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Inhibitory connections enhance pattern recurrence in networks of neocortical pyramidal cells

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Abstract

We consider biological neural networks of pyramidal cells in a quasistatic approximation. We argue that they can be treated as a coupled map lattice of inhibitory and excitatory site maps, where both maps are derived from perturbation response of rat neocortical pyramidal cells. Inhibitory site maps generate chaotic spike patterns on an open parameter set of positive measure [R. Stoop, K. Schindler, L.A. Bunimovich, submitted], excitatory site maps are nonchaotic. Our network simulations show that local chaos by inhibition may be used to synchronize cortical networks.

Although considerable progress has been achieved in the past, the way the brain works is still far from being understood [1]. Understanding the brain is intrinsically connected with questions such as how information is propagated, processed and stored. The common assumption is that for this a description in terms of spiking rates is sufficient. However, this point of view has not been completely successful in explaining the working of the brain. Moreover, it has recently been found that interspike distributions of neurons of the cat stellate cortex rather follow a power-law than an exponential decay, implying that average spike time and spiking rate may not be defined without problems [2]. Therefore, it has emerged that phase-coding [3] could be of importance, especially for the explanation of synchronization which is abundantly observed in the working brain. In this context, two still unresolved questions have received considerable attention. Firstly, can synchronization provide arguments why the brain uses excitatory as well as inhibitory connections between neurons, and what relation exists between synchronization and postulated chaos in the brain? [4]

Recently [5,6], we were able to prove that local firing patterns of biological neurons may be chaotic in the strict mathematical sense. Motivated to see the influence of chaotic inhibitory stimulation on the network level, here we investigate a ‘quasistatic’ network of cortical neurons, with ‘frozen’ firing rates. By this, we ideally mean to have: a)-no change in the neuron’s own intrinsic firing rate, b)-no change of the excitability of the neurons over the time of observation. In this situation, which is quite opposite to a description in terms of firing rates, information can only be encoded in terms of phase properties.

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We develop our quasistatic network model by distinction of three scales of input to the neuron:
1) strong input (periodic of 'small' periodicity, caused by direct stimulation by a primary partner neuron or a field of synchronized neurons), 2) medium size input (of longer periodicity or of chaotic nature, caused by indirect input by means of, e.g., interneurons, characterizing a structuralized environment), 3) small-size input (diffuse, decorrelated input, obeying the Gaussian law of large numbers, typically transmitted over many neurons). Expressed in terms of the maximal applicable stimulation strength, these inputs are in the ranges of 10^{-1},10^{-2} and 10^{-4}, respectively.

In the first part of the paper, we take into account sources of the largest and of the smallest size. That is, we consider the steady-state noise-driven neuron that obtains input from a neuron of the same type. To describe this binary system, we use new insight from experiments with cortical neurons from the somatosensory area of Sprague-Dawley rats [5]. A nonlinear dynamics approach can be used to show that single neurons may respond with chaotic firing patterns to periodic inhibitory stimulation, but not to excitation. Using the strong universality principles of the circle map class, we are able to prove that our experimental observations do not depend on artificial conditions, but rather are 'generic' for this type of experiment. In a second step, we also take into account medium-size inputs. Their influence is treated as a perturbation of dominant neuron-neuron couplings. That is, we end up with a lattice [7] of binary interactions, on which medium-size input is represented by diffusive coupling [8]. Using this model, we show that the inhibitory connections are responsible for enhanced pattern recurrence of quasistatic networks of neocortical pyramidal cells. This pattern recurrence, however, is only a weak form of synchronization. For truly coherent spiking of the network, i.e., for synchronization in the strong meaning of the work, chaotic neuron sites are needed. We see strong evidence that our conclusions extend beyond the model of quasistatic interaction considered here.

