NONLINEAR COOPERATIVE DYNAMICS OF LIVING NEURONS

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There is a substantial body of experimental evidence that neurons often produce oscillations to achieve their functional goals. They thus behave as dynamical systems despite the fluctuations we observe due to environmental noise and imperfections in their construction. In observations of neural behavior these oscillations can appear "intrinsic" as in the rhythmical pulsing of Central Pattern Generators (CPGs) or the oscillations can arise in response to a stimulus as in the actions of projection neurons in olfactory operation or even in the dynamical response of cortex neurons. When assemblies of neurons perform oscillations, their collective behavior is determined in an essential way by both the nonlinear dynamics of the individuals in the assembly and by the architecture of the neural circuitry.

The neurons inside an assembly can synchronize, possibly with an evident time lag, to produce particular patterns which control the rhythmic muscular activity of an animal, as in CPG operation. The component neurons may compete with each other in a dynamical fashion to solve the problem of pattern recognition, as in the cortex. They may collectively produce rich spatiotemporal behavior in response to specific forms of stimulus from sensory systems.

This is a review of these phenomena which are discussed in language familiar in the description of nonlinear dynamical systems including synchronization and competition. We illustrate our ideas with data from experiment and model simulations for both individual neurons and assemblies of neurons.

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1. Introduction

What is the role of neural units for living systems? Assemblies of neurons in the simplest animals to the most complex are organized to solve problems relating to the functional behavior of an animal in an often unpredictable, certainly changing, and sometimes challenging environment. In the face of such variability they must robustly, reliably, and reproducibly differentiate among different odors and sounds, identify muscle actions to acquire and digest food, and in humans provide memory and more elusively that behavior we label as consciousness. These and other tasks are accomplished by (1) the production of rhythms or particular spatiotemporal patterns of oscillation to control the rhythmic behavior of animals, and (2) processing information received from the environment. Each of these actions require activity which is **dynamical**, evolves in time and/or space, and **nonlinear**, requires the rich structure of nonproportional response to driving forces, external or internal.

The experience which has accumulated in the study of nonlinear dynamics for the description and prediction of cooperative behavior in physical and engineering systems has proven to be extremely valuable for understanding the organization and functioning of neural systems. At many levels of nervous system organization we observe complex spatiotemporal behavior related to the anatomical structure and the functional goals of the system. A substantial body of experimental evidence indicates that neurons often produce oscillations to achieve their functional goals, and in this manner act as dynamical systems and display their time asymptotic behavior in two ways: (1) they often produce statistically stationary time dependent activity whose mathematical image is that of an attractor, periodic or strange, and (2) they produce stimulus-dependent transient dynamics which corresponds to trajectories in state space which are stable for a finite time.

"Attractor dynamics" is often found in the oscillations of small neural assemblies, such as Central Pattern Generators (CPGs), and this may also be found in some functions of the mammalian cortex. Transient behavior is observed in many sensory systems. Each of these styles of behavior are the result of synchronization and dynamical competition between different groups of living neurons. These phenomena and their varied manifestation at different levels of animal neural activity are the subject of this review.

Every activity of living animals is accomplished by particular neural assemblies. Rhythmic behavior such as swimming, running, breathing, and the like are controlled by small groups of neurons as members of a CPG. This class of neural assembly often utilizes as few as tens of neurons. Sensory systems range from a few thousand neurons in invertebrates to many millions in vertebrates. Yet another order of magnitude appear to be involved in mammalian learning and "intelligent" activity. How can all these imperfect, nonidentical components, many of which exhibit chaotic oscillations when isolated, work together in a noisy, often unreliable environment? How do neurons produce specific stimulus-dependent or rhythmic behavior in such settings? To address these questions we must turn to the basic mechanisms of cooperative behavior among the neurons which comprise neural circuits.

The brain is a highly organized system in which its constituent units, the neurons, are connected in different fashions and hierarchical levels. The neurons in each subsystem usually have different morphologies, different intrinsic properties and, as a consequence, different activity patterns. We will discuss several mechanisms involved in the generation of rhythms and in the enterprise of information processing at three levels of the nervous system:

(i) in groups of small numbers of cells that control motor rhythms, the CPGs; (ii) in ensembles of moderate number of neurons that perceive and relay external stimuli in olfactory systems; and (iii) in very large arrays of neurons in the cerebellum.

2. Neural Oscillations

The membrane of neurons is a thin bilayer of lipids that isolates the extracellular medium from the intracellular medium. This barrier creates an electrochemical potential. Proteins inserted into the membrane form channels that control the inflow and outflow of ions. There are several active ion channels whose degree of permeability depends on the value of membrane electrical potential and on the concentration of particular ionic species such as calcium. The membrane potential of the neurons also changes as a function of the stimuli through the intrinsic biophysical properties of its passive and active ion channels.

The typical output of a neuron is an action potential or spike. This is a rapid change of membrane potential lasting about 1 ms. This high frequency electrical activity propagates along the body of the neuron and travels along axons to other neurons where it causes release of neurotransmitters that bind to the neuroreceptors of the receiving neuron in a chemical synapse. This causes a change in the local membrane potential of the receptor neuron, which in turn may develop its own action potentials and participate in the cooperative active of the connected neural assembly. In some cases the membrane voltage activity of a neuron can influence its neighbors by direct electrical connections or gap junctions of their membranes.

Several stimuli can arrive at the same time, and all of them are processed through the biophysical mechanisms of the membrane. When they are strong enough, another action potential is generated. The neuron's spiking activity can be sustained in time either in conjunction with the continued reception of the stimuli or, when the environment is appropriate, in its absence. Action potentials can be observed as isolated events, in repetitive firing activity with different frequencies and adaptation periods and on top of slow depolarizing waves of membrane potential called bursting activity. We display examples of such activity from our laboratory in Fig. 1. These time series come from intracellular recordings of the membrane potential
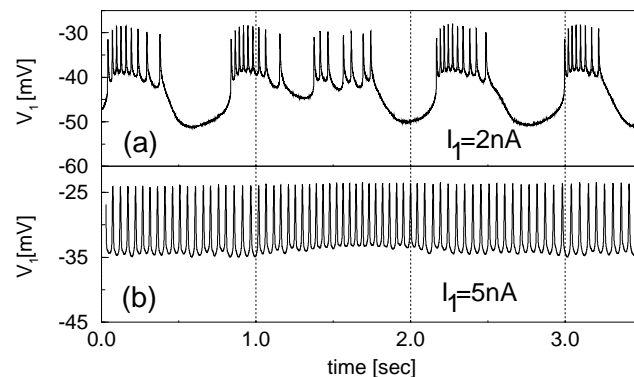

Fig. 1. Two different regimes of oscillations in a stomatogastric neuron obtained by applying two different injection currents. Top: bursting behavior. Bottom: spiking behavior [Elson *et al.*, 1998].

of one of a pair of strongly electrically coupled PD or pyloric dilator neurons, from the pyloric CPG of the California spiny lobster, *Panulirus interruptus* [Elson *et al.*, 1998a]. One of the PD neurons is deactivated by injection of a strong negative current. The other neuron is injected with a small positive external DC current I_1. This allows us to alter the behavior from chaotic bursting/spiking, Fig. 1(a), to nearly periodic spiking, Fig. 1(b), as well as to all intermediate oscillations.

This kind of spiking-bursting activity has been extensively modeled over the years. The membrane can be described as a set of isopotential compartments whose mathematical embodiment is obtained from the equivalent electric circuit of the portion of the membrane that they represent. We show this in Fig. 2. In these models the active channels are controlled by conductance variables described by the Hodgkin–Huxley [Hodgkin & Huxley, 1952] formalism. The detailed voltage dependence of the ingredients of these models can be obtained from experimental recordings in real neurons. Highly detailed models can be used to study the role of subcellular processes in generating the different firing patterns of individual cells and circuit activity. For large circuits, simplified integrate-and-fire dynamical models, substantially reduced from the details of the Hodgkin–Huxley descriptions can be used [Koch & Segev, 1998].

