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Mechanisms to synchronize neuronal activity

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Abstract. Temporal aspects of neuronal activity have received increasing attention in recent years. Oscillatory dynamics and the synchronization of neuronal activity are hypothesized to be of functional relevance to information processing in the brain. Here we review theoretical studies of single neurons at different levels of abstraction, with an emphasis on the implications for properties of networks composed of such units. We then discuss the influence of different types of couplings and choices of parameters to the existence of a stable state of synchronous or oscillatory activity. Finally we relate these theoretical studies to the available experimental data, and suggest future lines of research.

1 Introduction

Originating from the pioneering work of Berger (1929), experimental studies of the brain were initially based heavily on EEG recordings. Due to the properties of this technique, which renders a poor spatial but a high temporal resolution, the search for physiological correlates of cognitive processes concentrated on the overall dynamics of neuronal activity, specifically on its frequency components. Nevertheless, it was well known that external stimuli induced reproducible activation of individual sensory cells (Adrian and Zottermann 1926). Only in the late fifties and early sixties did a paradigm shift occur, when microelectrodes were developed that were suitable for recording activity of cortical neurons with a very high spatial resolution. It was discovered that external stimuli induced specific and highly reproducible responses in single cortical neurons (Hubel and Wiesel 1962; Hubel 1982). The regular relationship between neuronal activity and external events was captured in the concept of receptive fields, stating that the number of action potentials generated by single neurons reflects the presence or absence of an external stimulus at a particular location. This concept proved to be extremely powerful and led to a dramatic change in the design of experimental work. In the following years experimental studies concentrated on the detailed properties of neuronal receptive fields. The temporal structure of neuronal activity was not considered to be relevant and, therefore, the study of the dynamics of neuronal interactions was largely neglected.

In this context the idea was put forward that the observation of single neurons responding to specific retinal stimuli may be transferable to more complex representational tasks (Barlow 1972; see also Martin 1994). The vast amount of simple and unspecific information from the retina would be processed by a feed-forward scheme, compressing it onto smaller and smaller numbers of neurons. At later stages these neurons would code for increasingly complex features and behaviorally relevant entities. At the end of this process the receptive fields of the respective neurons – sometimes nicknamed "grandmother neurons", though "cardinal cells" seems to be a more appropriate name (Barlow 1995) – would directly relate to the presence of complex objects in the visual scene. Activity of these neurons is supposed to increase only for a specific object, and not to be elevated for other objects. Any visual scene would activate only a limited number of cardinal cells, forming a sparse representation. Different stimuli can be differentiated if their cortical representations are different. As these representations are supposedly sparse, this notion has been further generalized to the psychophysical linking principle: "Whenever two stimuli can be distinguished reliably, then some analysis of the physiological messages they cause *in some single neuron* would enable them to be distinguished with equal or greater reliability" (Barlow 1995). This hypothesis proposes a one-to-one connection between distinguishable stimuli of the outside world in the outside world, and neurons in the brain.

The psychophysical linking principle has received experimental support from studies of area MT in primate visual cortex. In these physiological recordings monkeys were presented with random dot patterns that

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had varying directions of motion. And indeed, information contained in the mean firing rate of single neurons was sufficient to explain the performance of the animal to discriminating stimulus movement in the preferred direction of the neuron from the opposite direction (Newsome et al. 1989). Although these experiments do not necessarily imply that single neurons are decisive (Shadlen et al. 1996; Parker and Newsome 1998), they have further strengthened the view that the relevant analysis of physiological messages is the mean activity or number of action potentials generated in individual neurons.

However, the concept described above encounters several problems. Most important, from our point of view, is the issue of invariant representation. Starting from the definition, if two stimuli are different and can be distinguished, it is obvious that some retinal cells generate different signals. In as far as differentiating these stimuli involves cortical processing, these differences are presumably relayed to higher stages of the visual system. The emphasis in the psychophysical linking principle is on *reliability*. On repeated presentation, stimuli will not be identical and, indeed, in the experiments cited above (i.e., Newsome et al. 1989) the random dot patterns were not physically identical, but had only identical motion vectors. Thus, any local analysis on the retinal level is clearly insufficient to differentiate these stimuli. Expanding this example to more real-world stimuli, let us – for the sake of the argument – imagine that you are viewing your grandmother while her face is illuminated from the left. When you differentiate this stimulus from a corresponding view of your grandfather, some neurons are supposed to signal this difference reliably. Compared to the situation when the faces of your grandparents are illuminated from the right, are the same neurons involved? It would be rather helpful to generalize knowledge regarding your grandparents to different illumination conditions, thus, to have one set of neurons coding faces for all illuminations. These neurons would not only be highly specific for some aspects of the visual stimulus, but simultaneously would not be sensitive to differences in other aspects either. Importantly, you are capable of differentiating illumination from left or right for any face shown. Applying the linking principle again, this has to be signalled by some other set of neurons. It is obvious that this example can be inflated by introducing translations, different sizes and colors, partly overlapping stimuli and other manipulations (a related and much more entertaining form of this *gedanken-experiment* is given in a letter by J.Y. Lettvin, reprinted in Barlow (1995)). As a consequence, even in the psychophysical linking hypothesis, due to the combination of specific and invariant responses a fair number of neurons have to be involved in the representation of any stimulus.

A competing hypothesis takes the view that individual objects are represented by a larger number of neurons, not as a problem, but as a starting point for the assembly concept (Hebb 1949). This hypothesis takes the stance that focussing of a representation to highly specific neurons is not necessary, and that a distributed representation involving a large number of optimally and suboptimally activated neurons is sufficient and has several desirable properties. First, since each neuron participates in assemblies coding for other entities as well, for a given acuity of representation this scheme is more efficient in terms of the number of neurons needed. Second, it is more robust since partial loss of neurons would lead to graceful degradation of performance. Third, the concept is also rather flexible with respect to the generation of new representations, since there is a canonical representation of new objects, made out of already known features. Fourth, as neurons participate in the representation of many objects, generalization across different representations occurs naturally. These properties make distributed codes attractive and they are at the heart of interest in connectionism (see Rumelhard and McClelland 1986).

However, smearing out a representation has a price: when several stimuli are simultaneously present in a scene and each stimulus is represented by an assembly of neurons, how can these neurons be assigned to the different assemblies and the representation be read out? This problem, of decoding distributed representations of individual objects, is known as the "binding problem" and is currently hotly debated (Gray 1999; Singer 1999; Shadlen and Movshon 1999). It may be solved utilizing the temporal structure of neuronal activity (Milner 1974; von der Malsburg 1981). Neurons coding for the same object could be bound together by their synchronous firing, and distinguished from neuronal assemblies coding for different objects by an absence of synchrony between them.

These proposals revived the interest in the detailed dynamics of neuronal activity, and they are supported by recent experimental evidence (Eckhorn 1994; König and Engel 1995; Singer and Gray 1995; Singer 1999). In these experiments correlated activity of neurons was observed, indicating that neurons can synchronize their activity in the range of milliseconds. Synchronization of neuronal activity was found in a variety of cortical areas and subcortical structures. Furthermore, this phenomenon was found to be stimulus specific. In accordance with the notion of temporal tagging in assemblies, single neurons could be synchronized with other neurons depending on global properties of the stimulus. In particular, within the context of simple geometric stimuli, synchronization properties reflect Gestalt laws (Köhler and Wallach 1944).

A prominent feature of neuronal activity in these experiments is an oscillatory temporal structure in the γ-frequency range (Eckhorn et al. 1988; Gray and Singer 1989). Compared to synchrony, which refers to simultaneous firing of two different neurons, oscillations refer to a regular firing pattern in individual neurons. It has been found that synchronous activity of spatially distant neurons is often accompanied by an oscillatory behavior of the neurons involved (Engel et al. 1992; König et al. 1995b). Thus, it is thought that oscillatory activity of single neurons or neuronal groups could act as a means of establishing synchrony between neurons.

However, synchronization of neuronal activity may not only express binding of neurons into an assembly, but may also be crucially involved in processing itself (Abeles 1982). Multi-electrode recordings in behaving monkeys demonstrate precise spatiotemporal patterns (Vaadia et al. 1995) and unitary events (Riehle et al. 1997) which are associated with behavior. Parts of networks that can sustain such accuracy in the temporal domain may serve as building blocks for cognitive processes (Abeles and Prut 1996).

A related concept is temporal order coding (Maass 1997, 1998; Gautrais and Thorpe 1998). Here, information is transmitted by the relative timing of action potentials; small deviations from synchronous activity represent relevant information. Indeed, experimental evidence is available that synchronization is not perfect, but systematic phase leads and lags occur depending on stimulus properties (König et al. 1995a), which is compatible with this hypothesis. In the temporal order coding scheme, oscillatory activity may play a role in defining a temporal frame of reference (Hopfield 1995).

In summary, there are a number of good reasons to investigate the temporal dynamics of neuronal activity and underlying mechanisms (Theunissen and Miller 1995; König et al. 1996). In the following we review theoretical studies of single neurons as well as of small and large networks of neurons with oscillatory behavior at different levels of abstraction. We discuss network properties which seem to be crucial for synchronization and for the existence of a stable state of synchronous activity. Finally, we discuss these results in the light of available experimental data.

2 Different choices for the basic unit of a network

As is true for any modeling of physical reality, some level of description has to be chosen for models of neural networks that try to capture key processes of synchronization. Therefore, assumptions have to be made as to which biological details are important for the process under investigation and thus must be included in the model. Irrelevant details will unnecessarily complicate the analysis, and may even obscure results if data are lacking for the aspects that are considered important. Thus, the selection of the proper level of description is an art, and opinions diverge about the best choice. This has resulted in a rich literature, which addresses the problem from many different points of view.

For the investigation of synchronization phenomena an important step is the selection of the basic unit. This can be a single neuron or even an assembly of neurons which we describe by its average activity. The particular choice will strongly influence the properties of the interactions between different units. To compare different approaches, we will also have to pay attention to "details" like the treatment of delays, refractory period and inhomogeneity of parameters.

2.1 Phase models

As outlined in the Introduction and discussed further below, experimental observations of synchronous neuronal activity are often accompanied by oscillatory activity. Thus, it seems natural to start the investigation of neuronal synchronization with a dramatic simplification and consider units with only one variable, the phase, which is a measure of the position of the system on its periodic orbit. Actually, it is possible to give a more sophisticated justification for this approach.