It is well known that single spiking neurons can be described as electronic oscillators [9]. Unfortunately, the integration of the resulting differential equations amounts to a rather time-consuming job, with a large set of constants to be adjusted. In our mesoscopic description, we directly take the true biological parameters into account by means of response measurements of biological neurons. From the point of view of nonlinear dynamics, periodically spiking neurons are represented by limit cycle solutions. Incoming information in the form of stimuli is reduced in this picture to a perturbation of the limit cycle. Going from the differential equation system to a discrete map (via a Poincaré section) considerably simplifies the problem. Our strategy is to provide this map from experimental data, an approach that has been pioneered by Glass and Mackey in their description of the embryonic chicken heart cell beating [10]. In our experiment, we took slices of rat brain in an in vitro preparation [5]. We concentrated on simple spiking pyramidal cells, which are believed to be the cells essentially responsible for neocortical tasks. The limit cycle behavior was triggered by the application of a constant DC current to the cell. The perturbation is achieved by means of direct stimulation [5] of the neuron, or, more recently, by stimulation of exciting nerve fibers leading to the neuron (this produces a *synaptic input*). The immediate effect is an addition (excitatory stimulation) or a subtraction (inhibitory stimulation) of a short-time current pulse of the duration of about 5 ms to the DC current, which leads to a modification of the phase at which the next spike appears. From the experiment, this phase can be determined using the equation [10,5] $T + t_2 = t_1 + T_s$, where T_s is the time between successive perturbations, T is the perturbed cycle length, t_1 is the time after spiking at which the perturbation was applied, and t_2 is the time after the spike at which the next perturbation will appear. This relation can be expressed in terms of phases. Dividing the equation by T_0, the cycle time of the unperturbed limit cycle, we obtain

$$P:\phi_2 = \phi_1 + \Omega - T/T_0 \pmod 1, \qquad (1)$$

where $\Omega = T_s/T_0$ is the frequency ratio between the periodic perturbation and the periodic limit cycle. This *Poincaré return map* is a natural example of a circle map [11]. The reaction of the cell upon the stimulation is essentially contained in the last right-hand-side contribution, the *phase-response* function $g:\phi = t_1/T_0 \to T/T_0$ [10]. g can be determined from experimental single-pulse stimulation.

The results from a large number of experimental inhibitory and excitatory stimulations of neurons are summarized in Figs. 1a and b, where we show the interpolating functions fitting the experimental data points (data basis comprising more than 100 neurons stimulated by inhibition and more than a dozen stimulated by excitation). Choice of individual neurons (up to $n = 15$ at a single condition) and stimulation techniques made no further substantial discrimination necessary (except for the occurrence of longer refractory periods especially for excitation, whose effect will be discussed separately). It also emerged that the dependence of g-functions on the stimulation strength $K \in [0, ko]$, where ko is the maximal applicable stimulation strength, is of a very simple form that allows the reduction to the prototypical forms shown in Fig. 1 (see below). According to Eq. (1), we may iterate the associated P-maps to predict the phases which should be observed upon a periodic perturbation of the system. Periodic behavior, for example, is identified by a set of phases of finite cardinality. At this point, it is worth emphasizing that the resulting phases are not determined by the g-maps alone. The phase shift Ω also is of importance; its essential role is to determine the grammatical structure of the system. Investigation of the

