

Control of Oscillations and Chaos in Canonical Neocortical Microcircuits

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We investigate a canonical microcircuit containing four neurons: two interacting pyramidal neurons N1, N2 that form the basic computational circuit, a (stellate) control neuron N3, and a pyramidal neuron N4 acting as a reading-out device. Using in-vitro experiments, we experimentally prove that under generic input conditions, the computationally most relevant neurons N1, N2 are on limit-cycle solutions. We propose a novel coding scheme, which is established through along Arnold tongues-organized neuron synchronization, and use it to estimate the computational properties of the microcircuit.

I. INTRODUCTION

It is undisputed that for the understanding of the brain, typical physiological, and, as can be speculated, also corresponding computational microcircuits play an important role. In our paper, we experimentally and theoretically study the properties of the simplest variants of canonical [1] microcircuits, whose wiring is depicted in Fig. 1. We find that their natural behavior is dominated by the phenomenon of locking, which can be understood as a generalized synchronized neuron spiking. This behavior is best understood from the assumption that the natural state of a biological neuron, when subject to sustained current injection from by network environment, is a limit cycle (=LC) solution of the underlying dynamical equations. The associated regular firing of the neuron can be considered as its simplest working state. Although several mathematical models of neurons [2] predict LC-solutions [3] of neuronal activity, under physiological conditions, experiments verifying this behavior thus far have lacked conviction.

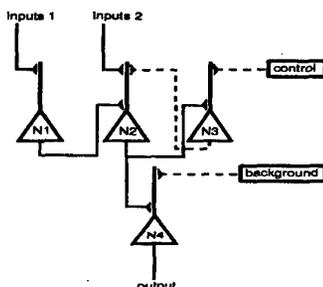


FIG. 1. Wiring of the canonical neocortical micronetwork.

In this paper, we first establish the LC nature of simple neocortical pyramidal cells. Pyramidal neurons contribute the vast majority of neocortical neurons; together with the stellate cells, they are generally considered to be responsible for the cortical integrative information processing [2]. When we compare LC-universality predicted locking behavior with in vitro synaptic perturbation experiments, we find excellent agreement: the synaptic interaction among pyramidal neurons is well-described by the phenomenon of locking along Arnold tongues.

We then refine our analysis of canonical microcircuits by discussing the possibility of dynamical control of Arnold tongues synchronization, by means of small additional control inputs. The control loop allows for switching from one periodicity to another, without requiring a change the firing frequency of one of the neurons in the main loop, an effect that might be either too resource demanding or too slow. Simple mechanisms like pre-/postsynaptic dendro-dendritic loops or even synaptic loops of the neuron onto itself can be sufficient for establishing this effect. Most flexibility is obtained if the control is performed by specific control neuron, equally well either by inhibitory or excitatory pathways, and the control process is most efficiently applied during transient behavior. There is anatomical evidence of such a control mechanism by means of a disinhibitory pathway from the thalamus, where N3 is an inhibitory neuron [4].

Arnold tongues structures that naturally emerge from of the basic computational N1-N2 loop naturally imply a coding scheme. The strength of the locking phenomenon leads us to infer that information encoding and processing in the brain is essentially through this phenomenon. In particular, we propose a resolution of a long controversy among groups favoring rate- and spike-time- coding of information, respectively [2]. We will show that both aspects are naturally embodied in the proposed coding of information. In our approach, we start from "quasi-static" network conditions, where the input to the main N1-N2- loop of the microcircuit is slowly varying in the considered time window. To arrive at this state, we assume the small-size inputs to arrive in large numbers and to essentially obey a Gaussian probability distribution. Given a surplus of the excitatory input, the neurons are thus supplied with constant driving currents from external cortical areas. Strong inputs are then produced by the interaction of strongly coupled neurons or neuronal

ensembles. The read-out properties by the neuron N4 are also taken into account. Finally, we discuss the possible role of recurrent excitation in our computational paradigm and then extrapolate from the microcircuit towards global *in vivo* network behavior.

We first experimentally prove our claim that the neurons N1-N2 displays limit cycle properties.