The typical spiking-bursting behavior of a model LP neuron from the pyloric CPG is shown in Fig. 7 in Sec. 3.2. This model is used to study the role of the slow calcium dynamics in the genesis of the chaotic behavior and in the regularization mechanisms of the stomatogastric CPG neurons. This study requires the highly detailed model
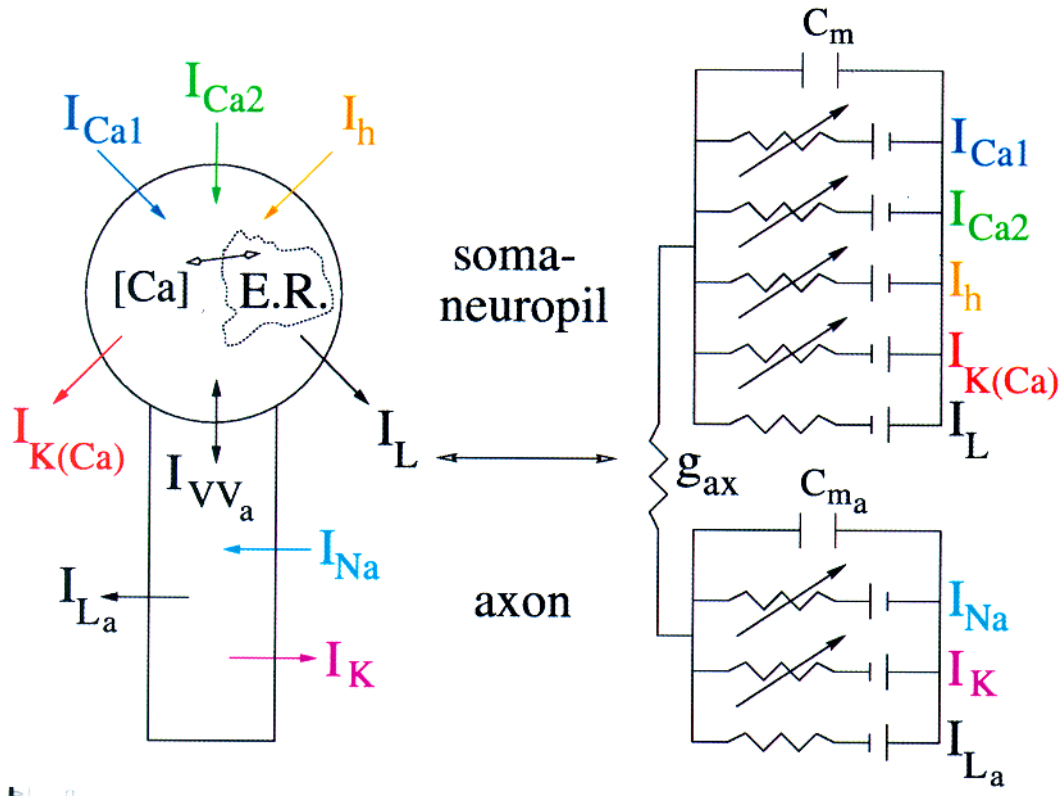
Fig. 2. A compartmental model of a stomatogastric neuron that includes a detailed characterization of the $[Ca^{2+}]$ storage and diffusion in the endoplasmic reticulum of the neuron. Capacitors represent the membrane capacitance, resistors represent ionic conductances (active and passive) and batteries represent reversal potentials for the different ionic species [Falcke *et al.*, 2000].

depicted in Fig. 2, with a two compartment architecture where the six active ionic currents used are distributed in the two compartments (soma-neuropil and axon) depending on their slow/fast evolution. A detailed calcium dynamics for the soma compartment includes Ca^{2+} storage in the endoplasmic reticulum and Ca^{2+} diffusion through the luminal and through the cytoplasmic membrane.

The integration of modeling and experimental techniques is useful to test hypothesis and draw important conclusions in the interpretation of physiological data from neural systems.

3. Synchronization and Competition in Minimal Circuits

In early 70's it was shown that the highly repetitive patterns of rhythmic motor activity of invertebrates could be sustained without any sensory stimulus, without any external influence or without neural signals from "higher functions." If a CPG is removed from an animal's body and placed in a salt solution that keeps the cells alive, this CPG may still generate essentially normal motor-output patterns for as long as many hours. There are several basic "minimal circuits" of neurons that are known to generate characteristic oscillatory behaviors. There circuits are responsible for the fast onset of synchronous behavior, rhythmic activity and regularization of neural signals. For example, in central pattern generators, parallel inhibiting and electrical interconnections, and parallel inhibiting and exciting interconnections are encountered [Getting, 1989; Grillner *et al.*, 1991; Selverston *et al.*, 1997; Kristan, 1980]. Thus to understand the origin of the synchronization phenomena in neural ensembles we have to begin from the simplest circuits: two neurons coupled together.

We discuss now several experimental results from our laboratory as well as the outcome from modeling this kind of essentially autonomous oscillation in individual or small collections of neurons taken from lobster CPGs depicted in Fig. 3.
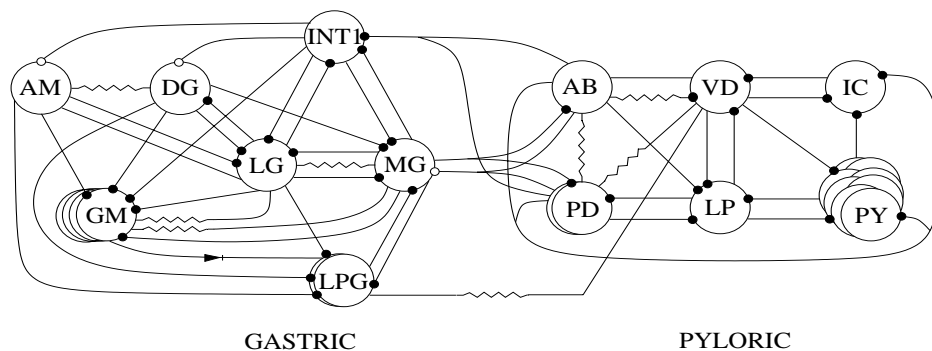
Fig. 3. Network organization in the pyloric and gastric CPGs in lobster. Types of neurons are indicated inside large circles [Selverston *et al.*, 1997]. Solid circles indicate inhibitory connections and open circles excitatory connections. Connection from GM to LPG is rectifying electrotonic.

3.1. *Experiments*

Experimental studies of synchronization in a pair of neurons that interact through naturally occurring electrical coupling have been reported in [Elson *et al.*, 1998a, 1998b]. Some of these experiments were carried out on two PD neurons from the pyloric CPG of the California spiny lobster. The strength of the natural electrical coupling can be altered during the observations of the preparation by use of a feedback device built for this purpose by N. F. Rulkov. The naturally occurring coupling characterized by a conductance of about 200 nS produces synchronization in the slow bursting oscillations, but the spikes are not synchronized by this coupling strength.

Individually, these neurons can generate highly irregular spiking-bursting activity [Fig. 1(a)]. Varying the control parameters injected DC current and interneuron conductance we found the following regimes of behavior [Elson *et al.*, 1998, 1999]:

Natural coupling produces state-dependent synchronization as shown in Fig. 4. With little or no applied current, the neurons fire spikes in irregular bursts in which the slow oscillations are well synchronized while the spikes are not; this is shown in Fig. 4(a). Changing the magnitude and sign of electrical coupling restructures the cooperative dynamics. Increasing the strength of coupling produces complete synchronization of both irregular slow oscillations and fast spikes. Compensating the natural coupling of about 200 nS leads to the onset of independent irregular pulsations as in Fig. 4(b). With net negative coupling, the neurons burst in antiphase, but now in a regularized pattern as in Fig. 4(c). When depolarized by positive DC

current, both neurons fire a continuous pattern of synchronized spikes as we show in Fig. 4(d). In this figure g_a is the externally controlled conductance level.

The dynamics of slow oscillations changed as the external coupling conductance g_a was altered. With natural coupling $g_a = 0$ nS the slow oscillations stayed synchronized as seen in Fig. 5(a) even though each neuron displays very complex dynamics as shown in Fig. 5(b) or Fig. 4(a). Additional dissipative coupling ($g_a < 0$ nS) led to desynchronization. The desynchronized slow oscillations remained complex and aperiodic as we see in Figs. 5(c) and 5(d); see also Fig. 4b.

Adding further negative coupling conductance which could represent an inhibitory synaptic connection caused the neurons to compete with each other and behave in an antiphase manner as seen in Fig. 5(e). This regime of antiphase behavior was characterized by the onset of more regular, "almost periodic" bursts as we see in Fig. 5(f).