Suppose the dynamics of a neuron or neuronal assembly is given by a set of coupled ordinary differential equations. If the system exhibits oscillatory behavior with a stable limit cycle its dynamics can be fully specified by the phase. This reduction of degrees of freedom is reasonable if it can be extended to a region around the limit cycle, such that perturbations can be studied within the same framework (Kuramoto 1984; Ermentrout and Kopell 1984, 1991).

We start with a general system of coupled ordinary differential equations of the form

$$\frac{\mathrm{d}X}{\mathrm{d}t} = F(X) \ . \tag{1}$$

Here, X is a vector characterizing the state of the system, and F a vector-valued function describing its change in time. We will investigate the system's behavior close to a stable T-periodic limit cycle. Let this orbit be parameterized by $X_0(t)$, implying that $X_0(t+T) = X_0(t)$. Then, for the points on the limit cycle, a phase Φ can be defined by

$$\frac{\mathrm{d}\Phi(X_0)}{\mathrm{d}t} = 1 \ . \tag{2}$$

A natural extension to an "asymptotic phase" can be given for any point X in the basin of attraction of the limit cycle. The trajectory starting at such a point X at time t_0 will tend towards the closed orbit as $t \to \infty$. Thus, it will asymptotically approach a trajectory that started simultaneously from some point X_0 on the limit cycle. The phase $\Phi(X)$ is then defined by $\Phi(X_0)$, since both points will lead to the same phase description as $t \to \infty$. By this method we obtain a one-parameter family of hypersurfaces $I(\Phi)$ which contain all points of constant phase Φ intersecting the limit cycle in the point $X_0(\Phi)$. These hypersurfaces are also sometimes referred to as "isochrons". We have herewith specified a function $\Phi = \Phi(X)$ for all X in the basin of attraction, and in this domain we have as well

$$1 = \frac{\mathrm{d}\Phi(X)}{\mathrm{d}t} = \nabla\Phi(X)\frac{\mathrm{d}X}{\mathrm{d}t} = \nabla\Phi(X)F(X) \ . \tag{3}$$

For a system with an asymptotically stable limit cycle, the phase description can now be maintained even when we are dealing with small perturbations. This may be understood by considering perturbations in the plane of an isochron and orthogonal to it. For small perturbations the former does not change the dynamics of the system, and effects of the latter can be captured by the

influence on the phase provided that the perturbations are small enough so as not to drive the system away from its limit cycle. This is further explored in Sect. 3.1.

Relating this approach to the biological system, the basic assumption of a stable limit cycle attractor has to be discussed. In experiments on rabbit olfactory bulb, spindles with a dominant 40-Hz rhythm have been observed (Freeman 1979a,b). The dynamics in the visual cortex have been accordingly nick-named 40-Hz oscillations but the phenomenon is actually much more complex. In the initial experiments on primary visual cortex (area 17) of anesthetized cats (Gray and Singer 1989; Gray et al. 1990) a broad peak in the frequency spectrum has been found in the range 35–70 Hz. This is in line with results by Eckhorn et al. (1988) who reported an even broader distribution of oscillation frequencies in areas 17 and 18 of the anesthetized cat, in the range 35–85 Hz. Using objective methods to define the relevant frequency range, Siegel et al. (1999) found in the awake behaving animal, optimal orientation tuning in the range 30–85 Hz, matching these results. Furthermore, these frequencies are not a sole property of neuronal circuitry, but depend on stimulus properties: they tend to increase with increasing speed and size of the visual stimuli (Eckhorn 1994). To make matters even more complicated, in earlier parts of the cat visual system, oscillations in a much higher frequency range have been observed. In the retina and lateral geniculate nucleus, neurons show periodic activity with frequencies of 60–120 Hz (Neuenschwander and Singer 1996). Upon presentation of flashed stimuli, the high-frequency activity in retina and lateral geniculate nucleus leads to a feed-forward synchronization of cortical activity (Castelo-Branco et al. 1998). For moving stimuli, cortical circuitry seems to dominate dynamics and 30–60 Hz oscillations are observed. Thus, the oscillation frequency is highly dependent on the experimental setup. Furthermore, the experiments cited above concentrate on phenomena in the γ-frequency range, and oscillatory activity in lower frequency bands is usually considered to be an independent phenomenon. However, recent experiments have demonstrated that activity in the γ-frequency range is often accompanied by lower frequency components with considerable power. Furthermore, the dynamics are not independent, but nonlinear correlations between high and low-frequency oscillations occur (Schanze and Eckhorn 1997; von Stein et al. 1999; Siegel et al. 2000). In the hippocampus the situation might be even more complex. Oscillatory activity has been observed in many frequency bands, ranging from ultra-low (0.025 Hz, Penttonen et al. 1999) to ultra-high frequencies (up to 500 Hz, Bragin et al. 1999). Furthermore, complex interactions between activity in these frequency bands is observed.

From these results it becomes obvious that the description of neuronal dynamics by a single phase variable is a first step, useful for restricted systems only. Nevertheless, due to their analytical tractability and numerical efficiency, phase models and their modifications are here to stay for some time.

2.2. The statistical approach

Given the gross simplifying assumptions that phase models are based on, it is natural to refine the description of neuronal dynamics. Wilson and Cowan (1972, 1973) argue that the identity of presynaptic neurons is not important, but only the distribution of their level of activity. This leads to the statistical description of activity in a neuronal network. The proportions of active excitatory and inhibitory neurons are chosen as model variables and are denoted by $E(t)$ and $I(t)$, respectively. The proportion of active neurons at a time $t+\tau$ is given by the number of nonrefractory neurons at time t which have additionally received enough input so that their membrane potential exceeds the threshold of firing.

As the identity of neurons is considered not to be relevant, we assume that all neurons receive the same average input. This input depends only on the activity of excitatory and inhibitory populations as well as on the external input. This assumption seems plausible for a fully interconnected network with homogeneous parameter values. The only inhomogeneity in this model is a variation of the firing threshold, which is assumed to vary to a limited degree in a population of otherwise identical neurons. If the input is much lower than the average threshold, $E(t)$ will be near zero. If it is much higher than the average threshold, $E(t)$ will approach one. In the region of the average threshold, a steep but continuous dependence of $E(t)$ on input strength is found. This is well captured by a sigmoidal population response function $S(x)$, which gives the proportion of neurons receiving enough stimulation to exceed their threshold as a function of the average level of excitation x. Assume that the input to the network by neurons activated at time t' is given by the kernel $\alpha(t-t')$. Then x can be written as

$$\int_{-\infty}^{t} \alpha(t-t')\left[c_{ee}E(t') - c_{ie}I(t') + I_E^{ext}(t')\right]dt' \quad , \tag{4}$$

where I_E^{ext} represents the external input to the excitatory population, and c_{ee} and c_{ie} are positive constants representing the connection strengths within the network from excitatory onto excitatory neurons and inhibitory onto excitatory neurons, respectively. After firing the neurons will be refractory, meaning that they will not be sensitive to input during a specific time r. The proportion of nonrefractory excitatory cells is then given by $1-\int_{t-r}^{t} E(t')dt'$.

Suppose further that the subpopulation that exceeds threshold is independent of the subpopulation which is nonrefractory:

$$E(t+\tau) = \left(1 - \int_{t-r}^{t} E(t')dt'\right) \cdot S_e\left(\int_{-\infty}^{t} \alpha(t-t') \times \left[c_{ee}E(t') - c_{ie}I(t') + I_E^{ext}(t')\right]dt'\right) \quad . \tag{5}$$

For the population of inhibitory neurons we may obtain an analogous equation. These are complicated integral equations and they cannot easily be investigated with analytical or numerical tools. Therefore, an important further simplification is introduced, which relates to temporal averaging of $E(t)$ and $I(t)$. First, if the significant changes in $E(t)$ occur on time scales that are long compared to r, the variable $E(t)$ may be replaced by a time average given by $\bar{E}(t) = \frac{1}{r}\int_{t-r}^{t} E(t')\mathrm{d}t'$. Second, for $\alpha(t)$ close to a square pulse in the interval $0 \le t \le r$, we have $\int_{-\infty}^{t} \alpha(t-t')E(t')\mathrm{d}t' = k\bar{E}(t)$, where k is a constant. Third, with a Taylor-series expansion in the small parameter τ we obtain for excitatory and inhibitory populations

$$\tau\frac{\mathrm{d}\bar{E}}{\mathrm{d}t} = -\bar{E} + (1 - r\bar{E})\,\tilde{S}_{\mathrm{e}}(c_{\mathrm{ee}}\bar{E} - c_{\mathrm{ie}}\bar{I} + I_{\mathrm{E}}^{\mathrm{ext}}) \tag{6}$$

$$\tau'\frac{\mathrm{d}\bar{I}}{\mathrm{d}t} = -\bar{I} + (1 - r'\bar{I})\tilde{S}_{\mathrm{i}}(c_{\mathrm{ei}}\bar{E} - c_{\mathrm{ii}}\bar{I} + I_{I}^{\mathrm{ext}}) \ . \tag{7}$$

These equations define the Wilson and Cowan model. It exhibits a wide variety of behaviors depending on the parameters chosen. In particular, there are reasonable parameter ranges for which the system engages in a stable limit cycle. In the statistical setting this corresponds to synchronized oscillatory activity. Changes in one parameter value, for example the external input to the excitatory population, can act as a switch between stable limit cycles and stable fixed points, corresponding to an asynchronous state (Borisyuk and Kirillov 1991).

A justification of the statistical approach can be given by the spatial clustering of neurons with similar response properties in cortex. Indeed, in their pioneering work, Hubel and Wiesel (1962) reported a columnar-like arrangement of neurons that prefer stimuli of similar orientation. With refined methods, some local variation of response properties has been observed (Maldonado and Gray 1996). Nevertheless, neighboring neurons have a tendency to respond to similar stimuli. As neurons within a cortical column share many inputs and are tightly interconnected, one basic assumption of the statistical approach – the spatial averaging – seems to be justified. Indeed, in the physiological measurements a related signal in the range 1–100 Hz is observed, i.e., the local field potential. It is measured by the same electrodes used to record spiking activity, and may be seen as an intracortical EEG measurement. It is related to spiking activity (Gray and Singer 1989), for example sharing its orientation tuning with neurons recorded by the same electrode. Thus, it is interpreted as a spatial average of neuronal activity or of inputs to these neurons giving rise to dendritic currents. Thus, spatial averaging as applied in the Wilson and Cowan model might be justified to a certain degree.