II. EXPERIMENTS

In our experiments with real neurons, slices of rat neocortex were prepared for *in vitro* recording. Following standard techniques, individual pyramidal neurons in layer 5 of barrel cortex were intracellularly recorded with sharp electrodes. A constant current was injected into the target neuron [5], bringing it into a regular firing state. This state then was periodically perturbed by extracellular stimulation of a synaptic input. Excitatory perturbations were generated by the stimulation of adjacent white or gray matter by means of bipolar electrodes, inhibitory perturbations were generated when fast excitatory transmission was blocked pharmacologically (by application of 1:5 DNQX and AP5) and stimuli were applied to fibers making synaptic contacts with the recorded neuron. In the context of *in vivo* neural networks, these perturbations approximate synaptic input from strong synaptic connections (see, e.g., [5]). For more details of the experimental set-up, preparation and recording, see refs. [6].

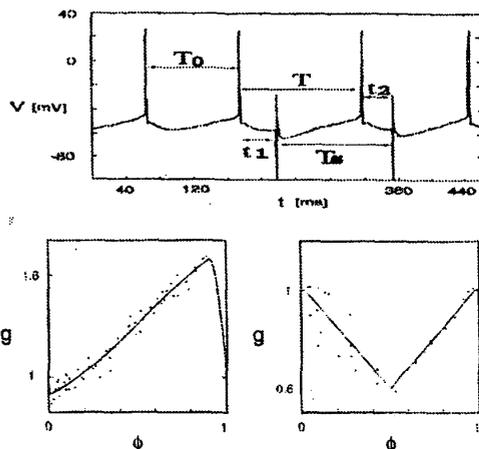


FIG. 2. Top: Experimental membrane potential $V(t)$. Inhibition changes the regular interspike time T_0 into a variable length T . Bottom: Measured neuron data (dots) and PRCs (interpolating solid lines). Left: inhibition, right: excitation.

Fig. 2 shows a spike-train $V(t)$, measured in this experiment. The first two spikes in the figure exhibit regular

spiking behavior. The last two spikes show the response of the regularly spiking neuron to strong perturbation represented by the downward deflection of the membrane potential V . At a fixed perturbation strength, the response depends in a nonlinear way on the phase ϕ with respect to the unperturbed cycle, at which the perturbation is applied. This property is revealed by the perturbation response curve (PRC) $g(\phi)$, which returns the quotient of the length of the perturbed interspike interval $T = T(\phi)$ to the length of the unperturbed interval T_0 , as a function of ϕ (i.e., $g(\phi) = \frac{T(\phi)}{T_0}$), see Fig. 2.

Simulations have shown that the noteworthy excitatory effect of inhibitory connections when perturbed at early phases is due to voltage-sensitive current dependent slowly reacting K^+ -channels [6a]. As a function of the perturbation strength, we found the characteristic responses to be well-described by the parameterization

$$g_K(\phi) = (g_{K_0}(\phi) - 1)K + 1, \quad (1)$$

where K denotes the perturbation strength scaled such that the reference curve g_{Ω, K_0} is at 75 percent of the maximal perturbation of the curve. The perturbation of g is fairly proportional to the physical stimulation strength. K can therefore be identified with a generalized perturbation strength that comprises both perturbation input and synaptic efficacy. Note that the parameterization of Eq. (1) allows us to extrapolate the perturbation response behavior beyond the biologically accessible range of $R = [0, 1.3]$. If the neuron is repeatedly perturbed with a constant period of perturbation (= "continued regular perturbation"), locking into periodic firing emerges (Fig. 3 (left)). As the frequency of perturbation is allowed to change (= "sweeping"), several bifurcations are observed that lead the system from one periodicity into another (Fig. 3 (right)). Similar plots are obtained for different individual neurons for variable perturbation strengths.

III. LC-INTERACTION MODEL

The LC-based nonlinear dynamics approach of Glass and Mackey [7] is suitable for explanation and description of the firing behavior of the perturbed neuron. According to Fig. 2, for two successive perturbations we have $T + t_2 = t_1 + T_s$, with T_s the time between successive perturbations, $T = T(\phi)$ the perturbed cycle length, t_1 the time after spiking at which the perturbation was applied, and t_2 the time after spiking at which the next perturbation will occur. Expressing this relation in terms of phases relative to the unperturbed cycle length T_0 yields

$$\phi_2 = \phi_1 + \Omega - g(\phi_1), \quad \text{mod}(1), \quad (2)$$

where $\Omega = T_s/T_0$ is the phase shift between the periodic LC and the periodic perturbation, and $g(\phi) = \frac{T(\phi)}{T_0}$ as above. From Eq. 1 we obtain the phase return map on the circle $I := [0, 1]$ [8], $f_\Omega(\phi_1) = \phi_2$, where $\phi_1, \phi_2 \in I$.