We now consider the competition between neurons in more detail. Spatiotemporal patterns of neural activity can be generated by competition mechanisms among the cells. Competition means that several units are active at the same time and through inhibition between the component neurons, even with simultaneous excitation, their states alternate as in the antiphase bursting of our two PD neurons coupled electrically with negative coupling as shown in Fig. 5(e). The results from another experiment in our laboratory with two different neurons (LP and PD from the pyloric CPG with an inhibitory connection from PD to LP) show that the neurons burst in a nearly periodic alternating temporal pattern and their individual chaotic activity
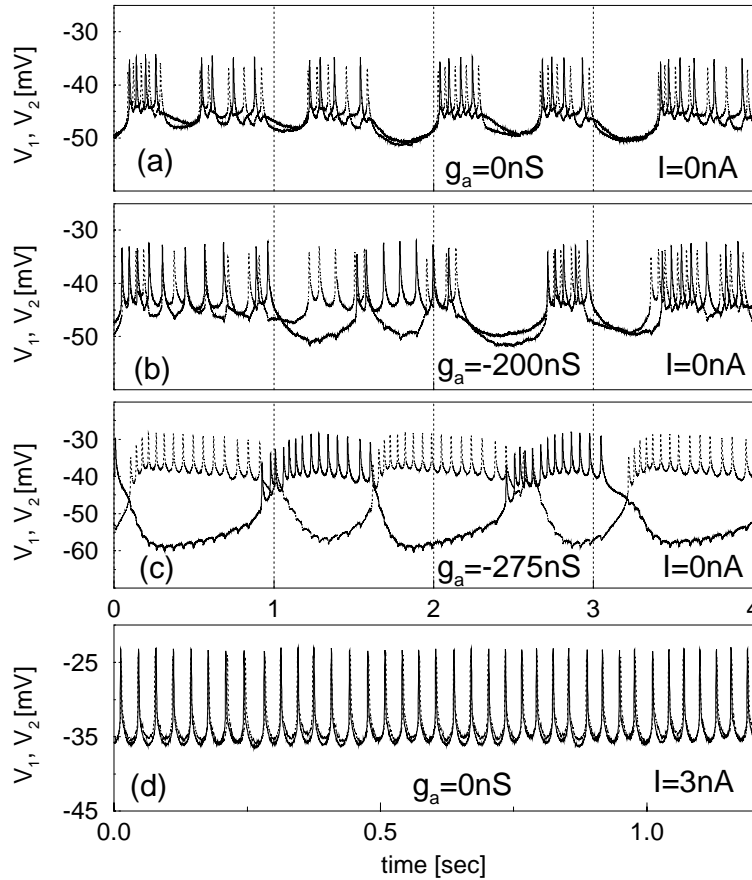
Fig. 4.   Regimes of oscillations in two coupled PD neurons from the stomatogastric ganglion of the California spiny lobster for different coupling conductances g_a. The first three rows show the bursting behavior of the two neurons with different levels of synchrony. The last row shows synchronous spiking behavior [Elson *et al.*, 1998, 1999].

is regularized [Elson *et al.*, 1998]. When the polarity of one of the mutual connections is changed to excitation, regularization of the bursting behavior is lost.

Inhibitory synaptic connections between neurons appear to have a distinctive, even critical role to play in neuron assemblies. This type of connection between nonlinear oscillators is not typically found in physical systems, and this lesson from biology in itself represents an important new direction for the dynamical systems study of collections of nonlinear oscillators.

3.2.   *Bifurcations and modeling*

The experiments we have just described indicate that the slow bursting oscillations and the fast spiking oscillations of these two neurons have different thresholds for the onset of synchronization. This can be understood in terms of the different spatial sites of origin of the two types of voltage signal, the different mechanisms of synchronization, and the different conduction pathways and attenuation factors involved. The slow voltage oscillations that underlie bursting activity arise as a result of voltage-dependent ion channel activity in the membrane of neuropilar processes. The summed voltage signal will suffer some attenuation as it spreads by local current flow in the leaky cable array of the neuropil. However, two factors favor its effective transmission between the neurons: (a) the location of electrical coupling sites close to the site of slow wave generation, and (b) the slow time course of the voltage signal itself. In combination, these should allow a relatively strong and continuous interaction between the irregular slow oscillators. This mechanism resembles the synchronization seen in dissipatively coupled chaotic electrical circuits [Afraimovich *et al.*, 1986; Heagy *et al.*, 1994]. In contrast, fast spike signals suffer strong attenuation as they spread between the spike initiation zone at the origin of the axon and
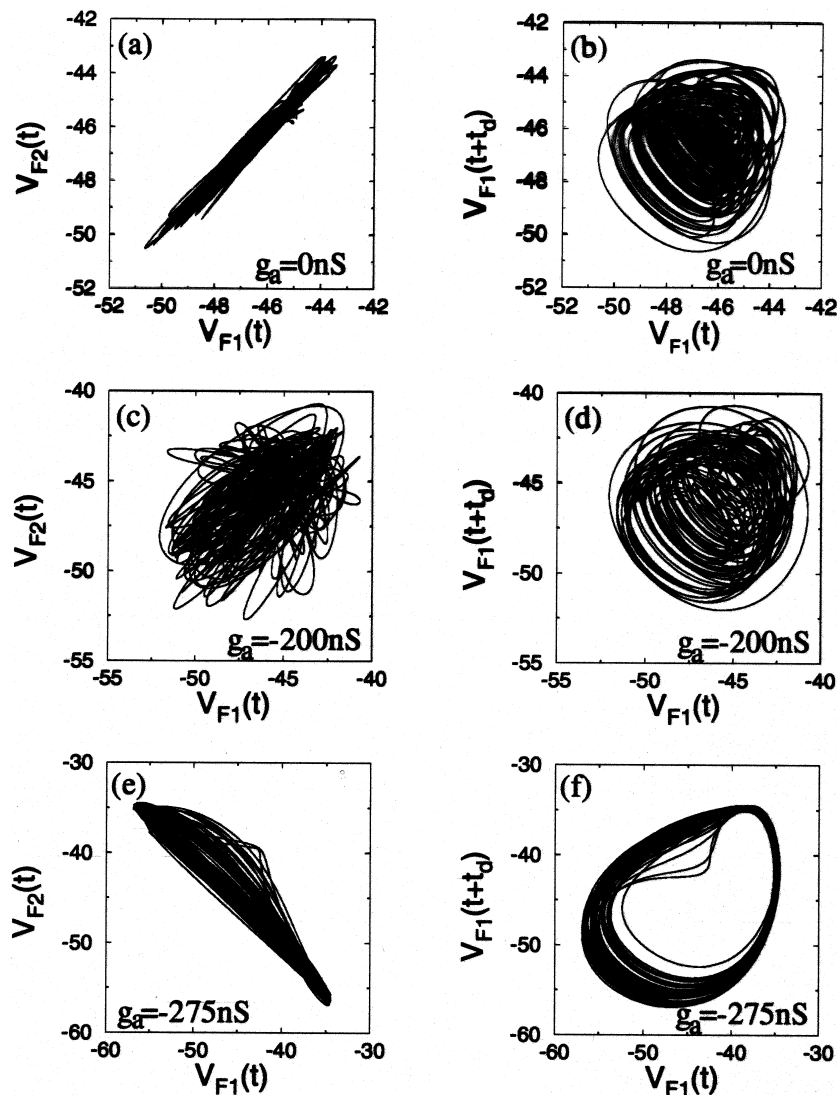
Fig. 5. Phase portraits of the slow components of oscillations in two coupled PD neurons as a function of the external conductance. The coordinates are the filtered membrane potentials of the two neurons [Elson *et al.*, 1998] $(V_{F1}(t), V_{F2}(t))$ in the left column. In the right column we display $(V_{F1}(t), V_{F1}(t + t_d))$, with $t_d = 0.3$ sec. There is no externally injected DC current here.

the coupling sites in the neuropil. These factors argue for weak current flow between spike generators. If the spike generator of a neuron is close enough to its threshold, the transient current from the coupling pathway may drive it to phase-locked firing. In electrical circuits, this type of chaotic pulse synchronization is known as threshold synchronization [Rulkov & Volkovskii, 1993]. With natural coupling, these threshold mechanisms can synchronize spike activity in tonic firing but not in the bursting regime. When the neurons generate slow voltage oscillations, ion channels open in neuropilar processes, decreasing the membrane resistance. This shunts the spike-evoked currents as they flow in their cou-

pling pathway, causing a failure in threshold synchronization.

As the strength of net coupling is decreased, the slow oscillations remain irregular with little change in waveform, but make a sharp transition from synchronous to asynchronous behavior (see Fig. 5). When the net coupling reaches an expected, negative conductance, the slow oscillations resynchronize in antiphase and become regular. These bifurcations argue for a dynamical origin of the irregular neuronal activity.