However, the main problem lies not with the spatial average, but with the temporal average. The dynamics are assumed to be slow compared to the time scales of the refractory period and the postsynaptic response function. Thus, it is long when compared to the duration of an action potential and cannot describe neuronal dynamics on a millisecond time scale. Synchronization on a fast time scale in cortical networks, however, is the experimental phenomenon of interest here, which forces us to look for more biologically plausible models.

2.3 Discrete spiking models

In the preceding section we argued that the statistical approach of Wilson and Cowan does not only introduce an average in space, but also in time. Being interested in the fast dynamics of neuronal networks on a millisecond time scale, this is an obvious problem. Here we will describe the integrate-and-fire type of neuron that is widely used to model spiking behavior. Furthermore, we review the spike-response model. It allows a statistical description of spatially homogeneous networks and simultaneously maintains a high temporal resolution. In this way the advantages of the tractable Wilson and Cowan model and the more biologically realistic integrate-and-fire approach are combined.

When we place the emphasis on spikes, i.e., action potentials, several of their properties are worth consideration (Kandel et al. 1991). First, the bulk of communication between cortical neurons is thought to be transmitted by action potentials. Thus, a model that faithfully describes network dynamics at the level of action potentials has a good chance of capturing essential features of the system. Second, action potentials are of uniform shape and their precise dynamics on a sub-millisecond time scale does not seem to be important for the postsynaptic potentials (PSPs) triggered in the targeted neuron. Thus, we may be satisfied with a description only of their time of occurrence. As a consequence the detailed history of the membrane potential of the presynaptic neuron is not available to the postsynaptic neuron, and the effects of an afferent action potential depends on local variables only. Third, action potentials are triggered at the soma or somewhere into the axon. For this reason emphasis is placed on the dynamics of the somatic membrane potential, and dendritic processes are often simply described by an integration of all inputs.

These aspects lead to the description of a neuron as an integrate-and-fire unit. The somatic membrane potential U is taken as the dynamic variable. It decays towards its resting value with a time constant τ. Furthermore, it is influenced by the external input I_i^{ext} as well as by input I originating from within the network. When the membrane potential reaches a certain threshold a unitary pulse is transmitted to all synapses of this unit. Immediately afterwards the membrane potential of the presynaptic neuron is reset to its resting value.

Without loss of generality we set the resting potential to be at zero, and the threshold to one. In this case the model is given by

$$\frac{\mathrm{d}U_i}{\mathrm{d}t} = -\frac{U_i}{\tau} + I_i + I_i^{\mathrm{ext}} \quad \text{for } 0 < U_i < 1 \ , \tag{8}$$

where U_i denotes the membrane potential of neuron i. Input to unit i from other units is given by I_i. It is the sum of the PSPs that are triggered by pulses of afferent neurons at times t':

$$I_i(t) = \sum_{\text{all spikes},\ j \neq i} w_{ij} v(t - t'_j) \ . \tag{9}$$

Here, w_{ij} denotes the connection strength of neuron i to neuron j corresponding to the synaptic efficacy, and the function $v(t)$ models the shape of the postsynaptic current corresponding to the PSP. Common choices for $v(t)$ are the delta function for pulse-like interaction as well as more physiological shapes such as

$$v(t) = \begin{cases} c(\exp(-\frac{t}{\tau_1}) - \exp(-\frac{t}{\tau_2})) & \text{if } t > 0, \\ 0 & \text{otherwise} \ . \end{cases} \tag{10}$$

where c is a constant of normalization and τ_1 and τ_2 specify the fall and rise time of the PSP, respectively. Another widely used choice is given by the so-called "alpha function":

$$v(t) = \begin{cases} c\alpha^2 t \exp(-\alpha t) & \text{if } t > 0, \\ 0 & \text{otherwise} \ . \end{cases} \tag{11}$$

We note that transmission delays can be taken into account by shifting these functions to the right. If constant external input I^{ext} is assumed, the uncoupled integrate-and-fire unit will reach its threshold in equal time intervals and fire regularly. The oscillation behavior will remain qualitatively the same if the synaptic input I is relatively small compared to the external input I^{ext}.

At this level of sophistication numerical treatment is already computationally intensive. On one hand, single neurons are simulated which means that large networks are required for appropriate representations of populations. On the other hand, the temporal resolution of a simulation has to be in the millisecond range for an adequate treatment of action potentials. After all, this was the reason for introducing them. As a result, the required processing time is often much larger than the simulated time. For real-time simulations (computer time = simulated time) special hardware and/or software has to be used.

The analytical treatment of the integrate-and-fire model (Eq. 8), however, is difficult. The effects of incoming and outgoing action potentials are treated differently. In the first case the effect on the postsynaptic membrane potential is described by a kernel $v(t)$. In the second an instantaneous reset to zero is used. A generalization of the integrate-and-fire neuron, the spike response model, alleviates this problem (Gerstner et al. 1993a). Here, the effect of outgoing spikes is described by a kernel $\eta(t)$, which causes a sharp drop followed by a slow and gradual rise of the membrane potential after firing. Thus, the membrane potential U_i of a model neuron is given by

$$U_i(t) = \sum_{\text{all spikes}} [\ \eta(t - t'_i) + \sum_{j \neq i} w_{ij} \epsilon(t - t'_j)\ ] \ , \tag{12}$$

where t' denotes the time of spike initiation. In the following we assume that these functions are sufficiently smooth. We obviously have $\eta(t) = 0$ for $t < 0$, since the function should only affect the membrane potential after firing. A standard dynamics is then defined by $\frac{\mathrm{d}\eta}{\mathrm{d}t} \geq 0$ for $t > 0$. The function $\epsilon(t)$ gives the contribution due to synaptic input from other neurons. Furthermore, transmission delays Δ can be incorporated by requiring that $\epsilon(t) = 0$ for $t < \Delta$.

It can be shown by integrating the linear differential equation, (8), that the equations for the integrate-and-fire model can be written in this form (Gerstner et al. 1993a) for

$$\eta(t) = k_1 - k_2 \exp\left(-\frac{t}{\tau}\right) \quad \text{for } t > 0 \tag{13}$$

$$\epsilon(t) = \int_0^t v(s) \exp\left(-\frac{t-s}{\tau}\right) \mathrm{d}s \quad \text{for } t > 0 \ . \tag{14}$$

Note that in the direct comparison with (8) we have $k_1 = I\tau$ and $k_2 = I\tau + 1$. Thus, the classic integrate-and-fire neuron is contained in this description as a special case and has standard dynamics. The description of neuronal network dynamics using this approach is continued in Sect. 3.5.

The high temporal resolution of spiking neurons is an essential feature to explain several biological phenomena. Based on selective neuronal activity little more than 100 ms after stimulus presentation in inferotemporal cortex (Tovee et al. 1993) and in evoked potentials in humans (Thorpe et al. 1996), it has been argued that only about 10 ms is available to traverse an area in the hierarchy of the visual system. Whether this high speed of processing allows synchronization of neuronal activity to occur must at present be left unanswered. However, we would like to point out that the relative timing of individual action potentials, i.e., their deviation from perfect synchrony, has been used to explain this rapid processing by the visual system (Maass 1997; Gautrais and Thorpe 1998). Furthermore, several recent experiments indicate that the fine temporal structure of neuronal activity might be related to neuronal plasticity and learning (Ahissar et al. 1992; Markram et al. 1997; Koester and Sakmann 1998). This matches learning rules proposed on theoretical grounds, which equally exploit the relative timing of action potentials on a millisecond time scale (Gerstner et al. 1996b; Körding and König 2000).

2.4 Models of single neurons with continuous dynamics

The integrate-and-fire unit has been introduced using the argument that action potentials are the main means of communication between neurons. Since they are uniform in shape and only their timing is important, the detailed processes within a neuron have been largely neglected by simplifying them to a mere linear integration of inputs. Actually, the delicate morphology of neurons gives much room for interactions of different inputs in the dendritic tree which would affect the membrane potential at the soma and, thus, the time of spike initiation. It is therefore important to look at more detailed neuron models in order to study its subthreshold dynamics.

The most detailed models of a single neuron try to capture the dynamics of the membrane potential U by a description of transmembrane currents. They arise due to charging and discharging the membrane capacitance C by ionic currents through channels situated in the cell membrane with conductance g, due to synaptic currents I_{syn}, and eventually, depending on the experimental setup, externally injected currents I_{ext}. Each ionic current drives the membrane potential towards a characteristic value where inward and outward currents – driven by osmotic and electric gradients – cancel. As a change of membrane potential crossing this value leads to a "reversal" of the direction of current flow, it is called the reversal potential U_i. Its value depends on the intra- and extracellular concentration of ion type i. Furthermore, the membrane potential influences the fraction of open channels p_i and, thus, the conductivity $g_i(p_i)$ of ion type i. We can formulate this dynamic by a set of coupled differential equations of the form

$$C\frac{\mathrm{d}U}{\mathrm{d}t} = \sum_i g_i(p_i)(U - U_i) + I_{\text{syn}} + I_{\text{ext}} \tag{15}$$

$$\frac{\mathrm{d}p_i}{\mathrm{d}t} = \frac{p_i^{\infty}(U) - p_i}{\tau_i(U)} \quad . \tag{16}$$

For a given membrane potential U, p_i relaxes towards a value $p_i^{\infty}(U)$ with a time constant given by $\tau_i(U)$. If the response of a channel is relatively fast, the dynamics of p_i can be approximated by $p_i = p_i^{\infty}(U)$. We observe from (15) that when many channels of the i-th type are open and $g_i(p_i)$ is large, the membrane potential is driven to the reversal potential U_i of this ion type. Leakage through the membrane may be described by a term of similar form. We write $g_{\text{l}}(U - U_{\text{l}})$ where U_{l} denotes the leakage reversal potential and g_{l} is a constant.