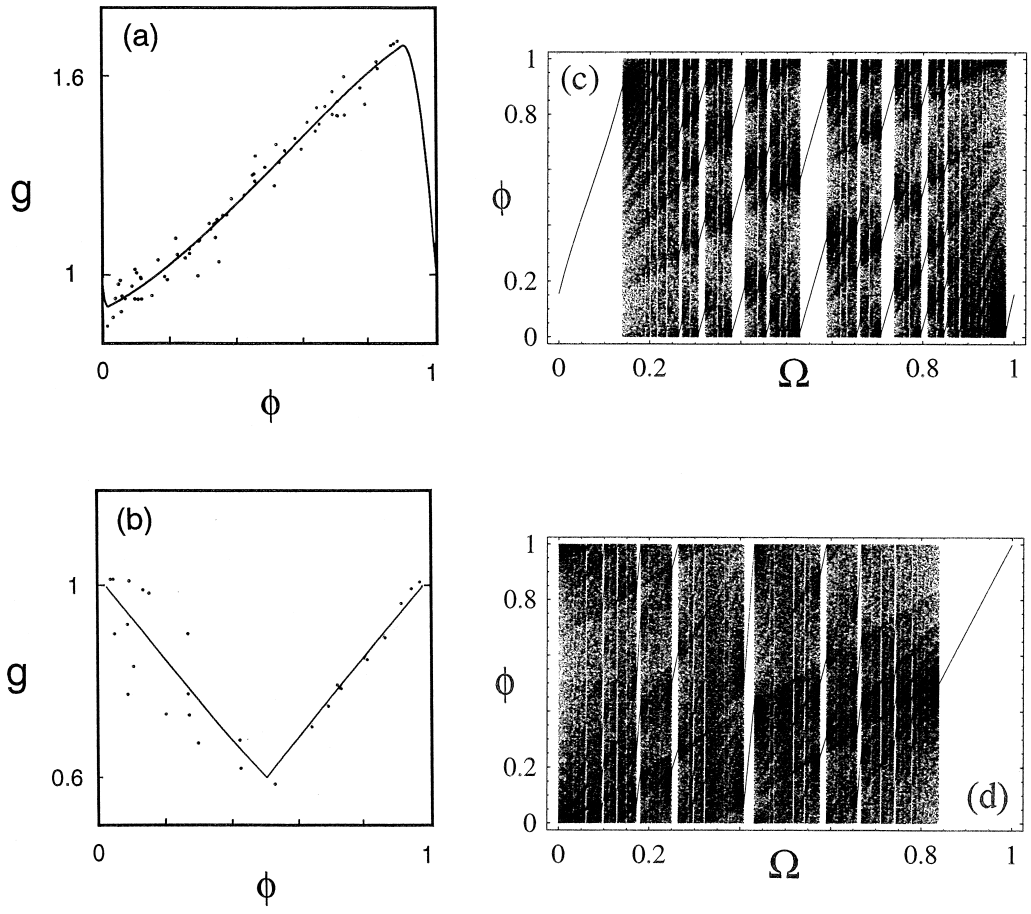

Fig. 1. Phase response functions $g:\phi \to T$ with superimposed data points from one neuron, for (a) inhibitory and (b) excitatory stimulation, with stimulation strength $K = 1$. g expresses how the limit cycle responds to a perturbation at the time t_1 after the last spike. The associated phase return map P (cf. Eq. (1)) determines at which phase the next perturbation occurs, given the phase of the old perturbation. Bifurcation diagrams for (c) inhibitory and (d) excitatory stimulation, for $K = 0.4$. The phases from a periodic perturbation with a fixed phase-shift Ω are drawn in the direction of the vertical axis. Regular firing corresponds to a discrete set of phases.

generated phases in dependence of Ω results in bifurcation diagrams. Typical examples are shown in Figs. 1c, d. Starting with periodic behavior at small phase shifts, soon bands of phases arise which indicate irregular response of the neuron upon the perturbation. Calculation of the Lyapunov exponents [12] shows that inhibition can lead to chaotic spiking behavior (first numerical evidence [5] has been corroborated by analytical investigations [6]). How can the dependence on K be reduced to the g-prototypes shown in Fig. 1? Our experimental evidence indicates this dependence can be modeled for $K \in [0, ko]$ as