Based on these observations we have built a two compartment model of neurons from stomatogastric ganglion. The model incorporates six active ionic
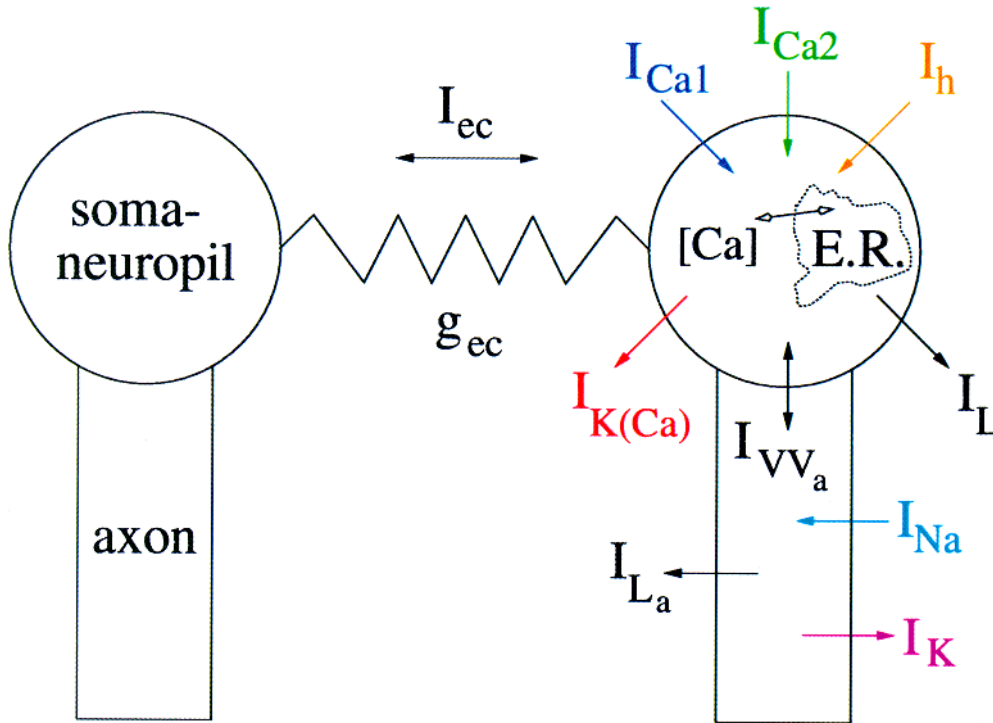
Fig. 6. Two stomatogastric model neurons that include a detailed characterization of the $[Ca^{2+}]$ storage and diffusion in the endoplasmic reticulum of each neuron. Each model neuron has two compartments: one represents the soma-neuropil activity, and the other represents the axon including the spike generating zone of the neuron. Except for the critical addition of the Ca^{2+} dynamics, this is a simple extension of many Hodgkin–Huxley models of this class of neuron. If this calcium dynamics is absent or the concentration $[Ca^{2+}]$ is fixed at some value, the model neuron does not exhibit chaotic oscillations, and it equally does not reproduce the behavior of these neurons [Rabinovich *et al.*, 1999a].

currents distributed in each of the soma-neuropil and the axon. It also accounts for **slow, intracellular Ca^{++} dynamics**. Two such model neurons, when electrically coupled, reproduce all five types of behavior found in our experiments and the transitions between the regimes are consistent with the observations [Varona, 1999].

The schematic description of our model of PD neurons from the lobster pyloric CPG is shown in Fig. 6. We coupled two of these model neurons with an electrical, so-called gap junction coupling, to study how well our model neurons reproduce the results of experiments in our laboratory [Elson *et al.*, 1998, 1999].

When the two model neurons are coupled with null or small coupling conductance, $g_{ec} \approx 0.001$ μS, independent chaotic behavior is observed. In [Felcke *et al.*, 2000] we present a detailed characterization of the chaos in the single neuron model as well as a detailed comparison of the model behavior with our experiments. Membrane potential bursts range from half a second to two seconds without periodicity as we can see in Fig. 7(a). The num-

ber of spikes on the top of the slow bursting waves also changes from burst to burst. Note that local maxima of cytoplasmic calcium concentration ($[Ca^{2+}]$) mark the end of the burst plateaus. Calcium concentration inside the endoplasmic reticulum ($[Ca^{2+}]_{ER}$) evolves slowly, thus modulating in an anti-phase manner the faster oscillations of cytoplasmic $[Ca^{2+}]$ and influencing the length of the voltage plateaus. We will discuss the evolution of these three variables for different coupling strengths g_{ec}.

For all three cases discussed so far, small, medium and high positive coupling conductance, the bursting activity remains irregular regardless of the degree of synchronization. Thus, synchronization occurs without regularization. When the two neurons are coupled with a small negative conductance $g_{ec} = -0.001$ μS, thus inverting the sign of the current coming from the electrical coupling in both neurons, anti-phase synchronization is observed in the membrane potentials as seen in Fig. 7(d). Furthermore, the two neurons regulate their bursting behavior in the sense that the lengths of the burst
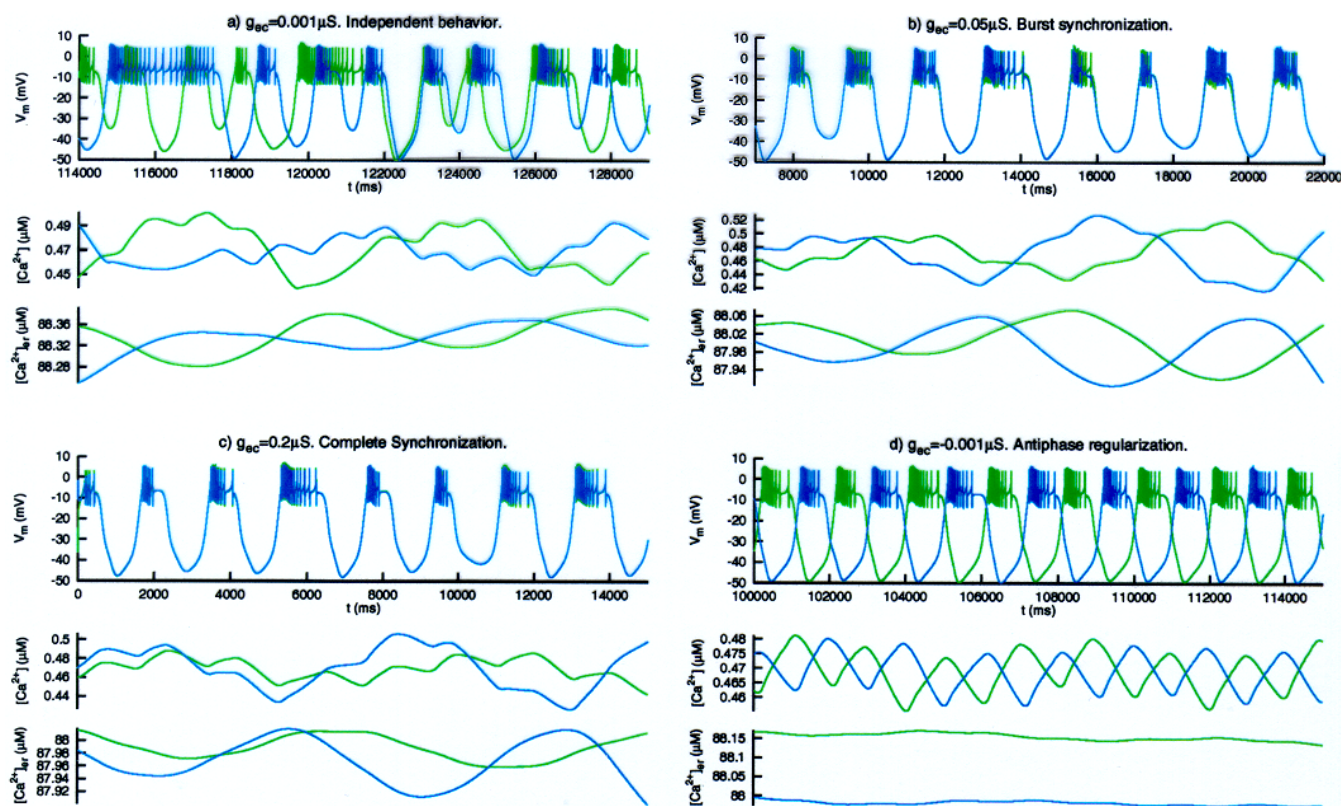
Fig. 7. Four different collective behaviors observed when two PD model neurons are coupled electrically as in Fig. 2 of [Elson *et al.*, 1998]: (a) independent chaotic bursting activity arising when $g_{ec} = 0.001$ μS, (b) burst synchronization associated with $g_{ec} = 0.05$ μS, (c) total synchronization which appears when $g_{ec} = 0.2$ μS, and (d) anti-phase synchronization with regularization which comes when $g_{ec} = -0.001$ μS. Activity for neuron one is plotted with a dark trace, while neuron two is represented with a light trace. In each of the graphs we display, from top to bottom: membrane potential V_m, cytoplasmic calcium concentration $[Ca^{2+}]$, and calcium concentration inside the endoplasmic reticulum $[Ca^{2+}]_{ER}$. This model describes six active ionic currents distributed in two compartments (soma-neuropil and axon) depending on their slow/fast evolution. A detailed calcium dynamics for the soma compartment includes Ca^{2+} storage in the endoplasmic reticulum and Ca^{2+} diffusion through the luminal and through the cytoplasmic membrane.