A model that is now widely used was introduced by Hodgkin and Huxley (Hodgkin 1948; Hodgkin and Huxley 1952) to simulate the membrane potential in the giant axon of the squid. It includes the dynamics of sodium and potassium channels as well as a leakage term:

$$\begin{aligned} C\frac{\mathrm{d}U}{\mathrm{d}t} = &-g_{\text{Na}}m^3h(U - U_{\text{Na}}) - g_{\text{K}}n^4(U - U_{\text{K}}) \\ &- g_{\text{l}}(U - U_{\text{l}}) + I_{\text{syn}} + I_{\text{ext}} \end{aligned} \tag{17}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{m_{\infty}(X) - m}{\tau_m(X)} \tag{18}$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \frac{h_{\infty}(X) - h}{\tau_h(X)} \tag{19}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \frac{n_{\infty}(X) - n}{\tau_n(X)} \quad . \tag{20}$$

The Hodgkin-Huxley model was very successful in explaining the experimental results during axonal transmission. Similar models were later designed to capture the membrane potential in other parts of the neuron. Although the distribution of conductances differs in different parts of a neuron, and large variations in dynamics are observed, the general framework proved extremely powerful (Koch 1994): coupling the differential equations for individual parts of dendrites, soma, and axon, and taking into account preservation of currents (Kirchhof's law) leads to the so-called compartmental models. These take into account the specific spatial structure of a neuron with its dendritic tree. For example, they have been used to model detection of synchronous input by supralinear interaction in the dendritic tree (Softky 1994).

However, it has also been argued that the effects of different voltage-dependent conductances cancel one another, resulting in an effective linear integration of synaptic inputs by cortical neurons (Cook and Johnstone 1997; Cash and Yuste 1998). At the other extreme, it is possible that different synaptic inputs add sublinearly due to a saturation of dendritic potentials near the reversal potentials of depolarizing ionic currents (Mel 1994). These alternatives are not exclusive, and indeed recent experiments in cultured hippocampal neurons point to a most interesting synthesis of these views. Using a refined technique to apply synaptic stimulation, a rapid switch between sublinear and supralinear summation was found, depending on the temporal properties of the stimulus train (Margulis and Tang 1998). In effect, this would make the neuron particularly sensitive to coincident synaptic inputs.

However, the incorporated detail leads to extremely large computational burdens in numerical studies. Studies of synchronization of small networks of neurons, modeled with a moderate number of compartments, require hours of supercomputer time (Jefferys et al. 1996; see also Sect. 3.6). Looking back at the history of including more and more detail into the description of model neurons, we have to remark that several simplifications can ease considerably the computational burden or problems of analytical treatment. The most common approximation of the Hodgkin-Huxley equations, (17)–(20), are given by the FitzHugh-Nagumo model in which the additional assumption is made that the sodium channels adapt rapidly so that the system is described by a set of only two differential equations. This makes a convenient phase plane analysis possible. Furthermore, Kistler et al. (1997) have shown in a simulation study that with a suitable choice of the modeling functions η and ϵ, the spike response model (12) approximates the behavior of the Hodgkin-Huxley model quite well. Lastly, we note that in certain parameter ranges (17)–(20) exhibit a stable limit cycle. Thus, under these conditions the equations can be approximated by a phase description as described in Sect. 2.1.

The most serious problem of the detailed description, however, is our lack of knowledge of the relevant parameters. These include membrane capacitance, leakage currents, axial resistance, ion channel densities, parameters describing voltage dependent channels, and the position and properties of synapses. This list is quickly multiplied for a correct description of all compartments. Thus, the large number of free parameters in these detailed models is not paralleled by an appropriate number of biological constraints.

3 Synchronization in networks of oscillatory elements

In the preceding section different choices of the basic unit and some implications for network properties were described. In addition to the immediate consequences of the choice of the basic unit and its form of interaction, several decisions have to be taken.

First, the topology of connections is a most important choice to be made. The units may be completely connected to resemble a local assembly of neurons. Studies addressing hippocampal function often assume random connectivity with a small probability, resultings in a sparse connectivity. Cortical topography is modeled by having the density of connections decaying with distance.

Second, the treatment of delays in the neuronal interaction turns out to be a crucial feature. Networks with instantaneous interactions show qualitatively different behaviors to networks with delayed interaction, whether due to finite transmission delays, slow postsynaptic processes, or refractory periods.

Third, the size of the network affects the dynamics. In large networks the inclusion of dynamic or static noise leads to irregularities of formerly observed behaviors and interesting new phenomena. Thus, the number of options is multiplied when considering different kinds of networks built with the basic units described above.

Different characteristic measures are being used to investigate properties of each network. First, many authors focus on the conditions required for the existence of a stable state of synchronous activity within the network. Second, they investigate the process of synchronization from a biological point of view. Here, switching between synchronous and asynchronous states, as well as the speed of synchronization, are important properties. Third, for modeling physiological experiments the emphasis lies on the effect of inhomogeneous input on synchronization and desynchronization.

In the following sections the above aspects are discussed for some prototypical neuronal networks. Obviously, all relevant combinations have not been addressed in published work, nor is it possible to cover everything that has been done in this review. Open issues which seem relevant are discussed in the final section.

3.1 Coupled phase oscillators

The advantages of a phase description lie in its simplicity, allowing a thorough mathematical analysis as pointed out above. For this reason many studies have used this approach.

In Sect. 2.1 a phase is defined in the basin of attraction of a stable limit cycle. Here we study the effect of known perturbations on the phase of an oscillator, given in its phase description. Let us consider a small perturbation $p(X,t)$

$$\frac{\mathrm{d}X}{\mathrm{d}t} = F(X) + p(X,t) \ . \tag{21}$$

The perturbation could be due to input from other basic neural oscillators. Using the definition of the phase variable $\Phi(X)$ from Sect. 2.1 gives

$$\frac{\mathrm{d}\Phi(X)}{\mathrm{d}t} = \nabla\Phi(X)\frac{\mathrm{d}X}{\mathrm{d}t} = \nabla\Phi(X)[F(X) + p(X,t)] \ . \tag{22}$$

Using (3) for the unperturbed state then leads to

$$\frac{\mathrm{d}\Phi(X)}{\mathrm{d}t} = 1 + \nabla\Phi(X)p(X,t) \ . \tag{23}$$

Equation (23) is not yet a closed expression in Φ because the right-hand side still depends on the precise location X in phase space, which is not fully specified by Φ since all points on one isochron are associated with a certain phase Φ. However, for small perturbations X will be close to X_0, the intersection point of isochron with limit cycle, and by considering the linear approximation one may take

$$\nabla\Phi(X) = \nabla\Phi(X_0) \ . \tag{24}$$

Furthermore, we can approximate $p(X,t)$ by $p(X_0,t)$. For the investigation of a synchronized state we may also assume that the perturbation is T-periodic, and is only implicitly dependent on time so that $p(X_0,t) = p(X_0)$. This results in the desired phase description

$$\frac{\mathrm{d}\Phi}{\mathrm{d}t} = 1 + \Omega(\Phi) \ , \tag{25}$$

where

$$\Omega(\Phi) := Z(\Phi)p(X_0(\Phi)) \quad \text{and} \quad Z(\Phi) := \nabla\Phi(X_0(\Phi)) \ . \tag{26}$$

The vector $Z(\Phi)$ is sometimes referred to as the phase response function, as it represents the change in phase caused by external perturbations. Geometrically, $Z(\Phi)$ is a vector normal to the isochron at the intersection point with the limit cycle. Thus, it is tangential to the limit cycle, and its length relates to the effect of a perturbation: it will be greater at points of the limit cycle at which the state of the system changes slowly. The slower the change in state space the higher the density of isochrons. In turn, a higher density of isochrons implies a greater length of $Z(\Phi)$.

We now introduce the phase disturbance Ψ given by $\Phi = t + \Psi$. The phase disturbance indicates the deviation in phase from the unperturbed state for which the phase is increasing with constant velocity one. Thus, (25) takes an even simpler form:

$$\frac{\mathrm{d}\Psi}{\mathrm{d}t} = \Omega(t + \Psi) \ . \tag{27}$$

Because Ω is a product involving the perturbation p, it takes on small values, and so the phase disturbance Ψ changes only slowly. Thus, neglecting higher-order effects we obtain the average phase disturbance by averaging the right-hand side over one period T, which leads to

$$\frac{d\Psi}{dt} = \omega, \quad \text{where} \quad \omega := \frac{1}{T}\int_0^T \Omega(t+\Psi)dt$$
$$= \frac{1}{T}\int_0^T \Omega(t)dt \ . \tag{28}$$

Note that in the expression for ω we have assumed that Z and p and, therefore, also Ω are T-periodic functions, and that the change of Ψ over one period is small compared to T.

The same scheme can be generalized to a system of N coupled oscillators that are slightly different. Let their dynamics be given by

$$\frac{dX_i}{dt} = F(X_i) + f_i(X_i) + \sum_{j=1}^{N} I_{ij}(X_i, X_j)$$
$$\text{for } i = 1, \ldots, N \ . \tag{29}$$

Here, $f_i(X_i)$ denotes a small individual component of the i-th oscillator's dynamics. The small perturbation $I_{ij}(X_i, X_j)$ represents the influence of the j-th oscillator on oscillator i, and can be thought of as synaptic interaction. Analogous considerations then lead to

$$\frac{d\Phi_i}{dt} = 1 + g_i(\Phi_i) + \sum_{j=1}^{N} Z(\Phi_i) I_{ij}(\Phi_i, \Phi_j) \ , \tag{30}$$

where

$$g_i(\Phi_i) = Z(\Phi_i) f_i(X_{0i}(\Phi_i)) \ . \tag{31}$$

This last term results from the slightly different dynamics of the oscillators. Changing the variables $\Phi_i = t + \Psi_i$ and averaging as before gives the final set of differential equations

$$\frac{d\Psi_i}{dt} = \omega_i + \sum_{j=1}^{N} \Gamma_{ij}(\Psi_i - \Psi_j) \ , \tag{32}$$

where

$$\Gamma_{ij}(\Psi_i - \Psi_j) = \frac{1}{T}\int_0^T Z(t+\Psi_i) I_{ij}(t+\Psi_i, t+\Psi_j)dt \ , \tag{33}$$

and

$$\omega_i = \frac{1}{T}\int_0^T g_i(t+\Psi_i)dt = \frac{1}{T}\int_0^T g_i(t)dt \ . \tag{34}$$

We observe that the interaction function Γ indeed depends only on the difference in phases by again using the T-periodicity of the functions and the fact that Ψ does not change significantly during one period. Assuming identical oscillators we would have $f_i = 0$ and, thus, $\omega_i = 0$, which results in an even simpler form of (32).

It has been noted that the dependence of the interaction on the phases themselves, rather than on the difference in phase, can lead to a greater variety of more complex behaviors (Ermentrout and Kopell 1991; Golomb et al. 1992). In our derivation the simplification is due to the assumption that perturbations are weak and do not explicitly depend on time, thus making it possible to justify time averaging. Weak coupling has also been used for the definition of the phase. However, equations that are dependent on the phases can also be obtained for a limit cycle of strong attraction without the assumption of weak coupling. More detail and also a more rigorous derivation of the above results can be found in Ermentrout and Kopell (1984, 1991).