$$g(K,\phi) = (g(ko,\phi) - 1)K + 1. \qquad (2)$$

Contrary to inhibition, excitatory stimulation allows on $[0, ko]$ only nonchaotic response. Otherwise, the two stimulation paradigms have many features in common (cf. [6]): On the whole interval $[0, ko]$, the qualitative properties of the bifurcation diagrams are equivalent, within one stimulation class, and comparing the two stimulation classes. More precisely, the topological properties agree (e.g., existence and ordering of lockings), whereas the metric properties may strongly differ (e.g., the Ω-locations of these intervals, or the stability properties of the associated solutions). Responsible for this are the universality properties of the circle map class, to which our P-maps belong. The same fact also explains the strong stability of results with respect to choice of interpolating functions (in Fig. 1a, a polynomial of third order for the middle part has been connected in a differentiable manner with two hyperbolic branches, which gives an excellent agreement with our experimental results. However, even seventh order polynomials yield comparable results. Under the change of the interpolating function, the metric properties such as the 'thickness' of the fractal and the ability to produce chaos may be affected. This especially holds for the piecewise linear cases). In Fig. 2 we give an overview on the situation. We observe that with increasing values of K the bands of complex behavior get narrower and Arnold tongues structures emerge. It is worthwhile emphasizing that by a suitable choice of Ω (which involves a change of the firing rate of, e.g., the targeting neuron), any desired periodicity can be established. In the realms of our quasistatic model, a corresponding effect can be achieved by adjustment of the perturbation strength K (alternatively, K can always be interpreted as an excitability). This is quite opposite to the usual controlling chaos techniques which start off from a chaotic 'ground' state and then apply control to obtain the desired periodicity [13]. Finally, let us reconsider the implicit assumption of a limit cycle stable enough to recover after a perturbation before the arrival of the next perturbation. We compared our theoretical predictions with results from experimental periodic stimulation and found good agreement which even improved when we included into our iterative approach additive Gaussian distributed white noise of the size observed in our experiment. In the experiment we observed stable periods up to order 5–8.

What now is the role of chaotic inhibitory connections on the network level? In networks of neocortical neurons, large-scale ordering and coherence in firing over large distances are observed abundantly. For some time it was widely believed that excitatory stimulation is responsible for the observed synchronization effects [14]. However, evidence originating from purely inhibitorally connected, but strongly coherent spiking cells in the thalamus, later questioned this point of view [15]. In the first case, chaotically spiking neurons could be speculated to be needed to break global synchronization obtained in this way. In order to relate our results to the network level, we consider a specific model of the network, which we call 'quasistatic'. In this model, the firing rates are assumed not to change over the time of observation. Pair-stimulations dominate the network activity and can be separated from the higher-order background activity by assuming allowance of distinction of three levels of interaction, as has been outlined above. In favor of the model we will argue below that our description yields strong self-consistent results and does not require more specific assumptions.

For our cortical network in the quasistatic state, we used our experimental P-maps as site maps on a lattice. In these maps, the inputs of the strongest and the weakest kinds are already taken into account. Medium-size input is incorporated in the form of diffusive next-neighboring phase coupling and mediates between the site maps. We focused on small-