are kept uniform. Note in Fig. 7(d) that $[Ca^{2+}]_{ER}$ remains nearly constant for the two neurons, while $[Ca^{2+}]$ oscillates regularly but in anti-phase with respect to the other neuron. In the previous cases $[Ca^{2+}]_{ER}$ oscillated slowly with a large amplitude. In our model, chaotic behavior is sustained in the single neuron model whenever $[Ca^{2+}]_{ER}$ oscillations are present. If $[Ca^{2+}]_{ER}$ is kept constant, the model produces regular bursting activity. For a small negative electrical coupling, the calcium dynamics in the ER of each neuron is maintained constant, since the fast oscillations of calcium in the cytoplasm are rapid enough and regular enough to have no influence on the slower calcium diffusion through the endoplasmic reticulum membrane. Again, if the calcium concentration in the ER is kept constant, regularization of the chaotic behavior occurs. This behavior is also observed when the regularization is

obtained by periodic driving through small periodic pulses of current injection and when the two neurons are coupled with mutual inhibitory chemical synapses.

3.3. *Lessons from modeling small assemblies*

In this section we described both our work on individual neurons based on experiments using the pyloric CPG from the stomatogastric ganglion of the California spiny lobster and our modeling and experiments on small subcircuits of this CPG. We found that the **inhibitory** synaptic couplings appearing in the natural networks were essential for producing the regulation of the chaotic oscillations prevalent in the dynamics of the isolated neurons. Further we identified the need for an

additional slow dynamical process, beyond the traditional Hodgkin–Huxley ionic currents if we wish to account for the chaos observed in individual neurons. In our modeling we suggested that this additional slow dynamics is due to calcium exchange between the intracellular medium and the endoplasmic reticulum. This is now being tested in various laboratories, including our own, where we are trying to establish the qualitative presence of this kind of calcium dynamics.

Starting with the description of an individual neuron, we established further arguments for the kind of modeling we have performed by comparing the observations on two electrically coupled PD neurons from the pyloric CPG to our modeling of the same situation. In the experiment as well as in the model we established a clear quantitative comparison between the two. It is important to note that the experiments also included variations of an externally imposed conductivity so the range of dynamical behavior described in the model and seen in the experiments was quite broad: from synchronized spiking firing to out-of-phase oscillation to unsynchronized chaotic oscillations.

To this point then we have established a clear set of models whose biological ingredients are clear and testable and whose dynamical behavior we understand. Working with this knowledge we are now going to move on to explore the importance of inhibitory connections among neurons in a wider arena. We shall find, as indicated in our Introduction, that both the details of the neural dynamics of each component and the architecture associated especially with inhibitory connections in neural assemblies provides a suggestive basis on which we may understand complex and rich behavior of these assemblies, and further, the model behavior, at least in a qualitative sense reflects phenomena known from many observations on such assemblies.

4. Sensory Dependent Dynamics of Neural Ensembles

4.1. *Microcircuits with antagonistic coupling*

When one of our small circuits viewed as a dynamical system has more than one attractor for the same settings of its biological parameters, we have a situation of multistability. Which attractor "wins" depends on the initial conditions of the system, and

we can "reset" those initial conditions by applying stimuli of various characteristics. We discuss here the ability of oscillating neural circuits to switch between different states of oscillation in two basic examples. We model two quite distinct small neural circuits, which are presented in Fig. 8.

Figure 8 (left) shows a neural couple from the lobster stomatogastric ganglion (STG) (cf. LG–MG connection in Fig. 3) [Selverston & Moulins, 1987], and Fig. 8 (right) a typical vertebrate thalamocortical (RE–TC) circuit [Steriade *et al.*, 1993]. Although the functional role played by these circuits is very different, the presence of antagonistic couplings between different parts of the circuit makes them exhibit common dynamical features. The STG circuit is composed of two neurons coupled via both gap junction and inhibitory synapses. The second consists of coupled pairs of interconnected thalamocortical relay and thalamic networks passing sensory information to the cerebral cortex. Both circuits have contradictory coupling between symmetric parts. The thalamocortical model has excitatory and inhibitory connections and the STG model has reciprocal inhibitory and electrical coupling. We describe the dynamics of the individual neurons in these circuits by conductance based ordinary differential equations of Hodgkin–Huxley type. Both model circuits exhibit bistability and hysteresis in a wide region of coupling strengths. The two main modes of behavior are in-phase and out-of-phase oscillations of the symmetric parts of the network.

We investigated the response of these circuits to trains of excitatory spikes with varying interspike intervals T_i and with quite small amplitude pulses. These are a simple representation of spike trains received by the basic circuits from sensory neurons.

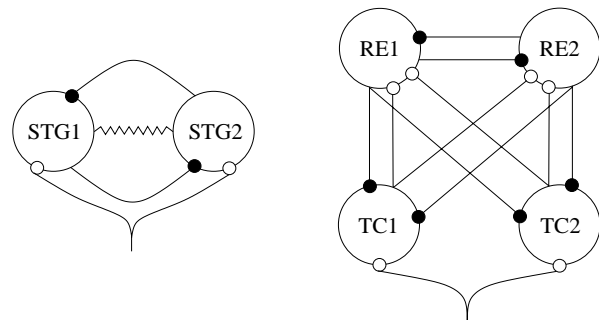Fig. 8.   Two basic neural microcircuits. Left, a STG circuit and right, a thalamocortial circuit. Solid circles indicate inhibitory connections and open circles excitatory connections. The resistor symbol in the STG circuit denotes a gap junction, an electrical connection between the two neurons.
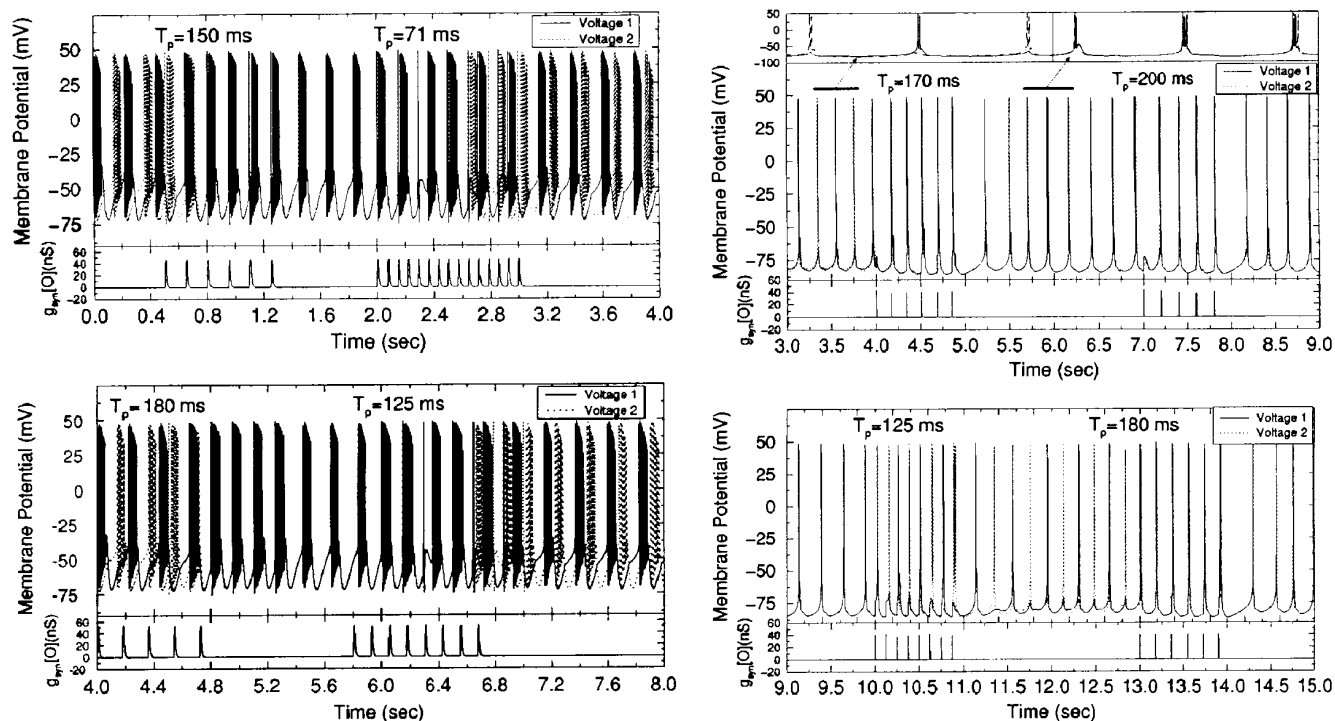
Fig. 9.   Left: time series showing the effect of $1s$ of the periodic external forcing in the CPG circuit at several values of T_p: 150, 71, 180 and 125 ms. Right: the effect of $1s$ of the periodic forcing in the RE–TC circuit at the same values of T_p as in the CPG circuit. There is an expanded time scale view of the membrane voltage in the RE–TC circuit above the upper panel [Rabinovich *et al.*, 1998a].