Two approaches have been taken to utilize the above derivation. First, a detailed neural oscillator can be reduced to its phase description. In this context it should be mentioned that the phase response function cannot be obtained analytically in most cases, since the trajectory of the limit cycle is not known exactly; thus it has to be approximated numerically. Also, the differential equation (32) will in general not be solvable analytically, although some analysis of synchronous states can be performed.

Therefore, many studies have taken a second approach by assuming a simple interaction function Γ. Since Γ is a T-periodic function, it can be decomposed into its Fourier series. The first-order approximation given by a sinusoidal function will render a reasonable and simple choice for analysis. It is for this reason a widely studied model system of coupled oscillators.

Here we present one study that addressed the physiological data obtained in the mammalian visual system (Sompolinsky et al. 1990, 1991; see also Schuster and Wagner 1990; Kammen et al. 1992). These authors introduce a scheme to separate the effects of the level of activity from the oscillatory dynamics within the framework of a phase description (for an investigation of the relationship to Wilson and Cowan types of models, see Grannan et al. 1993). The probability of firing $P(r,t)$ of a neuron at location r and time t is given by

$$P(r,t) = V(r)[1 + \lambda \cos(\Phi(r,t))] \ , \tag{35}$$

where

$$\frac{d\Phi(r,t)}{dt} = \omega + \eta(r,t) - \sum_{r' \neq r} J(r,r') \sin(\Phi(r,t) - \Phi(r',t)) \ . \tag{36}$$

Without coupling, the progression of the phase is given by the constant speed ω which is slightly disturbed by a noise term $\eta(r,t)$. Since the connections $J \sin(\Delta\Phi)$ tend to globally synchronize the network, the incorporation of this noise term plays an important role in desynchronization. The connection strength of different units is not only dependent upon their connectivity $W(r,r')$, but also on their activity level

$$J(r,r') = V(r) W(r,r') V(r') \ . \tag{37}$$

Thus, unstimulated oscillators do not interfere with the network dynamics. The units are arranged in clusters that are thought to represent cortical columns. Within each cluster neurons receive input from the same position in the visual field, whereas their individual orientation preference covers the full range of 180 degrees. The connections are strong and independent of the preferred orientation, resulting in rapid synchronization within a column during stimulation with a single stimulus of any orientation. Between different clusters the connectivity is weak and a decreasing function of the difference of the preferred orientation. Different shapes of this connectivity function have been investigated. Plausible choices for $W(r, r')$ led to stimulus-specific synchronization of different clusters. Note that these were not obtained by derivation from an explicit neuron model underlying the phase description, but rather they were chosen to reproduce the phenomena observed in experiment. For a stimulus consisting of two short bars presented to different receptive fields, coherence arises only if they have similar orientations. For distant receptive fields, the synchronization of neuronal oscillators turns out to be dependent on the type of stimulus. If the angle of the stimulus varied continuously between the receptive fields, i.e., such as an arc, coherent activity could be observed. In contrast, a discontinuity in orientation, i.e., such as a wedge, led to uncorrelated activity of the two clusters.

These results match experimental observations on stimulus-specific synchronization in the mammalian visual system. For example, it has been found that neurons synchronize when they are activated by a single moving bar simultaneously passing over their individual receptive fields (Gray et al. 1989; Freiwald et al. 1995; Brosch et al. 1997). However, if two short bars were presented to the receptive fields their activity would not be correlated even though their mean firing rate would be increased equally in both cases. Thus, for the simple types of stimuli used, neurons tend to synchronize if they are activated by features that are likely to be part of the same object.

The assumptions on connectivity in these simulations are compatible with results of recent anatomical studies. Long-range connections in visual cortex are slightly biased to connect sites with similar feature preferences (Malach et al. 1993; Kisvárday et al. 1997). Furthermore, recent studies have found an anisotropy of connectivity in visual cortex in the direction of the preferred orientation (Fitzpatrick 1996; Bosking et al. 1997; Schmidt et al. 1997). In this sense, the anatomical connections implement *Gestalt* laws.

3.2 Networks of excitatory and inhibitory spiking units

Taking one step into biological realism and choosing elements that are either excitatory or inhibitory as basic units of a network leads to the investigation of the effect of different coupling.

Starting with a model of excitable elements that was designed to model the synchronization of the flashes in fireflies, Mirollo and Strogatz (1990) showed that globally excitatory interaction results in synchronization with zero phase lag. In this analysis generalized integrate-and-fire oscillators are used. The starting point is a unit as described by (8). The differential equation can be easily integrated over one period T after which the cycle begins anew. Performing a change of variable to a phase description, such that $\mathrm{d}\Phi/\mathrm{d}t = 1/T$, we obtain the membrane potential $X = f(\Phi)$, where $f : [0,1] \to [0,1]$. In the following analysis it is only assumed that f is smooth, monotonically increasing ($f' > 0$), and concave down ($f'' < 0$), which is not only true for the leaky integrate-and-fire unit but also for certain choices of functions in the spike response model given by (12).

The oscillators are pulse coupled, meaning that the input is given by delta impulses. After integration this leads to the interaction rule

$$X_i(\Phi) = 1 \quad \Rightarrow X_j(\Phi^+) = \min(1,\ X_j(\Phi) + \epsilon) \quad \text{for all } j \neq i \ . \tag{38}$$

Thus, the firing of one oscillator instantaneously gives a small standard input ϵ to all other oscillators, thereby advancing them on their cycle or putting them to their firing threshold if they are already sufficiently close. We now investigate the behavior of two coupled oscillators via return maps (Mirollo and Strogatz 1990). Let us consider the situation where oscillator 1 has just fired and the phase of oscillator 2 is given by Φ_2. The return map $R(\Phi_2)$ is defined to be the phase of oscillator 2 immediately after the next firing of oscillator 1. Note that the relative phases only change when one oscillator is firing. This means that oscillator 2 will fire in the meantime, specifically after a time $1 - \Phi_2$, and this will advance oscillator 1 on its cycle. At this instant the membrane potential of oscillator 1 is either set to one, in which case the system is already synchronized, or is given by $X_1 = f(1 - \Phi_2) + \epsilon < 1$. Its phase then defines the firing map h:

$$h(\Phi_2) := \Phi_1 = f^{-1}(f(1 - \Phi_2) + \epsilon) \ . \tag{39}$$

Now the situation is reversed because oscillator 2 has just fired, and the return map is obtained by applying the same reasoning and the firing map one more time so that

$$R(\Phi_2) = h(h(\Phi_2)) \ . \tag{40}$$

Assuming that synchrony is not reached we always have $X_1 = f(1 - \Phi_2) + \epsilon < 1$, which implies that $\Phi_2 \in (\delta, h^{-1}(\delta))$, where $\delta = 1 - f^{-1}(1 - \epsilon)$. We will now see that in this interval there exists only one fixed point of the system, which is a repeller. Fixed points are given by the zeros of

$$F(\Phi_2) = \Phi_2 - h(\Phi_2) \ , \tag{41}$$

because fixed points of h are also fixed points of R. We note that $h'(\Phi_2) < -1$ because of the chain rule, and $f'(1 - \Phi_2) = (f^{-1\prime}(f(1 - \Phi_2)))^{-1}$ implies that

$$h'(\Phi_2) = -\frac{f^{-1\prime}(f(1 - \Phi_2) + \epsilon)}{f^{-1\prime}(f(1 - \Phi_2))} \ . \tag{42}$$

Concavity of f gives convexity of f^{-1}, and the statement follows. This leads to $F'(\Phi_2) = 1 - h'(\Phi_2) > 0$. It can also be verified that

$$F(\delta) < 0 \quad \text{and} \quad F(h^{-1}(\delta)) > 0 \ . \tag{43}$$

Therefore, there is a unique fixed point Φ^* in the given interval for which $R(\Phi^*) = \Phi^*$. Since

$$R'(\Phi^*) = h'(h(\Phi^*))h'(\Phi^*) > 1 \tag{44}$$

we have

$$R(\Phi) > \Phi \text{ for } \Phi > \Phi^*$$
$$\text{and} \quad R(\Phi) < \Phi \quad \text{for } \Phi < \Phi^* \ , \tag{45}$$

such that this fixed point is unstable. Biologically this does not represent a realistic solution since noise is omnipresent and the system would not stay at this steady state.

In summary, this means that the two oscillators with excitatory pulse coupling will always be synchronized. The system has been analyzed explicitly for a biologically plausible and mathematically convenient choice of the function f. The interesting results obtained in this special case may hold for a whole class of similar functions. Both coupling strength given by the value of ϵ and dissipation, which is a measure for the leakiness of the model and, therefore, for the concavity of the function f, prove to be important parameters. The speed of synchronization is inversely proportional to their product. They also have an effect on the location and stability of the fixed point. It tends to be closer to the in-phase solution for greater values of dissipation and connection strength. It can also be shown that in the case of negative ϵ, corresponding to inhibitory coupling, the counterphase situation will be stable such that the oscillators will not necessarily synchronize. The case of a large network has also been investigated. Intuitively, one might argue that oscillators will be absorbed into groups of synchronously firing units. Note that in the given dynamics, once two oscillators fire in synchrony they cannot break apart. Thus, such groups can only become larger in time. Indeed, it can be shown, using return maps and a similar argument, that the set of initial conditions for which the oscillators will never be absorbed into one single synchronized group has measure zero and is as such biologically irrelevant. This conclusion has been confirmed in numerical studies.

These results suggest that excitation rather than inhibition leads to a synchronous solution. An extreme case of excitatory coupling can be found in the hippocampus. Recent in vitro experiments suggest direct axonal-axonal excitation of pyramidal neurons by gap junctions (Draguhn et al. 1998). Indeed, even a low incidence of such connections is sufficient to explain the observed synchronization in the high frequency range (100–200 Hz, Traub et al. 1999).

3.3 The effect of transmission delays

In the considerations above, idealized interactions without any transmission delays have been assumed. This is not only an unphysiological assumption. In a numerical study, Ritz et al. (1994) showed that a coherent oscillation of period T in two disjoint domains of spiking neurons connected by axonal delay lines with a uniform distribution of transmission delays remains coherent *only if* the mean delay is less than approximately $T/3$ (mod T).