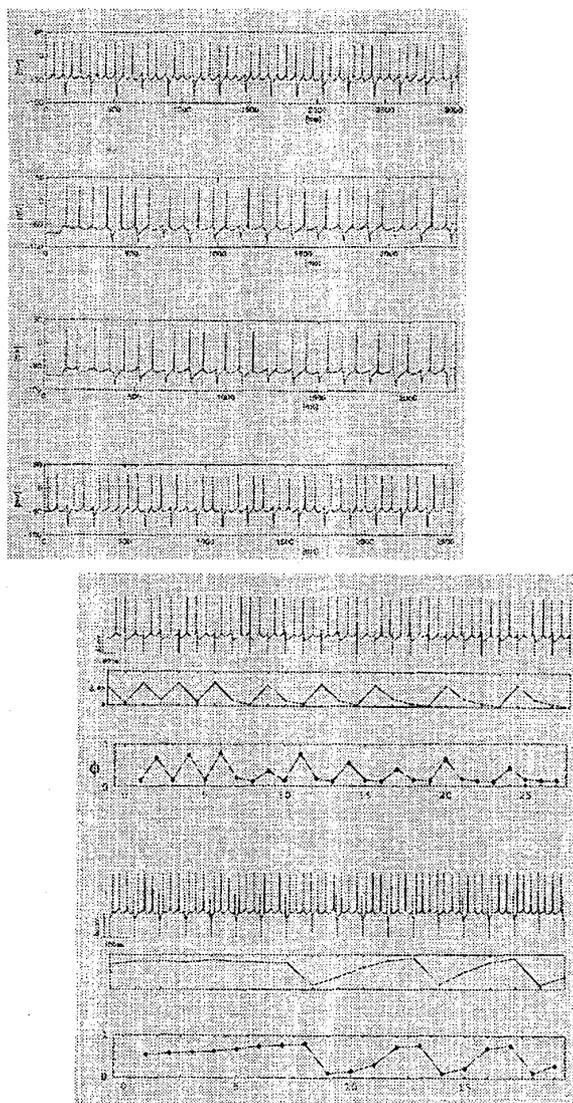


FIG. 3. Continued experimental inhibitory perturbations. From top: Fixed conditions (4 runs), followed by two sweepings showing membrane voltage, phases ϕ of arrival of inhibitory perturbations (experimental), theoretically predicted phases. First run f : $\Omega \in [0.8, 0.9]$, $K \sim 0.85$, entrained periods $p = 2, 3, 4$, followed by a high p and by $p = 1$ (not shown). Second run s : $\Omega \in [0.65, 0.7]$, $K \sim 1.05$, entrained $p = 1, 5, 4$, followed by $p = 3$ and $p = 2$ (not shown).

PRCs are derived from single, isolated perturbations. Iteration of f_{Ω} describes the effect of continued perturbations, provided that the stability of LCs is strong enough

to ensure the LC-relaxation before arrival of the next perturbation (that this is indeed the case in our experiment is shown below). When the through iteration of f_{Ω} generated set of phases $P = \{\phi_i\}_{i \in N}$ has a finite cardinality $p = \text{card}[P]$, p is the periodicity of the spiking. However, p can also be infinite. To obtain an overview on the response of the noise-driven neuron under asymmetric pair-interaction, we investigated the dependence of p on the stimulus type (inhibition/excitation) and the perturbation strength.