Circuits operating in a bistable region are sensitive to the T_i of these excitatory inputs. T_i variations lead to changes from in-phase to out-of-phase coordination or vice versa. The signaling information contained in a spike train driving the network can place the circuit into one or another state depending on the interspike interval. It is important to note that this happens within a few spikes, and then these states are maintained by the basic circuit after the input signal is completed, and the circuits remain in the reset state until a new spike train of another T_i is received. When a new signal of the correct T_i enters the circuit, the state can switch again. Our main results are presented in Fig. 9. See [Rabinovich *et al.*, 1998a] for further details.

Bistability occurs when there are two distinct solutions to the conductance based differential equations describing the circuit that coexist over a range of settings of the various parameters in the equations. In [Rabinovich *et al.*, 1998a] we explored a range of electrical couplings over which the STG circuit had two distinct solutions and we investigated a range of the strength of the inhibitory coupling over which the RE–TC cells act in the same fashion. In the state space of the systems we see

two distinct orbits or phase portraits for the two solution sets. These represent two distinct attractors for the dissipative neural dynamics. Whether, after an initial transient behavior, the circuit ends up on one attractor or another depends on the initial conditions for the solution of the differential equations. In state space each attractor has a set of initial conditions that bring the solution to it, and this collection of initial conditions is called its basin of attraction. Figure 10 shows the two attractors for the RE–TC system in the same state space. As one can see, the two attractors are quite close in this space, supporting the fact that transitions between them can be easily induced by the periodic spike trains we introduce.

Two potential uses may be made of the reset capability of bistable circuits. First, in lobster STG circuits it is known that neuromodulators can alter the character of neural oscillations in accordance with selected functional behavior [Selverston & Moulins, 1987]. The reset capability of sensory spike trains may also be used to achieve this goal. Second, this reset capability may be a way in which neurons interpret information coming from sensory sources and reformat it for use further along in the
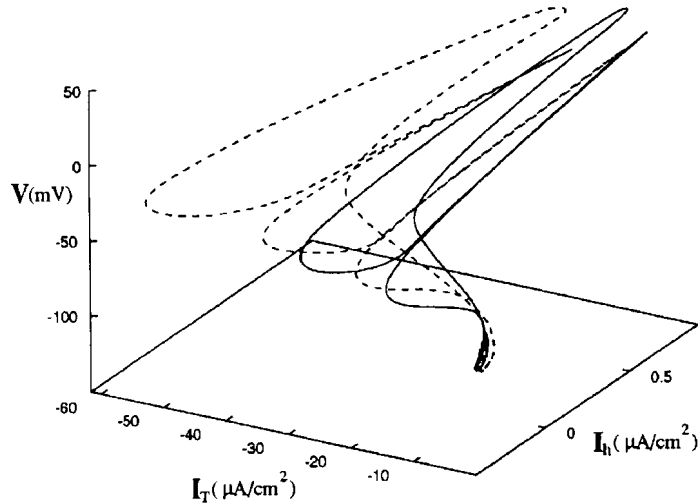
Fig. 10.   State space portrait of the two coexisting attractors for the RE–TC system. The solid line is the orbit in $[V(t), I_T(t), I_h(t)]$ space of the in-phase oscillations. The dotted line is the path taken in the same state space by the out-of-phase oscillations. The closeness of the two attractors leads to the ease with which spike trains with appropriate T_p can induce transitions between them.

animal's processing and decision system. If this "learning" function is correct, the mechanism could potentially be useful in short term memory where more complex circuitry would be reset for such a purpose.

The behavior of these two basic neural circuits are examples of what we call "calculation with attractors." In the phase space of a neural assembly the number of such attractors can be very large, and if their basins are widely enough separated such a system could function as an associative memory (see [Rolls & Treves, 1998] for a review and references). Recent experimental results show that "calculation with attractors" is not so typical for sensory systems. Let us discuss this problem in more detail using the olfactory system as an example.

4.2.   *Transient dynamics in olfactory systems*

Consider the first stages in odor processing of the olfactory systems, namely the actions of the olfactory bulb (OB) in vertebrates or antennal lobe (AL) in insects. The OB or the AL receives information about odors from the sensory neurons through special terminals or junction boxes called glomeruli, and then they reorganize the spatial information associated with the sensory spike trains in a spatiotemporal way and present it to the cortex in vertebrates or the mushroom body in insects; we depict this in Fig. 11. The OB or AL plays the role

of a "contraster" and "amplifier" of the sensory information. Both OB and AL consist of two types of neurons. The first are representative or projector neurons which send the information to the cortex. These are PN neurons in the AL and mitral and tufted cells in the OB. The other type is an interneuron (IN) which acts within the OB or AL itself. The PN are excitatory neurons, and the IN are inhibitory.

The complex inhibitory connections in OB or AL are extremely important for organizing the spatiotemporal representation of the sensory stimuli. In particular, this connection establishes complex antagonistic interactions between PN cells with the goal of forming an "odor opponency" mechanism, thus preventing certain odor conditions being reported simultaneously [Pearce, 1997]. In nonlinear dynamics language this "odor opponency" arises from competition between the PN cells. Such mechanisms could be similar to the "color opponency" mechanism found in color perception. In the visual system, ganglion cells may be excited by one particular frequency, yet inhibited by another [Mori & Shepherd, 1994].

Competition between groups of PN cells is important not only for the simple differentiation of distinct odors, but also for the representation of a single odor in a spatiotemporal fashion. As experiments [Laurent *et al.*, 1996] and modeling [Rabinovich *et al.*, 1998b, 1999b] have shown AL represents incoming sensory information to the
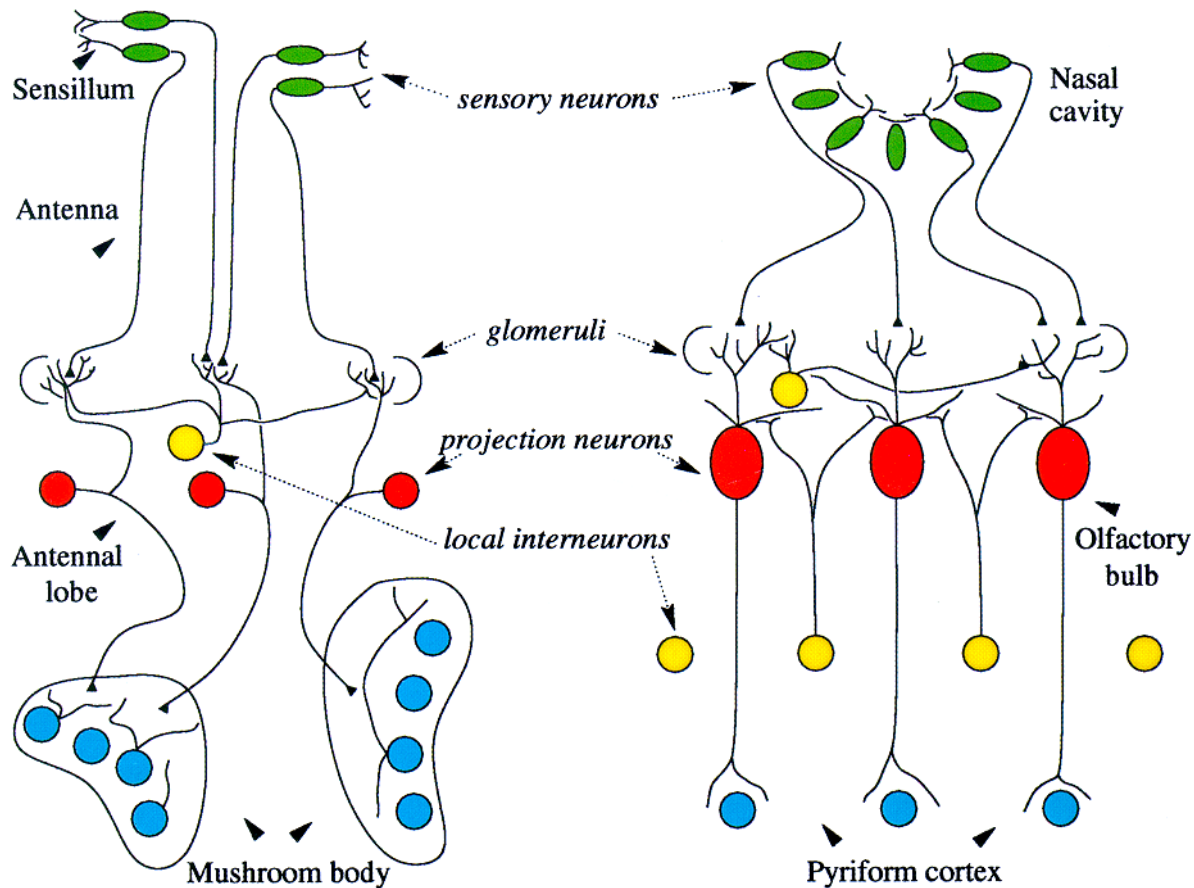
Fig. 11.   The principal neural circuits in the olfactory systems of insects (left) and vertebrates (right).