Ernst et al. (1995) analyzed a system of two integrate-and-fire neurons using the same method as Mirollo and Strogatz (1990). Due to transmission delays, various cases for the return map had to be distinguished. In a network of excitatory elements and for the same function f as in the example chosen by Mirollo and Strogatz (1990), the synchronous state is repellent. Additional out-of-phase fixed points exist which are stable at Δ and $[f^{-1}(1-\epsilon) - \Delta]$; here Δ denotes the transmission delay. Therefore, in-phase solutions will not occur in this setup.

In contrast, the picture is reversed for a network with inhibitory connections and excitatory input; without input there is no response. The behavior can be deduced from a "locking theorem" due to Gerstner et al. (1996b, Figs. 2 and 3). Under rather general assumptions (in the limited of a large number of presynaptic neurons and standard dynamics), an asymptotically stable coherent oscillation in a homogeneous network of spiking neurons occurs if and only if the total postsynaptic potential is rising at the time that the postsynaptic spike is triggered. Thus, if delays are not too small, so that spikes are triggered in a phase when the effect of the IPSP decays, i.e., when the potential is rising again, they have a synchronizing effect. Excitatory input requires that the delays be not too large so as to attain the same effect.

Van Vreeswijk et al. (1994) investigate as a special case a pair of leaky integrate-and-fire neurons with non-instantaneous interaction, which is represented by an alpha function; see (11). A finite slope for the post-synaptic potential can mimic the effect of delays and in reverse, the finite slope of experimentally observed post synaptic potentials is similar to a delayed transmission of signals between two neurons. They found that in the two-unit system the synchronous state is only stable for mutually inhibitory connections.

To understand this we present some of their analysis, considering possible phase lags when the oscillators are phase locked. We use the equations given in (8) with $\tau = 1$ and constant external input I^{ext}. Suppose neuron 1 fires at times $t = nT$, where n is an integer and T denotes the period, while neuron 2 fires at times $t = (n - \Psi)T$, whilst ensuring that Ψ is a constant phase lag between them. Let Φ denote the phase. The input to neuron 2 at times $t = \Phi T$ for $0 < \Phi < 1$ is then given by

$$I_T(\Phi) = \sum_{n=-\infty}^{0} v((\Psi - n)T) \ . \tag{46}$$

Outside the range $0 < \Phi < 1$, I_T is extended by making it a periodic function. Input to neuron 1 is analogously given by $I_T(\Phi + \Psi)$, and a consistency condition immediately follows from our assumption that neuron 1 fires again at time T. At this time the membrane potential reaches threshold at one and is reset to zero. Integrating the original equation, (8), gives

$$X_1(T) = I^{\text{ext}}(1 - \exp(-T)) + T\exp(-T)\int_0^1 \exp(\Phi T) I_T(\Phi + \Psi)\mathrm{d}\Phi = 1 \ . \quad (47)$$

Similarly the consistency condition for neuron 2 reads:

$$X_2((1-\Psi)T) = I^{\text{ext}}(1 - \exp(-T)) + T\exp(-T)\int_0^1 \exp(\Phi T) I_T(\Phi - \Psi)\mathrm{d}\Phi = 1 \quad (48)$$

Here we have exploited the periodicity of I_T. Subtracting the two equations and dividing them by T leads to the condition

$$G(\Psi) = \exp(-T)\int_0^1 \exp(\Phi T)(I_T(\Phi+\Psi) - I_T(\Phi-\Psi))\mathrm{d}\Phi = 0 \ . \quad (49)$$

Thus, the synchronous solution $\Psi = 0$ will always be a steady state and, because of the periodicity of I_T, $\Psi = \frac{1}{2}$ as well. The stability of the solutions is determined by

$$G'(\Psi) > 0 \ . \quad (50)$$

This condition becomes apparent by substituting (47) into (48) and replacing the integral by $G(\Psi)$, which gives

$$X_2((1-\Psi)T) = 1 - TG(\Psi) \ . \quad (51)$$

If Ψ is now a bit larger than at the steady state then neuron 2 should tend to fire later in order to return to the equilibrium phase lag. So $X_2((1-\Psi)T)$ should be smaller than one and, therefore, $G(\Psi) > 0$. By looking at the reversed case we obtain the above condition.

We note that the zero phase-lag solution is always unstable for excitatory coupling but stable in the inhibitory case, which can easily be shown analytically for the assumed alpha function. Similar to the observation of Ernst et al. (1995), other steady states can be stable for inhibitory connections depending on the values of α which determine the time course of the dynamics. Smaller values of α, corresponding to slower dynamics, tend to have only the synchronous state as a realistic solution. Thus, the analysis of this model with a more realistically shaped synaptic input instead of a delta-impulse implies as well that inhibitory rather than excitatory connections lead to a stable synchronous solution for two coupled oscillators.

In a study using Wilson and Cowan oscillators (König and Schillen 1991; Schillen and König 1991), the interaction of overlapping visual stimuli was investigated. Similar to (6), the basic neuronal assembly is modeled using statistical approach. The important modification is the inclusion of transmission delays in the coupling between different neurons. Under these conditions excitatory-to-inhibitory coupling leads to synchronous activity, whereas excitatory-to-excitatory coupling favors desynchronization. Studying a system with connections of the first type between units of similar response properties, and connections of the second type between units of dissimilar response properties, the following experimental results could be reproduced: overlapping stimuli with orthogonal motion vectors were represented by different assemblies which had no consistent phase relationship between each other (Engel et al. 1991; Kreiter and Singer 1996). Furthermore, the correlation length in the network turns out to be dependent on the number of stimuli shown, a prediction confirmed by physiological experiments (Engel et al. 1991).

Traub and Whittington (Whittington et al. 1995; Traub et al. 1996) find an interesting twist to the story on synchronization mechanisms. In a simulation of the hippocampal network using detailed compartmental model neurons they observed that the synchronization of γ-activity is governed by the network of inhibitory interneurons. In particular, spike doublets of these cells induce synchronization of interneurons and principal cells without phase lag, as well as the synchronization of the active pyramidal neurons (Jefferys et al. 1996).

3.4 Analysis via the phase response function

If a system of coupled differential equations is transferred to its phase description, the phase response function of different neuron models has proven valuable in the analysis of the influence of the timing of the synapses on the stability of coherent oscillations.

The phase response function $Z(\Psi)$ has already been introduced as a vector in Sect. 3.1. For most neuron models it can be reduced to a scalar function because only one component is relevant for the further analysis. This is due to the fact that in most cases only the equation for the dynamics of the membrane potential is directly perturbed by coupling to other neuronal oscillators. Thus, there is only a contribution from one component of $Z(\Psi)$ to the vector product in (33). In this case it can be seen directly that if the phase response function is positive the next spike will be advanced by a depolarizing pulse; conversely the firing will be delayed if the perturbation takes place in a negative region of the phase response function.

Hansel et al. (1995) and van Vreeswijk et al. (1994) use the equations as a starting point to derive expressions that indicate steady states of phase lags Ψ as well as their stability between oscillators which are coupled without a delay. In this phase-locked situation we have $\Psi_1 = \Psi_2 + \Psi$ and, thus, $\frac{\mathrm{d}\Psi_1}{\mathrm{d}t} = \frac{\mathrm{d}\Psi_2}{\mathrm{d}t}$. When the oscillators are symmetrically coupled, subtracting (32) written for the two oscillators gives the following condition for steady states:

$$H(\Psi) = \frac{1}{2}(\Gamma(\Psi) - \Gamma(-\Psi)) = 0 \ . \quad (52)$$

Because of symmetry $\Psi = 0$ as well as $\Psi = \frac{1}{2}$ are again solutions to this equation. Considering small deviations

from this steady state one can see that its stability can be determined through

$$\frac{\mathrm{d}H(\Psi)}{\mathrm{d}\Psi} < 0 \ . \tag{53}$$

From (33) we have by substitution and the periodicity of the functions that

$$\Gamma(\Psi_1 - \Psi_2) = \Gamma(\Psi) = \frac{1}{T}\int_0^T Z(u)I(u, u-\Psi)\mathrm{d}u \ . \tag{54}$$

In particular, the stability of the synchronous state is then determined by

$$\frac{\mathrm{d}H}{\mathrm{d}\Psi}(\Psi = 0) = \Gamma'(0) = -\frac{1}{T}\int_0^T Z(u)I'(u,u)\mathrm{d}u < 0 \ , \tag{55}$$

where $'$ denotes differentiation with respect to Ψ. This expression is not only valid for integrate-and-fire units but also for conductance-based models like the Hodgkin-Huxley equations, where spiking interactions are reduced to their phase description; this has been done by Hansel et al. (1995). These authors contrast the synchronizing behavior of two qualitatively different phase response functions. Phase response functions of type I are positive over the whole cycle whereas type II phase response functions are negative at the beginning of the cycle and positive towards the end of it. The stability in each case is determined by the interplay of rise time and decay time of the synaptic input, the shape of the phase response function, and the refractory period.

Excitatory connections tend to be desynchronizing for type I response functions, since the integral is generally dominated by the destabilizing contribution of the fall time of the input. For type II phase response functions, however, sufficiently fast excitation can be synchronizing. The negative region of the phase response function also accounts for the formerly surprising result that an increase in excitation can act as effective inhibition and decrease the overall firing rate (Hansel et al. 1993).

This method also explains the qualitatively different behavior of seemingly similar conductance-based models. The Hodgkin-Huxley neuron model, for example, exhibits a type II response. However, another quite similar conductance-based model, the Connor model (Connor et al. 1977), which includes an additional A-current, is of type I. On the other hand the Morris-Lecar equations (Morris and Lecar 1981), a simplified version of the Hodgkin-Huxley model, can be either of type I or II depending on the parameter values (Ermentrout 1996). It has been shown that these qualitative differences in the phase response functions of the models can be linked to the mechanism underlying the transition from the resting state to repetitive firing (Ermentrout 1996). Models that allow for the onset of arbitrarily low frequencies have a phase response function of type I. Models that undergo a Hopf bifurcation to stable limit-cycle oscillations have a phase response function of type II close to the bifurcation point where the interaction is approximately sinusoidal.

Let us now compare the results to the studies presented above. The phase response function can be computed analytically for the standard integrate-and-fire model given in (8) to $Z(\Psi) = \frac{1}{7}\exp\Psi$. Generally, these models have a response of type I since they are always advancing the next spike. We obtain consistent results with the previous example. However, the linear stability analysis can only be performed if the phase response function and the synaptic input function are sufficiently smooth. Therefore, the results do not apply to pulse coupling (Mirollo and Strogatz 1990; Ernst et al. 1995). With the results of the previous sections in mind it becomes apparent that the network's behavior may be very sensitive to the choice of the neuron model, the form of interaction, and crucial parameters such as transmission delay and refractory period.