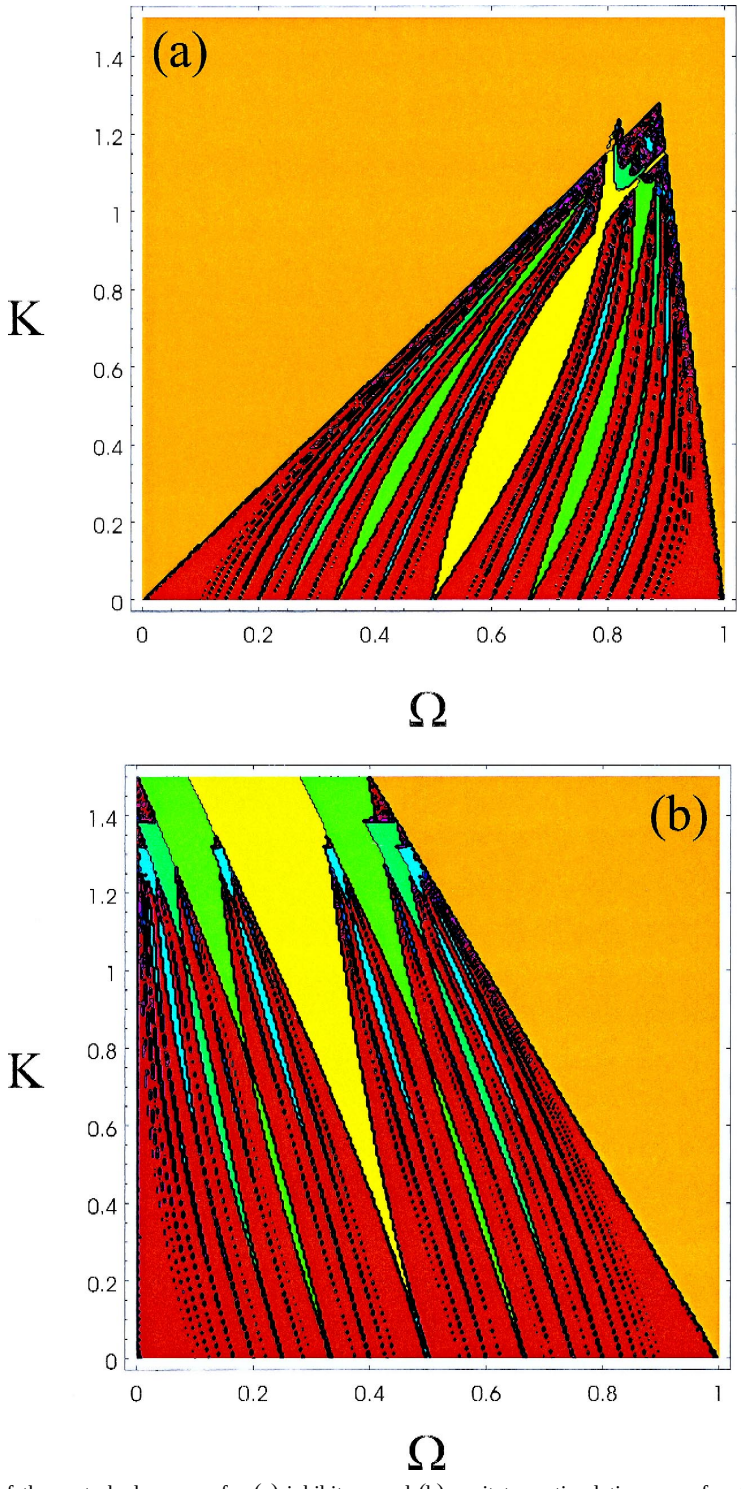

Fig. 2. Possible response of the perturbed neuron, for (a) inhibitory and (b) excitatory stimulation, as a function of K and the ratio Ω between self-spiking and perturbation frequency (Eq. (1)). Each color indicates a specific periodicity $p_e \in \{1,..,9, \geq 10\} =$ {orange,yellow,green,..,red}.

scale networks (network size varying between 500–700 sites on a rectangular $M_1 \times M_2$-grid). From a mathematical point of view, for our setting very few analytical statements can be expected (this in contrast to networks of, e.g., fully chaotic tent maps [8], or identically distributed ensembles of sigmoid neurons [16]). We therefore resorted to performing numerical simulations. Our networks were of the fully excitatory, fully inhibitory, and mixed type, parametrized by the percentage p of inhibitory connections. The coupling was characterized by an overall coupling strength k_2 and random coupling strengths $\tilde{k}_{i,j}$ between site maps and next neighbors, taken from a uniform distribution over [0.5,1.5]. For the site maps, we similarly chose $\Omega \in [0,1]$. The corresponding excitabilities K (cf. Eq. (2)) were taken from the interval [0.3,0.8], monitoring in this way rather massive coherent packages of transmitted information. To incorporate medium-size input, we require the diffusive coupling update-rule

$$N_{i,j} = \left(1 - k_2 \tilde{k}_{i,j}\right) P_{i,j} + \frac{k_2}{|nn|} \tilde{k}_{i,j} \sum_{k,l}^{nn} P_{k,l}, \qquad (3)$$

where P is the phase return map at the indexed site, and $|nn|$ denotes the cardinality of the set of all next-neighbours of site $\{i,j\}$. The first term of Eq. (3) reflects the degree of self-determination of the phase at site $\{i,j\}$, the second term reflects the influence by nearest neighbours, where nearest is to be understood in the sense of strongest interaction. The pattern recurrence of the overall network performance was measured by calculating the metric

$$\delta(t) = (M_1 M_2)^{(-1)} \sum_{i,j} |\left(N_{i,j}(t) - N_{i,j}(t_0)\right)|, \qquad (4)$$