mushroom body using both spatial and temporal competition as well as temporal synchronization between PNs. Such odor-specific temporal behavior is enormously robust against noise and remarkably reproducible when the initial conditions of the circuit are different when the stimulus arrives. An example of the range of temporal patterns of response to a single odor across neurons is shown in Fig. 4.2. We hypothesize the inner inhibition of AL is responsible for the temporal encoding of the sensory information in a "winner-less competition" fashion [Rabinovich *et al.*, 1999b].

4.3. *Lessons from sensory dependent neural dynamics*

Simple models of basic neural circuits taken from widely different areas of use show substantially the same bistability in their behavior. Incoming spike trains can select one out of many possible attractors of such a system by varying their interspike intervals which effectively resets the circuit in the basin of attraction of one attractor or another. Short-

term "memory" can be accomplished by setting a circuit in some attractor and leaving it there as long as required to achieve some desired behavior.

Competition among neurons in an assembly through an architecture of inhibitory connections allows robust identification of incoming sensory signals as well as allowing them to be formatted for further processing by higher cortex functions. Reliable signal identification occurs for a very large range of initial conditions and appears quite robust against external as well as internal noise in the neural circuitry.

5. Synchronization of the Mean Field in Large Neural Assemblies

5.1. *"Coarse Grained" dynamics of chaotic neurons*

The emergence of spatiotemporal order or coherent structures in heterogeneous neural ensembles having individual elements with irregular behavior is one of the most intriguing problems in

PN G50047

PN G50120

PN G50156
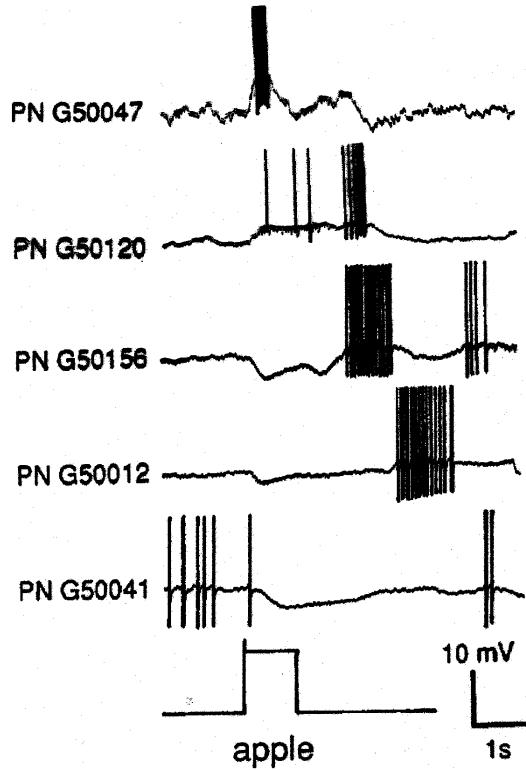
PN G50012

PN G50041

10 mV

apple   1s

Fig. 12.   Range of temporal patterns of response to a single odor across neurons. Temporal response patterns of five different antennal lobe PNs in response to the odor of apple. The recordings (all intracellular) were performed sequentially in the same animal over a 3.5 h period. Traces have been aligned on the odor pulse. From [Laurent *et al.*, 1996].

neuroscience. Over the last decade spiral patterns in the cortex of animals and humans have been observed [Prechtl *et al.*, 1997; Shevelev *et al.*, 1993]. We have investigated this phenomenon of "order creation" using a simple, well-tested model of a two-time-scale chaotic neuron.

We consider a lattice of N different chaotic neurons electrically coupled to their nearest neighbors. We select as the component element in the network the three-dimensional Hindmarsh–Rose (HR) [Hindmarsh & Rose, 1984; Wang, 1993; Huerta *et al.*, 1997] model neuron. We describe a two-dimensional lattice composed of such HR elements by the equations

$$\frac{dx_i}{dt} = y_i + ax_i^2 - x_i^3 - z_i + e_i - g\sum_j (x_i - x_j)$$

$$(1)$$

$$\frac{dy_i}{dt} = b - cx_i^2 - y_i \qquad (2)$$

$$\frac{1}{\mu}\frac{dz_i}{dt} = -z_i + s(x_i + d). \qquad (3)$$

The index i runs over $[0, N]$, and the index j runs over the four nearest neighbors of unit i. The constants a, b, c, d, s, e_i, and μ are model parameters in which $\mu \ll 1$ gives rise to slow bursting dynamics, and g is the homogeneous coupling strength among neighboring units. Numerical simulations of two-dimensional lattices built up with heterogeneous HR neurons show that cooperative behavior among the elements produces large-scale coherent structures with slow periodic oscillations, even though the circuit is built from different neurons which are individually chaotic. We show such a coherent pattern in Fig. 14. The parameter e_i is chosen from a random collection to make the individual components of the network behave differently.

In order to understand the origin of these large-scale coherent structures we investigated the cooperative behavior of a cluster of such chaotic neurons [Rabinovich *et al.*, 1999c]. We found a striking new phenomenon: when the size of this cluster is sufficiently large the average activity is regularized. In contrast, small groups of neurons clearly exhibit three different kinds of chaotic dynamics depending on the value of the diffusive coupling g: (i) well-developed chaos whose dimension increases with the number of chaotic neurons for a small value of the coupling, (ii) chaotic synchronization of the burst oscillation for moderate coupling, and (iii) complete chaotic synchronization of both spikes and bursts for strong coupling [Afraimovich *et al.*, 1986; Pecora & Carrol, 1990].