3.5 Analysis of the spike response model

The subtle interplay between mutually excitatory or inhibitory connections, transmission delays, and the PSP shape has been further illuminated by van Hemmen and his coworkers (Gerstner et al. 1993a, b, 1996a; Ritz et al. 1994). Using the spike response model introduced in Sect. 2.3, these authors derived analytically that perfect synchrony is only possible if the total synaptic input is still increasing with time when the firing threshold is reached.

Consider now the existence and stability of the synchronous solution in a homogeneous network of N units in the formalism of the spike response model. Suppose that for $t < 0$ the neurons have fired in synchrony with period T. The membrane potential of a neuron for $0 < t < T$ is the given by

$$X_i(t) = \sum_{k=0}^{\infty}\left[\eta(kT + t) + \sum_{j\neq i} w_{ij}\epsilon(kT + t)\right] \ . \tag{56}$$

The threshold θ should be reached again at time $t = T$ for the assumption to be consistent. This leads to the condition

$$\theta = X_i(T) = \sum_{k=1}^{\infty}\left[\eta(kT) + \sum_{j\neq i} w_{ij}\epsilon(kT)\right] \ . \tag{57}$$

This condition specifies the periods T for which synchronous firing in the network is a consistent solution.

Let us now turn to the stability of the solution and assume that the firing of neuron i occurred at slightly different times given by $-kT + \delta_i(-k)$ where $k = 0, 1, 2, \ldots$, and $|\delta_i(-k)| \ll T$ is a small perturbation. Then, the time shift $\delta_i(1)$ for the next firing satisfies the condition

$$\begin{aligned}\theta &= X_i(T + \delta_i(1)) \\ &= \sum_{k=0}^{\infty}\Bigg[\eta((1+k)T + \delta_i(1) - \delta_i(-k)). \\ &\qquad + \sum_{j\neq i} w_{ij}\epsilon((1+k)T + \delta_i(1) - \delta_j(-k))\Bigg] \ . \end{aligned} \tag{58}$$

We linearize this equation with respect to $\delta_i(1) - \delta_i(-k)$ and $\delta_i(1) - \delta_j(-k)$, and subtract (56) which leads to

$$\delta_i(1) = \frac{\sum_{k=0}^{\infty}[\eta'((1+k)T)\delta_i(-k) + \epsilon'((1+k)T)\sum_{j\neq i} w_{ij}\delta_j(-k)]}{\sum_{k=0}^{\infty}[\eta'((1+k)T) + \epsilon'((1+k)T)\sum_{j\neq i} w_{ij}]} \ . \tag{59}$$

This is a linear map which gives the dependence of the present perturbation on all previous perturbations. For stability we must have that, on iteration, the perturbations will eventually die out. Note that in this form it has been assumed that firing of other neurons at the present time step does not affect the membrane potential. Since the firing irregularities are small this will be true as long as there is a true transmission delay between the neurons. However, for comparison with results from the previous sections another term would have to be included in the analysis.

In a homogeneous network one may assume that $\sum_{j\neq i} w_{ij}\delta_j(-k) = W_0$, where $\langle\delta_{-k}\rangle$ is independent of i. In this $W_0 \approx \sum_{j\neq i} w_{ij}$ represents the average total connection strength to a neuron and $\langle\delta_{-k}\rangle$ denotes the mean firing shift. For stochastic noise as the source of perturbations it is a plausible assumption that the perturbations are random, which implies that $\langle\delta_{-k}\rangle = 0$. The above expression then reduces to

$$\delta_i(1) = \frac{\sum_{k=0}^{\infty}\eta'((1+k)T)\delta_i(-k)}{\sum_{k=0}^{\infty}(\eta'((1+k)T) + W_0\epsilon'((1+k)T))} \ . \tag{60}$$

Realistic shapes for the functions ϵ and η have then decaying to zero after they reach their maxima. If transmission delays are relatively short and the decay fairly rapid as compared to the oscillation period one may focus on the situation that the sums will be dominated by the contribution from only the last firing. This "short-term memory" of the neurons then leads to

$$\delta_i(1) = \frac{\eta'(T)}{\eta'(T) + W_0\epsilon'(T)}\delta_i(0) \ . \tag{61}$$

The numerator as well as denominator of this fraction are positive, the numerator because of standard dynamics and the denominator because it gives the derivative of the membrane potential when the threshold is reached from below. We will, therefore, obtain stability if $W_0\epsilon'(T) > 0$, which makes the fraction smaller than one and, thus, leads to decaying perturbations. Likewise $W_0\epsilon'(T) < 0$ indicates instability. An analogous condition can also be verified for the more complex case for which short-term memory is not assumed, which reads

$$\sum_{k=0}^{\infty} W_0\epsilon'((1+k)T) > 0 \ . \tag{62}$$

This mathematical condition can be put into biological terms by stating that for a stable synchronous state the total synaptic input still has to be rising at the time of the next firing.

In this framework it follows that purely inhibitory connections generally produce stable coherent oscillations if the delay is smaller than an upper bound that depends on the network parameters. Coherent oscillations exist for purely excitatory connections provided that the transmission delays are long enough for the chosen setup.

The formalism can also be used for a network containing excitatory as well as inhibitory connections with different transmission delays for each connection type. From the above result it follows immediately that short-range inhibitory connections combined with long-range excitatory connections sustain stable collective oscillations.

Considering delays in a neuronal network does not only add complexities, but also allow qualitatively new features. Using the spike response model to investigate a network with realistic distributions of axonal delays, Gerstner et al. (1993b) demonstrated learning of sequences of patterns. Furthermore, depending on a parameter of the neurons (threshold), these patterns could be replayed at varying speed. Remarkably, the relevant information about spike patterns is lost when only mean firing rates or ensemble activities are considered. The full information on a pattern is contained in the spike raster of a single run. This work stresses the importance – and advantage – of coding by spatio-temporal spike patterns instead of by firing rates and average ensemble activity, and of considering the fast temporal dynamics of neuronal activity.

However, the above analysis cannot be applied directly to the case of zero delay with very fast rise time. Linear approximations are not valid for functions that are not smooth enough; specifically, they do not apply to pulse coupling. For this class of interactions a separate analysis was performed by Gerstner et al. (1996a) for collective oscillations with excitatory connections. The results showed that these states are locally unstable and therefore in agreement with the studies mentioned above.

3.6 Temporal dynamics in larger networks

Many investigations of synchronization of neuronal activity have concentrated on small and/or homogeneous networks. For simulation studies, computational resources are a constraint; for analytical studies, the treatment of pairs of oscillators is often taken as a first step. However, the investigation of the temporal dynamics in large networks is important for several reasons.

First, several types of noise are present in biological systems. Static noise, such as inhomogeneous distribution of parameters, is found in real systems and its effects on highly ordered states like synchronous activity have to be considered. Stochastic noise has a slightly different nature and arises from small random fluctuations of the dynamic variables in time that are omnipresent in biological systems. Actually, a discussion of whether the high variability of neuronal activity ob-

served is noise or a signal is an issue in itself, and beyond the scope of the present article. Here we concentrate only on some phenomena that can be found when stochastic and static noise are taken into consideration.

Second, in larger systems phenomena that are qualitatively new can be found. Different rules for the spatial summation of mean activity and oscillatory activity have been observed in primary visual cortex of the cat (Bauer et al. 1995). Apart from a completely asynchronous or synchronous firing pattern, a variety of more complex behaviors such as more irregular, partially synchronized, and alternating states may emerge in large networks. These phenomena may occur in networks whose configuration has been found to be synchronizing under homogeneous conditions, as well as in frustrated networks consisting of units that do not exhibit synchronous activity in a two-unit system. These mixed states may account for some aspects of dynamics in the brain, as experimental findings show that synchronous behavior is a rather transient phenomenon that alternates with irregular activity.

Third, the anatomy of the cerebral cortex seems to be neither completely random nor completely regular. Thus, realistic models have to incorporate the specifics of our knowledge of anatomical connectivity. This naturally leads to large neural networks.

The effect of static noise arising from distributed individual frequencies due to different external input has been studied (Tsodyks et al. 1993) for integrate-and-fire units (compare (8) with $\tau = 1$). The neurons are coupled all-to-all by excitatory synaptic input currents given by

$$\frac{\mathrm{d}U_i}{\mathrm{d}t} = -U_i + I_i + I_{\mathrm{i}}^{\mathrm{ext}} \tag{63}$$

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} = -\frac{I_i}{\tau_0} + K\rho(t) \tag{64}$$

$$\rho(t) = \frac{1}{N} \sum_{\text{all spikes}} \delta(t - t') \ . \tag{65}$$

We observe by integrating (64) that input currents I are of decaying exponential form, referring to the instantaneous rise and exponential fall of the input. If equal and constant external inputs are assumed, this setup tends towards synchrony (compare Sect. 3.2). For a certain frequency distribution the system is divided into two subpopulations, one which is still locked to a common frequency but not perfectly phase locked, and one for which the oscillators are bursting at their natural frequencies, creating a periodic background spiking density if the network is large. To see this, suppose that the synaptic input is given by a T-periodic function $I(t)$. Let t_n denote the time of firing relative to this periodic background such that a neuron fires at time $nT + t_n$. By integrating (63) we find the consistency condition

$$\exp(t_{n+1}) = \exp(-T) \int_{nT+t_n}^{(n+1)T+t_{n+1}} \exp(s - (nT + t_n)) \times (I(s - (nT + t_n)) + I^{\mathrm{ext}})\mathrm{d}s \ . \tag{66}$$

For phase locking to period T we are interested in a fixed point of the time shifts, implying that $t_n = t_{n+1} =: t_0$. Using the periodicity of I we get a condition for t_0 in relation to the external input I^{ext}

$$I_0^{\mathrm{ext}} = \frac{1 - \exp(-T) \int_0^T \exp(s) I(s + t_0)\mathrm{d}s}{1 - \exp(-T)} \ . \tag{67}$$

Assuming that I is largest immediately after firing at time 0, after which I decays, it can be inferred that the stable fixed time shift t_0 is monotonically decreasing with increasing external input I_0^{ext} around the average input level, and there exists a critical value $I_{\mathrm{C}}^{\mathrm{ext}}$ above which there is no fixed phase solution. This implies that neurons are frequency locked up to a certain input threshold. Furthermore, neurons within this subpopulation fire earlier for larger external input, as has been noted before in experiments (König et al. 1995a) and models (Wennekers and Palm 1999). It is also noted that the unlocked neurons whose input is still close to the critical value $I_{\mathrm{C}}^{\mathrm{ext}}$ have a tendency to fire at times nT. The spike density ρ for both of these populations, and therefore I, can be determined from these results and substituted back into (66), which gives a consistency condition for the parameters – specifically the size of the phase locked population. The assumption of a periodic synaptic input also has to be investigated. In this study the assumption has been justified for a small frequency distribution around the critical value $I_{\mathrm{C}}^{\mathrm{ext}}$. Interestingly, it turns out that the size of the phase-locked population reaches a maximum for a finite rise time of the synaptic coupling, for which the system cannot be completely synchronized even in the case of homogeneous input, as has been seen in Sect. 3.4.