using $t_0 = 5500$ discarded initial iterations for $t = 100$ consecutive time steps. In our numerical simulations we found it reliable to quantify pattern recurrence of the network by $\Delta = \min_t(\delta(t))$ over one hundred time steps, as a function of 1) the percentage of inhibitory site maps for different coupling strengths and 2) the coupling strength. Our main result is that the coherence of the network is governed by the percentage p of inhibitory site maps, i.e., inhibitory connections are responsible for a coherent pulsing of the network. Our second result is that our model has self-consistency properties that should be required: a) For too small perturbation strengths ($k < 0.1$), no effect can be obtained by increasing the percentage of inhibitory sites. b) Without coupling, the network cannot be made coherent (a slight bending of the curve is due the focusing effect of nonhyperbolicity). c) Making all site maps chaotic yields perfect phase coherence (in order to simulate the effect, we used Eq. (2), but had to leave the biologically accessible stimulation range). These results are summarized in Fig. 3a. The largest deviations from the curves may be generated by the random choice of the stimulation strengths in the

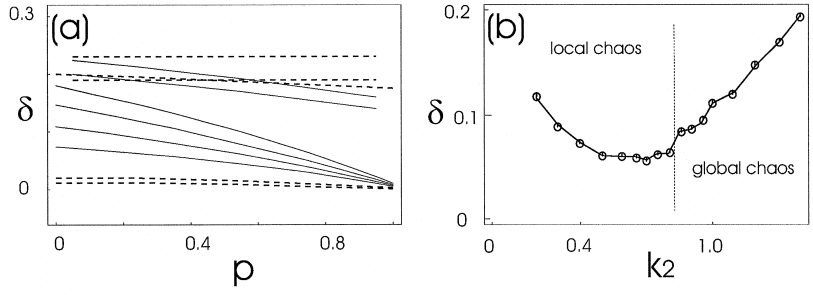

Fig. 3. Overview on the pattern recurrence for different phase-coupled networks, Eq. (2), as a function of the range of local excitability K, the overall coupling strength k_2 and the proportion p of inhibitory site maps. (a) $\delta_{\tilde{N}_{\tilde{N}}}$ measured in terms of $\Delta = \min_t(\delta)$. From top, dashed: $K \in [0.001,0.05]$ (too low!), couplings 0.1, 0.2; fully extending dashed line: $K \in [0.3,0.8]$, zero coupling; top pair of full lines: $K \in [0.125,0.25]$, couplings 0.1, 0.2; fully extending full lines: $K \in [0.3,0.8]$, couplings 0.05, 0.1, 0.2, 0.4, 0.8; Bottom: $K \in [1.2,1.4]$ (i.e., both site map types are near to the threshold to potential chaos), couplings 0.1, 0.2. (b) Dependence of $\langle \delta_{\tilde{N}_{\tilde{N}}} \rangle_t$ on coupling strength k_2, showing a minimum. Identical initial conditions were used for all measurements.

network. They usually are within the range of $\Delta_\delta = 0.02$. A dependence on the specific topological structure of the network with fixed p exists, but is small ($\Delta_\delta < 0.01$). The dependence of the pattern recurrence on extended refractory periods (which can be found especially for excitatory site maps) is small.

Phase-coding of information means to assign information content to the phase at which a spike is delivered rather than to the number of spikes. If such mechanisms are useful, then they should be applicable for pattern discrimination. That is, different inputs in our network should result in different network states. Differences between two networks $\tilde{N}, \tilde{\tilde{N}}$ can be measured by a time-average of the quantity

$$\delta_{\tilde{N}\tilde{\tilde{N}}}(t) = (M_1 M_2)^{(-1)} \sum_{i,j} \left| \left(\tilde{N}_{i,j}(t) - \tilde{\tilde{N}}_{i,j}(t) \right) \right|. \quad (5)$$