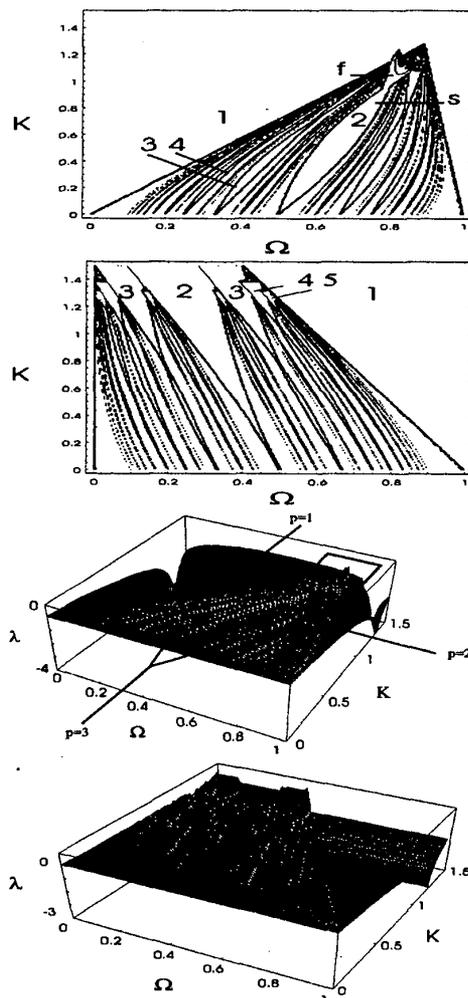


FIG. 4. Top: Arnold tongues as predicted response of synaptically perturbed pyramidal neurons (inhibitory, excitatory interaction). Numbers: Periodicity of the main tongues. Bottom: Corresponding Lyapunov exponents. Chaos is prevalent for inhibition in the boxed region. Horizontal lines: Directions of the sweepings of Fig. 3 (f : first, s : second run).

Investigation of the returned periodicities as a function of $\{\Omega, K\}$ results in typical Arnold-tongue structures [3], as shown in Fig. 4. For each p , there are different Arnold tongues that comprise areas of the $\{\Omega, K\}$ -parameter space having stable solutions of the same periodicity p . In fact, the Arnold tongues are extensions of the Farey-tree structures from the Ω - to the $\{\Omega, K\}$ -space. For the different tongues and as a function of the perturbation strength K , the stability properties of the solutions, measured in terms of Lyapunov exponents [9], are of interest, see Fig. 4 (bottom). Positive Lyapunov exponents indicate chaotic behavior, negative exponents indicate stable behavior. Zooming in reveals that for strong inhibitory synaptic input ($K \in R$), chaotic response is possible. Analytic investigations [10] confirm this observation. They further yield that chaotic response occurs on an open set of positive (Lebesgue) measure in the parameter space [11]. A comparison between inhibition and excitation shows that the excitatory bifurcation structure is shifted towards high K -values. The size of this shift, taking into account the normalization of K , implies that chaos cannot be reached by excitation [12].

IV. MODEL VERIFICATION

The predicted LC-assumption based interaction was compared with continued experimental perturbations of pyramidal neurons for a fine sample of parameter specifications in the $\{K, \Omega\}$ -space. We obtained full confirmation of the theoretical prediction. Experimentally, periodicities up to 5, sometimes 8, could consistently be resolved quite at the expected parameter locations. To confirm these observations also under conditions of changing cortical activity, we also considered sweepings. The two horizontal lines in Fig. 4 indicate the directions of the sweepings of Fig. 3 (with f for the first, s for the second run). To understand the results of sweeping, observe that sweeping automatically restricts the response to low periods, due to the strong stability properties of these periodicities, where the convergence onto these orbits is within one interspike interval. Fig. 3 shows the good agreement between experiment and model. Not only the periodicities, but also the ordering of phases is correctly predicted. Rather unexpectedly, the specific form of the fitting function $g(\phi)$ is only of little relevance for the obtained results. The circle-map universality [3] implies that qualitative results like topological properties (e.g., structure of periods) will persist under different fits.

The as a function of Ω generated of phase bifurcation diagrams are typical of the circle-map universality class [3]. The two PRC's shown in Fig. 2 are from a set of more than 100 experimentally investigated cells [6] that all produced relatively identical response to perturbations. The largest deviations among the individual responses were caused by sometimes more extended refractory periods; for all statements that follow below, the

influence of these variations has been checked. The lack of variation in the Arnold tongue structure allows us to concentrate our investigations to two characteristic PRC response curves, one for excitatory and one for inhibitory perturbation as a paradigm for the generic behavior of by synaptic interaction perturbed pyramidal neurons. However, it when p is displayed as a function of Ω , for both stimulations the identical characteristic ordering of the periodicities emerges (the Farey-ordering, c.f. [3]). This is an intrinsic property of interacting LCs and ensures the existence of all possible periodicities p from the set of positive integers. The lack of significant individual variation of Arnold tongues also implies that coding is very unlikely a dynamic property that is mediated by the specific neuron considered. Below we will investigate the problem of information coding in the micronetwork in detail.

