), \quad (1)$$

where  $g(t) = we^{-t/\tau}$  embodies the dependence on the synaptic weight  $w$  and the decay time constant  $\tau$ , and  $v - e$  is the excess of the presynaptic-synaptic membrane potential over the reversal potential.

### 4. Results

In the following, we show the effects of the coupling to the firing frequency and to the firing phase. In the first observational approach, the coupling changes the dependence of the firing frequency on the driving input from a slightly nonlinear one into a devil's staircase.

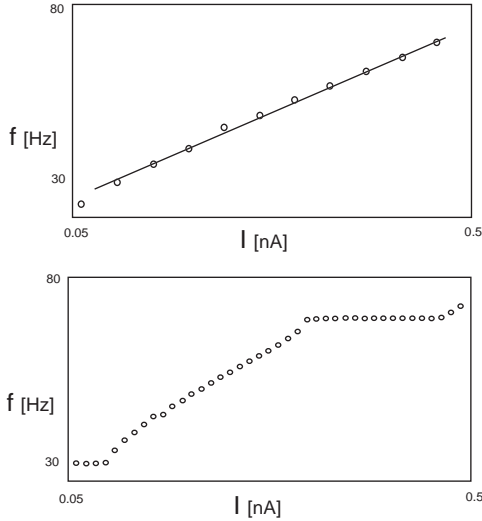


Figure 5: In this numerical experiment with two coupled detailed neurons,  $I_1$  was held fixed, whereas  $I_2 \in [0.06, 0.46]$  increased in steps of 0.02. Top: Autonomous, non-locked case ( $K = 0$ ). Bottom: Nonzero coupling ( $K = 0.007$ ) leads to frequency locking, indicated by the devil's staircase frequency dependence.

If the firing frequency is plotted as a function of the driving currents  $I_1, I_2$ , locking is reflected in contour lines that are deflected into the horizontal and the vertical directions. On each strip, we have a fixed periodicity, see Fig. 6.

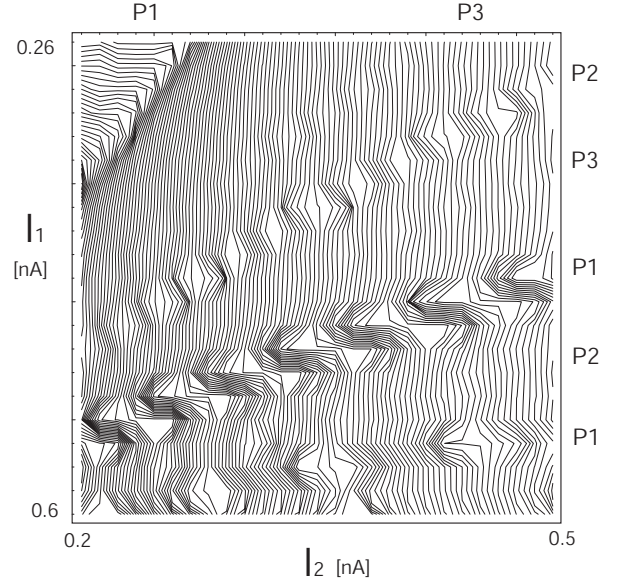


Figure 6: Contour plot of the firing frequency, using variable neuronal inputs  $I_1, I_2$ , with fixed coupling strength  $K = 0.007$ . The figure clearly shows locking in the form of multiple rescaled Arnold stripes. The main periodicities 1,2,3 are indicated. Horizontal lines: the first neuron is locked to the second, vertical lines: the second is locked to the first.

By properly zooming into the first tongue of Fig. 6, we recover a part of the structure from Fig. 2, indicating that frequency and phase locking emerge together (Fig. 7).