The introduction of noise can also cause alternating oscillatory and stochastic activity (Deppisch et al. 1993). In a large simulated network conductance-based neurons (see McGregor and Oliver 1974) are connected via delayed excitatory pulse coupling. The external input stems from stochasticly spiking elements that project to a variable number of units in the network. For a low divergence of this projection and low internal coupling strengths the network engages in stochastic firing. For high coupling strength and large convergence of the input projection a globally correlated activity pattern is observed. The neurons engage in synchronized oscillatory activity, in which each neuron contributes one or more spikes per cycle. In between these two extremes, a region exists for which the network spontaneously switches between irregular and synchronized behavior. This compares well with experimental observations in cat visual cortex (Eckhorn 1994; Singer and Gray 1995).

Let us now consider the behaviors of large networks that are not necessarily synchronized, in the limit of only two interacting oscillators. Many studies dealing with these "frustrated networks" have not only found the completely asynchronous state, but also rotating-wave states as well as clustering states. Clustering states occur when the system breaks up into several subpopulations that are each fully synchronized. In this state the system as a whole exhibits activity at a multiple of the frequencies of

the subpopulations. Whenever the ratios of the subfrequencies are not rational the overall activity appears to be aperiodic. Note that the amplitude of the activity is dependent on the size of the clusters. Clustering states can represent the transition from the synchronous to the asynchronous state, since complete synchrony can be regarded as a single cluster state whereas many small clusters with non-related frequencies correspond to the asynchronous state for a large network.

Clustering has been reported in the phase description at a variety of large systems of globally coupled oscillators. In phase models for which the coupling function depends only on the difference of the phases, the occurrence of clustering (other than the one-cluster state) has been linked to higher Fourier modes of the interaction function (Okuda 1993). He investigated the stability of n symmetrical clusters of equal size starting with (32) for N homogeneous oscillators with coupling strength N. For the phases $\Psi_i^{(n)}$, $(i = 1, \ldots, n)$ of the clusters we have the equation

$$\frac{\mathrm{d}\Psi_i^{(n)}}{\mathrm{d}t} = \frac{1}{n}\sum_{j=1}^{n} \Gamma(\Psi_i^{(n)} - \Psi_j^{(n)}) \ . \tag{68}$$

The analysis of small disturbances around these states suggests that higher Fourier modes of the interaction function Γ may be essential for clustering states. Thus, clustering is not a general property of the widely considered oscillators with sinusoidal coupling. This is also thought to account for the results of this study, namely, that clustering does not occur in the vicinity of a Hopf bifurcation at which the dynamics can be approximated by the first harmonic.

A similar analysis for a phase description, in which the coupling term depends on the phases themselves rather than only on their differences, has been performed by Golomb et al. (1992). They used the form

$$\frac{\mathrm{d}\Phi_i}{\mathrm{d}t} = \omega + f(\Phi_i) - \frac{1}{N}\sum_{j=1}^{N} g(\Phi_j) \quad (i = 1, \ldots, N) \ . \tag{69}$$

Such a phase description can be valid in a wider regime since the assumptions made about the system are less strong. In this configuration it has also been found that for higher harmonics in the periodic interaction functions f and g, the system is often divided up into subpopulations of synchronous activity. The phase distributions for these clusters widen if stochastic noise is introduced, but the asynchronous state becomes stable only above a certain noise threshold.

This agrees well with a study by Golomb and Rinzel (1994), who investigated a large network of conductance-based model neurons that had been introduced by Wang and Rinzel (1992). The interaction is all-to-all and of inhibitory type. For a two-unit system it has been observed that slow and strong synapses favor synchrony, whereas out-of-phase states have been reported with other parameters ranges. In the large network there exist a variety of behaviors, enabling the system to overcome its frustration. Clustered states as well as partially clustered states have been observed beside fixed points of the dynamics. In numerical simulations the system converges mainly to the synchronous or two-cluster state, which is gradually destroyed with increasing noise as neurons start to miss a cycle or drop out of the collective oscillation. For high noise levels a stationary distribution is reached for all parameter regimes.

In this section we have seen that it cannot generally be inferred that out-of-phase solutions in a small network indicate complete asynchrony in a large network. Clustering is a very widely observed phenomenon in models of larger neuron networks. Higher levels of noise tend to break up the system into smaller and smaller clusters, transcending into complete asynchrony. It has been speculated that the seemingly arbitrary grouping of oscillators in different clusters may be related to the patterns of the external input. Thus, recognition and amplification of such external patterns might be possible, which could also provide a mechanism for binding and segregation within the assembly concept.

New issues are raised when inhomogeneous networks are considered. Indeed, cortical connectivity is far from being random or all-to-all. A prominent example is the asymmetric reciprocal coupling between areas on different levels of the hierarchy of the visual system. Lumer et al. (1997) constructed a network taking into account such anatomical data, in order to investigate the interaction between synchronous firing and the mean activity level. By jittering the action potentials of neurons, they found that even if the membrane time constants of individual units are rather long, a population can act with surprisingly high precision.

Another source of specific connectivity are manipulations of visual experience during development. Disrupting coherent stimulation of the two eyes by induced strabismus leads to a segregation of tangential fibers so that only those regions with similar ocular dominance are connected (Löwel and Singer 1992). As a consequence, only neurons that are activated by the same eye show synchronized activity (König et al. 1993). Indeed, when such animals are exposed to rivalrous stimulation, synchronization of neuronal activity of the primary visual cortex is a better predictor of induced eye movements (which presumably reflect the perception of the animal) than their activity level (Fries et al. 1997). This can be understood in a simulation of spiking units. Congruent input leads to a synchronous representation, which in turn protects the coactivated neurons from lateral inhibition (Lumer 1998). In contrast, conflicting stimuli are represented by asynchronous assemblies, which leads to rivalry and suppression at later processing stages.

Reviewing neuronal dynamics within neocortex, we have hardly touched upon the wealth of phenomena observed in hippocampus and cortico-thalamic interactions. Indeed, cortico-thalamic interactions have been investigated intensively for many years, and a large number of results are available (Steriade 1997, 1999). Neurons in thalamus and cortex display oscillatory activity over several different frequency ranges. Cortical neurons oscillating at fast and slow rhythms can entrain thalamic

neurons. Thalamic neurons partly show oscillatory activity of their own. These complicated phenomena can only be appreciated when the detailed anatomy of this system is taken into account (Destexhe et al. 1996). Furthermore, cortical synchronization may depend on subcortical modulatory influences, which are related to learning and plasticity (Munk et al. 1996; Herculano et al. 1999; Steriade 1999). In the CA3 region of the hippocampus the seemingly random connectivity has inspired work on associative neural networks. Viewed on a larger scale, however, this network is embedded in a highly structured circuit which is interacting with neocortical structures (Buzsaki 1996). As discussed above, inhibitory mechanisms play an important role for the synchronization of γ-activity (Buszaki and Chrobak 1995; Traub et al. 1996). Mechanisms to synchronize neuronal activity in other frequency ranges, and their complex interactions in the different parts of the hippocampus, are the focus of current work (Dragoi et al. 1999).

4 Conclusions and open issues

In spite of the impressive amount of work done, which could not possibly be fully covered within this review, it is clear that many questions in this rich field of study have not been settled and therefore remain open.

We have seen that the choice of the neuron model as well as the modeling of the interaction can have a profound impact on the dynamics of the network. In particular, by concentrating on the synchronization of neuronal activity it has been shown that small changes in parameters such as transmission delay and the form of synaptic interaction can lead to opposite results. Nevertheless, general trends do emerge. For example, fast-acting excitatory connections tend to synchronize, whereas, in the case of slow interactions, inhibitory connections have been shown to be synchronizing. As axonal propagation, synaptic transmission, and dendritic integration inflict signal transmission with finite delays, the latter effect might be of physiological significance. This leads to the question of whether inhibitory neurons really play a decisive role in synchronization, as has been stressed in many other recent studies. However, the inhibitory neurons are outnumbered four to one by the excitatory neurons in the cortex. Also, these inhibitory neurons come in a large variety of types with different morphological and physiological properties (Gupta et al. 2000). Not all of these seem to be suited to influencing cortical dynamics on a millisecond time scale. Thus, do we have to view the cortical neuronal network as a two-class society, where a special and presumably small set of neurons decisively dominates the temporal dynamics?

Linking the principal insights from studies of homogeneous networks with the complexities of known anatomy poses new and exciting problems. Neurons within a cortical column tend to have similar response properties. The connectivity within a column is dense and complex. This does not, however, justify the treatment of such a population of neurons as if it were behaving like a single unit. Indeed, depending on their origin afferent projections target different subpopulations and have characteristic laminar termination patterns. Given our improving knowledge of intracellular communication mechanisms (Stuart and Sakmann 1994; Larkum et al. 1999), different interactions of synchronous and not-synchronous inputs arriving at different parts of the dendritic tree are expected. A prominent example is the interaction of bottom-up input arriving in the granular layer, and top-down input prominently terminating in the uppermost layers of the grey matter (Cauller and Conners 1994; von Stein et al. 1999).

Other aspects have not even begun to be investigated. For example, in all models the detection of coincident input and the generation of spike timing were assumed to be one process. This, however, might turn out to be an unwarranted assumption. If coincidence detection relies on fast processes in the distal dendritic tree, and the spike timing is determined at the soma, they might be independent processes. Thus, as so often is the case, with each answer more questions turn up, and there is a field, at least as large as the one covered in this review, to be explored in future studies.

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