V. ARNOLD TONGUE CODING

The N1-N2 micronetwork naturally defines a dynamic system, an encoding of which consists of a partition of a usually continuous phase-space of the evolving system into areas that then are symbolically labeled, for example, by letters. Each time the system's trajectory enters a specific area of the phase-space, the associated letter is reported. The code is useful if it succeeds in the discrimination of states in an unambiguous way, up to a chosen precision, by a symbol sequence of sufficient length. For the micronetwork, the Arnold tongue structure provides a local coding scheme of the network evolution, where noise levels and neuron excitabilities, which fully describe the local states, are encoded by the periodicity of the spiking of the targeted neurons and by their spiking frequencies:

$$\text{Coding : } \quad \{f_1, f_2\} \rightarrow \{p, f'_2\}, \quad (3)$$

where f_1 is the frequency of the perturbing neuron, f_2 is the intrinsic frequency of the perturbed neuron, f'_1 is the frequency of the perturbed neuron (bracketed since it generally differs only little from f_2), and p labels the periodicity. When the local network state changes in time, this corresponds to a trajectory in the $\{\Omega, K\}$ -space. Along the trajectory, various periodic spiking patterns are emitted. They constitute an encoding of the trajectory. Fig. 4 can be used to estimate how the encoding sequence looks like when Ω or K is slowly varied (e.g., due to slow local gradients of the noisy input). Theory and experiment reveal that Arnold coding:

- is robust against adaptation and relaxation processes (the relaxations towards the asymptotic solutions observed in experiments are very fast, of the order of one interspike interval, for periods ≤ 10 , s. Fig. 3),

- is independent of the level of excitation in homogeneously excited area $\Omega = T_n/T_0$ is able to respond to local gradients of the noise level, but remains fixed under homogeneous changes of the network activity),
- has optimal coding properties, similar to the Huffman code [13] (the shortest code (period 1) corresponds to the largest partition element in the parameter-space, the second shortest (period 2) to the second largest, etc. For signals that are equidistributed on the $\{\Omega, K\}$ -parameter space, this coding is therefore optimally efficient),
- is self-refining under increased network activity. In *in vitro* experiments with neocortical pyramidal neurons, we found that the returned periodicities are related with the spiking frequency in the following way, s. Fig. 3: For low activity per parameter change, only the lowest periodicities $\{1, 2, 3, 4, \dots\}$ are returned. To return longer, more complex periodicities, higher spiking frequencies must be used. In this way, increased spiking activity leads to a hierarchical refining of the low-activity encoded signal),
- is able to represent spike-time coding as well as frequency-coding (frequency-encoded network-input essentially modifies Ω , whereas spike-time coded input essentially leads to an increase in K . In this way, both presently discussed coding schemes are naturally embedded in the Arnold code).

VI. CONTROL OF CODING AND READ-OUT

Whereas the interaction N1-N2 is the heart of the computational unit, the role of neuron N3 is to control or modify this result, with the help of small inputs applied at the correct time [14]. Why should this be an advantage for the neural network? Recent investigations [15] have shown that in the neocortex, strong identifiable correlations exist between the spiking of an individual neuron and the network state, identical for evoked compared with spontaneous activity. This implies strongly connection-dominated overall response of individual neurons. However, neurons also need to respond in a fine-tuned way, e.g. to small inputs from the thalamus (that essentially represents the short-time memory). The control unit is able to change the result of the computation, without the need of spike-frequency adjustment of N1 or N2, a strategy that biologically makes sense. In Fig. 5 we show how, after the arrival of a strong perturbation (whose possible origin will be discussed at the below), small applied perturbations (of the order of 10^{-15} of the original signal) are sufficient for modifying the periodicity of the output. The paradigm implies that the dynamical process must "have been taught" to perform a proper

job. A biological plausible pathway is that the control is mediated by means of observed disinhibitory inputs from the thalamus.