Since the whole network responds spatiotemporally sensitive towards applied patterns (which means that initial differences in patterns are amplified in time), for faithful pattern representation the network is faced with the problem of keeping the generated differences under control. Since the ability of a network to respond in a fine-tuned way to different input patterns can be measured by a time average $\langle \delta_{\tilde{N}\tilde{\tilde{N}}} \rangle_t$ of $\delta_{\tilde{N}\tilde{\tilde{N}}}(t)$, the optimal performance of the network as a function of the coupling strength k_2 would be achieved at the non-zero minimum of $\langle \delta_{\tilde{N}\tilde{\tilde{N}}} \rangle_t$, if it exists. We calculated $\bar{\delta}_{\tilde{N}\tilde{\tilde{N}}}$ as a function of the overall coupling, k_2, to find the optimal performance of mixed networks. Fig. 3b shows that there is indeed a sink, which to the right is bounded by the value $k_{2_c} \approx 0.83$ (for $p = 0.2$). Careful examination reveals that at k_{2_c}, the network undergoes a transition from local chaos (LC) to 'turbulence' (global chaos, GC), as is seen in many examples of coupled map lattices [8]: Below k_{2_c}, some sites are periodic, while others are chaotic. Due to the coupling, the instability of chaos promotes synchronization of the maps, resulting in global (possibly high order) periodic behaviors of $\delta(t)$. In this regime, the network reacts with periodic spatiotemporal patterns in response to inputs. Above k_{2_c} the diffusive coupling is so strong that the network is in a 'turbulent' state. Periodicities break down, and the network is no longer able to faithfully return patterns. We think that the deviation of k_2 from the expected value of unity is due to enhancement of pattern recurrence by means of synchronization due to secondary effects. This interpretation has been corroborated by the calculation of the largest Lyapunov exponent of the network. The discussed pattern recurrence properties are valid under longer and shorter refractory period conditions alike.

So far, the connection weights of the networks were randomly assigned $k_{i,j} \in [0.5,1.5]$ and then kept constant. One simple way to promote synchronisation is to have the $k_{i,j}$ dynamic, enhancing the connection strengths between neighbouring sites that fire in phase and reducing the connection strengths between those that fire out of phase, similar to Hebbian learning. When we imposed this phase coincidence detection on our network, we observed that after a short time-lap t_r the dynamical activity on the connection strengths had converged to temporally stable patterns. Calculation of a pattern difference $d_{i,j} = |\tilde{N}_{i,j}(t_r) - \tilde{\tilde{N}}_{i,j}(t_r)|$ showed that the non-marginal differences are confined to a small number of 'coding' network sites, and not distributed over the entire network. The location of the coding sites is highly input specific and the coding patterns do not depend on the initially chosen phases. However, they do to some extent depend on the chosen distribution of frequency ratios Ω, reflecting in this way a historical 'state' of the network. In addition to the dynamic spatial structure of the coding sites, the coding sites themselves express the applied patterns in a temporal way which reflects a metricity of the applied input patterns. When the site maps were endowed with longer refractory periods, this led to a certain degree of connectivity among the coding sites which a considerable tendency towards synchronization. These effects, along with possible aspects of hardware implementation for computational and cognitive tasks, are still under investigation.

In conclusion, we have determined the reaction of regularly spiking rat cortical neurons to periodic stimulation, and we investigated the consequences at the network level. For excitatory and inhibitory stimulations, we found nontrivial bifurcation diagrams; for inhibitory stimulation we found chaotic response. We developed the quasistatic network model, which relies on our experimentally measured g-functions.

Simulation results show that inhibitory connections contribute most to recurrence of network states. Possible chaotic behavior does not desynchronize, but rather helps to synchronize the network. By comparing the effect of different input layers on a given network, we found that our network is able to respond to these in a fine-tuned way. This aspect was further investigated by imposing a phase-coincidence detection onto the network. Under its influence, the change of the network patterns due to applied input patterns is restricted to highly localized, input-specific coding sites, with a potential for pattern discrimination. The network model that we have arrived at is highly biologically attractive and suggests that phase-coding is possible and may be important for the processing of information by the brain. We finally would like to a second, important conclusion of our investigations: In quasistatic neocortical networks of pyramidal cells, only weak synchronization in the form patterns recurrence is possible. Local periodic site maps alone will directly lead to chaotic, complex spiking networks, where the latter observation has been confirmed by calculation of the Lyapunov exponents of the network. Locally chaotic site maps, however, are good candidates for global synchronization, by which we understand constantly globally periodic patterns (there are good biological candidates for this role in the cortex). In this way, a seemingly paradoxical situation arises that locally chaotic site maps may generate global periodicity, while periodic site maps generate global chaos.

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