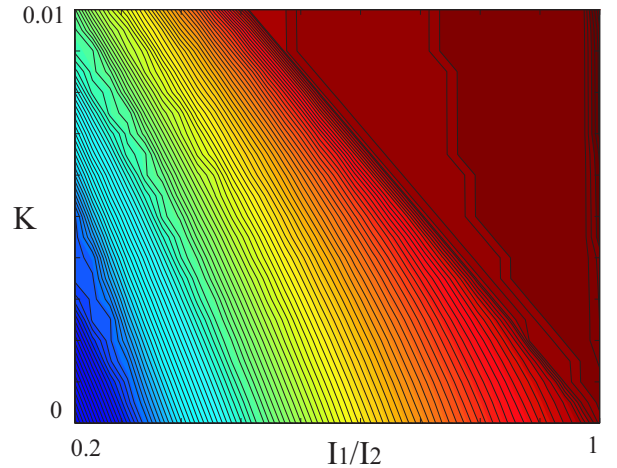


Figure 7: Frequency locking, first Arnold tongue set alone. The similarity with Fig. 3 (phase picture) is apparent.

By choosing the inputs from a  $I_1/I_2$ -combination from one of the frequency-locking tongues of Fig. 6, we can directly verify that frequency locking emerges together with phase-locking. In Fig. 8 we show the phases for the firing

on two of the most basic tongues. However, also higher stable periodicities can be similarly found, with ease.

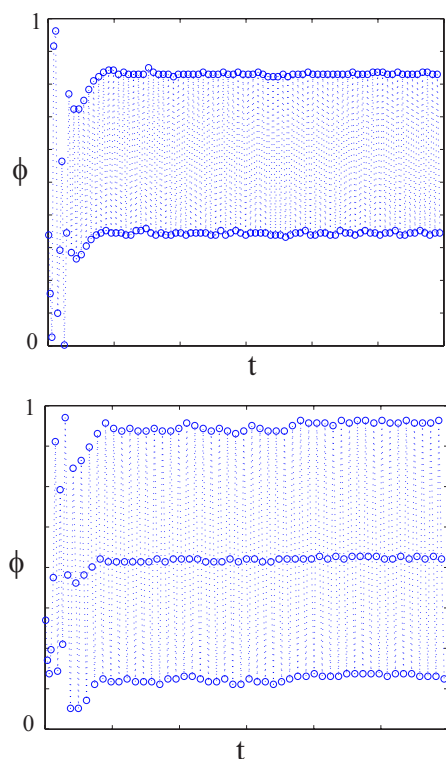


Figure 8: Top: locked phase of period 2, bottom: locked phase of period 3.

These tongues of fixed periodicity are rather stable, with respect to the phase representation. In Fig. 9 we quickly sweep along the tongues (at fixed ratio  $I_1/I_2$ ) without losing the periodicity.

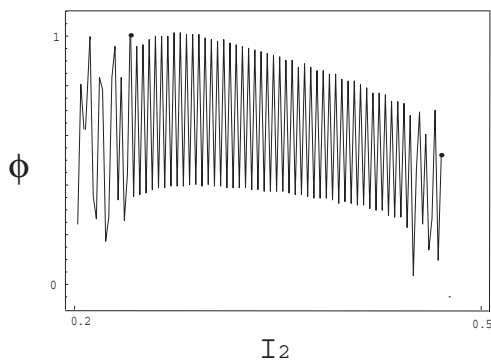


Figure 9: Locking persists upon quickly sweeping along the period-2 Arnold tongue, from low to large inputs.

## 5. Discussion and conclusions

Frequency and phase locking naturally emerge for detailed neuron models, if the neurons are driven by – variable or constant – currents and connected by stronger (but still weak, in the mathematical sense) synaptic coupling. In comparison to the corresponding slice experiments, the stabilization appears to be delayed (as it is in the mathematical simulations using the phase-response curve). We therefore conclude that a mechanism is built into the biology that leads to a faster stabilization. This mechanism, obviously, is not yet captured in the detailed modelling approach.

The outcome of the experiments indicates that locking could provide a valuable means for information coding, in the frequency as well as in the temporal coding sense. The question of whether the brain uses a frequency or a temporal code has been discussed fiercely, but is still not resolved. Our work shows that locking provides a mechanism that is working in both paradigms. The only necessary condition for locking to take place is a sufficient discrepancy between the modulations of the driving and the neuron's intrinsic firing frequency, and a separation between weak and strong synapses, where many of the weak ones drive the neurons, whereas the strong ones – or a few of them – provide the locking. As a mechanism for the latter, synaptic plasticity emerges naturally.

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