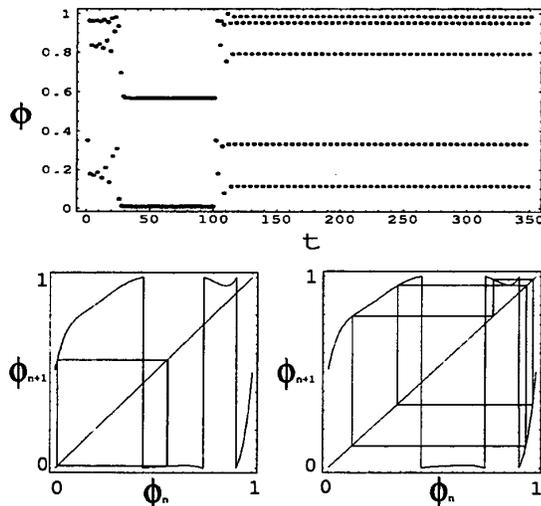


FIG. 5. Top: Controlled neuron interaction, from (stable) period 2 to stabilized period 5 (generated phases). Bottom: Corresponding orbits.

The read-out of the generated computational result by neuron N4 is also nontrivial. For simplicity, we shall assume that the neuron's membrane potential is below threshold, although it also may be locked to the read-out input. Our key observation is that, in either case, the read-out by neuron N4 will depend on its own state (specified by the membrane potential level and its decay-time constant), implying state-specific read outs. This puts the computational circuit in a similar role to the quantum computing scheme, where, using different preparations of the read-out, an exponential number of calculations can be done in one computational step. Since natural quasistatic conditions can be estimated to extend up to some hundreds of milliseconds, the *in vivo* length of a fixed-conditions coding may typically be limited to a few dozen significant spikes. As a function of this number, n , 2^n different states could be distinguished asymptotically. Note, however, that not in all cases the whole periodic message might need to be transmitted. Computationally of primary importance is, that locking to a well-defined state occurs.

VII. BEYOND BINARY IN-VITRO COUPLING

How much of the Arnold structures can be expected to be *in vivo* observable? First of all, Arnold structures also emerge if more than two LCs interact [16]. For natural neocortical neural networks, we propose that

these responses play a role similar to the unstable periodic orbits in chaotic dynamical systems [14]. There, the periodic orbits provide a firm backbone for the complex structure that is hidden in the seemingly intractable chaotic activity. Recent experimental evidence from cat neocortex is consistent with this view [15]. To verify the assumption, we simulated 2-d quasistatic networks where experimental PRCs were the only sources of interaction. The network topology was defined by strong synaptic interaction among the four checkerboard neighbor neurons using cyclic boundary conditions. Random physiological synaptic interaction strengths and spiking frequencies were applied. From this network, similar to *in vivo* complex and variable neuron spiking emerges. Often neurons are observed that show periodic spiking riding on top of a complex long-time behavior that is dictated by the collective network influence (see Fig. 6). This supports our view that local synchronization continues to exist and remains detectable when embedded into the network environment:

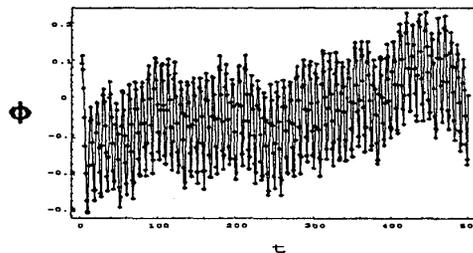


FIG. 6. Example of network-embedded periodicity ($p=8$).

- Locally, short-time low-periodic spiking behavior may be expected in abundance, by the interaction of otherwise freely spiking neurons. This periodic response is organized along Arnold tongues and obeys the circle-map class universality.
- As a consequence, the network is able to respond locally with any desired periodicity. While for weak local interaction the local spiking behavior is dominated by a wealth of different periodicities, for stronger interaction there is a tendency for the response to settle towards simpler, and more stable, spiking patterns.
- These stable spiking patterns are in sharp contrast to the chaotic response that exists for strong inhibition on an open set of nonzero Lebesgue measure in the parameter space.
- Using the universality principles of the circle-map class, we are able to prove that our experimental observations are not dependent on specific preparations of the system, but are "generic" results.

In *in vivo* neocortical networks, the time needed to extract spatio-temporal pattern features is very short (as

few as ≤ 10 spiking cycles are estimated to be sufficient [17]). This means that *in vivo*, the observation of locked states may be difficult, since quasistatic network conditions may only be needed to be sustained for these relatively short time. Additionally, the detection of locking phenomena for low spiking frequencies will be difficult, although (since Ω is the ratio between spiking frequencies) they may identically exist with high frequency lockings.

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