The dynamical mechanism leading to ordered average behavior of the cluster relies on synchronization and regularization of the activity of the neurons inside the grain. The degree of synchronization of a single neuron with the average activity of the whole cluster depends on the strength of the coupling, as one can see from the left panel of Fig. 13. In the case of regular behavior, when $g \approx 0.1$, single neuron activity is highly synchronized with the periodic mean field. For $g \approx 0.05$, the synchronization between mean field and individual behavior disappears, and one observes spatiotemporal disorder as is visible in the right panel of Fig. 13. Thus, for a moderate value of g the cluster of neurons behaves as a single element with periodic slow dynamics. This mechanism for the regularization of oscillations in disordered neural assemblies could be a quite general principle for many systems.
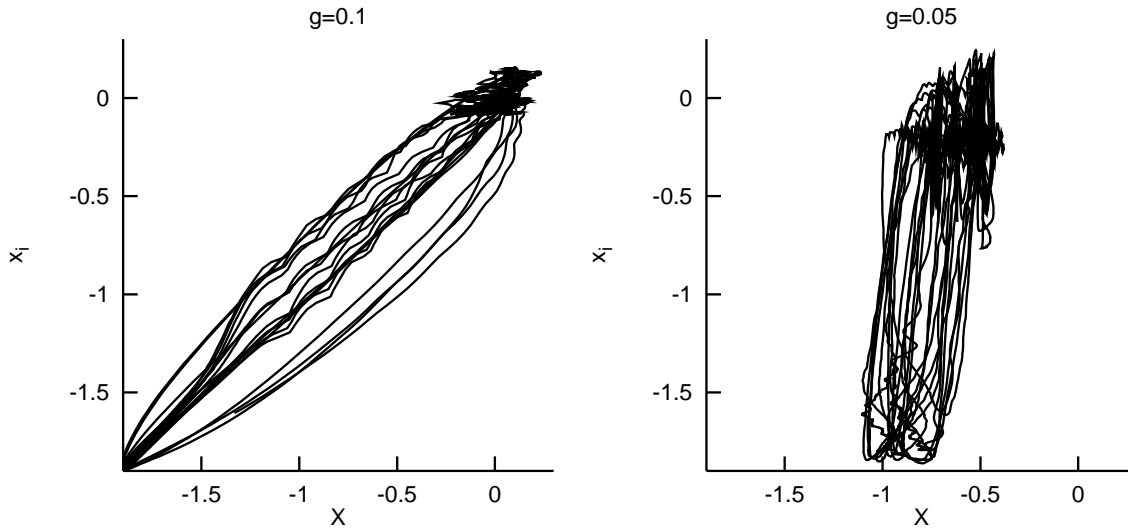
Fig. 13. Activity of a single HR unit x_i *versus* the average activity X ($X = 1/M \sum_{i=1}^{M} x_i(t)$, where M is the number of neurons in the cluster) for two values of the coupling g.
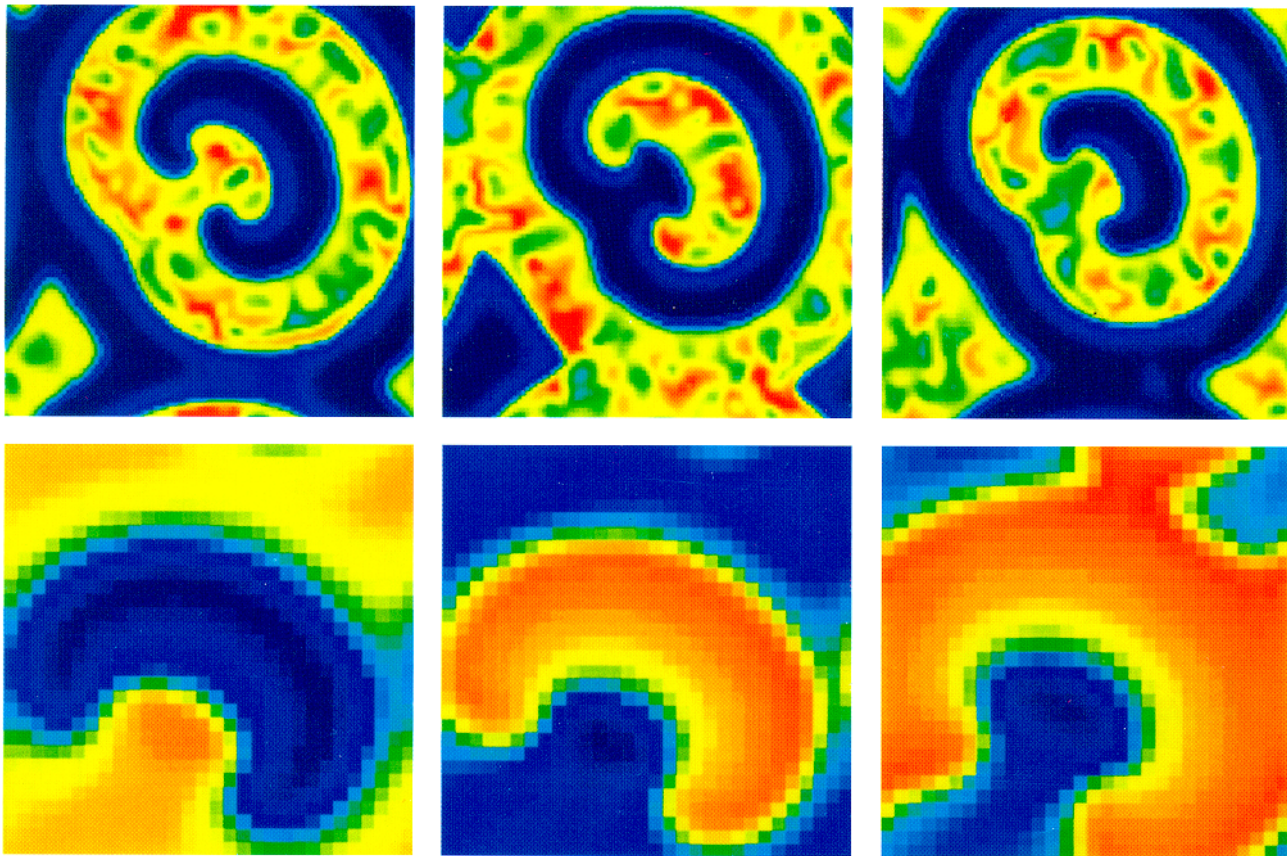

Fig. 14. Top row: Evolution of a periodic spatiotemporal pattern observed in a network of 100×100 Hindmarsh–Rose elements. Bottom row: Periodic spatiotemporal patterns observed in a network of 30×30 coarse grained elements.

5.2. *Regular spatiotemporal patterns in disordered neural assemblies*

Now we can explain the existence of regular spatiotemporal patterns in neural ensembles which extend over a very large number of individual component neurons. First, the existence of such large-scale structures is not possible in weakly diffusive ensembles because the local oscillations of

neighboring neurons are not correlated for small couplings g and the mean field of the assembly becomes homogeneous and stable. For moderate values of the coupling the coarse grain assembly should exhibit regular spatiotemporal patterns. As confirmation of this conjecture, we have checked the behavior of a network consisting of coarse grained units with slow periodic behavior. The results are shown in Fig. 14 [Rabinovich *et al.*, 1999c].

Thus, the formation of large-scale coherent structures in neural networks consisting of HR chaotic neurons with fast and slow oscillations exhibits two key features. The first is the regularization phenomena inside clusters of chaotic neurons, i.e. the coarse grains. This regularization of the behavior results from the action of the average activity of fast pulsations in the slow coarse grained dynamics. The second feature is the instability of the homogeneous oscillation modes in a neural network considered to be a collection of coarse grained elements.

6. Synchronization and Competition in the Activity of the Inferior Olive

We begin with a few words about the role of dynamical modeling for understanding neural activity. When we talk about different neural systems, modeling may have quite different goals. For example, it is clear what kind of job is required of the antennal lobe. It must contrast and amplify the information about the odor as presented to it by the sensory neurons, and then it must send this information to the mushroom body for further processing to accomplish recognition and storage. We do not presently have detailed anatomical knowledge about the architecture of the antennal lobe but we can still model this clear function, and we can establish several general ways to realize this function. The situation is not always so. For instance, the architecture of the inferior olive and the cerebellar circuits of mammals has been investigated anatomically and physiologically in great detail. However, the functional role of these complicated circuits is still unclear [Llinas *et al.*, 1997]. In contrast to the situation in olfactory processing, our challenge is to utilize this detailed knowledge and understand what such a system is able to do. Now we try to address this answer to this question.

The inferior olive (IO) has been proposed as a system that controls and coordinates different rhythms through the intrinsic oscillatory properties of the individual IO neurons and the modulated inhibition by another set of neurons in this system: the cerebellar nuclei [Llinas & Welsh, 1993]. We show this in Fig. 15. The inferior olive cells are electrically coupled and have strong oscillatory activity. Their axons transmit synchronous and rhythmic excitatory synaptic input to both the cerebellar nuclear cells and to the Purkinje cells of the cerebellar cortex. The phasic response of the Purkinje cells is transmitted as inhibitory inputs to the cerebellar nuclear cells. Thus the nuclear cells are excited by the inferior olive cells and later inhibited from the Purkinje cells. This inhibition leads to rebound excitation. The nuclear cells also send an inhibitory feedback to the inferior olive, thus closing this loop.

The IO neurons generate subthreshold oscillations and spiking activity as shown in Fig. 16. The time series shown in this figure come from the model IO neurons used in constructing a network of such cells connected with gap junctions among close neighbors. These networks incorporate a simple inhibitory feedback that implements the action of the cerebellar nuclei neurons. The model is realistic enough to generate subthreshold oscillations as well as spiking behavior in the amplitude and frequency ranges reported for the inferior olive neurons. Different oscillation frequencies can be obtained by applying a constant DC current to the model neurons. Network architectures were built up to 200×200 neurons connected electrically to their nearest neighbors and with an inhibitory feedback from the nuclei. These inhibitory connections are modeled without neither the detailed implementation of the other cell types involved in the inhibitory loop (Purkinje cells or cerebellar nuclei). A simple integrate and fire unit takes into account whether a group of neighbor IO neurons (typically three to nine) have a synchronous spiking event (in a time window of 5 ms) and it evokes a delayed IPSP in this small cluster of IO neurons. Then the integrate and fire neuron has a refractory period where it cannot fire for a short time. The real circuit and our simplification of the inhibitory loop are shown in Fig. 15. With this architecture, the network is able to generate spatiotemporal patterns as those shown in Fig. 6. Sequence goes first from left to right in line 1 and continues in line 2. Regions with the same color have synchronous behavior. Light colors mean depolarized potential. The spatiotemporal patterns consist of propagating wave fronts
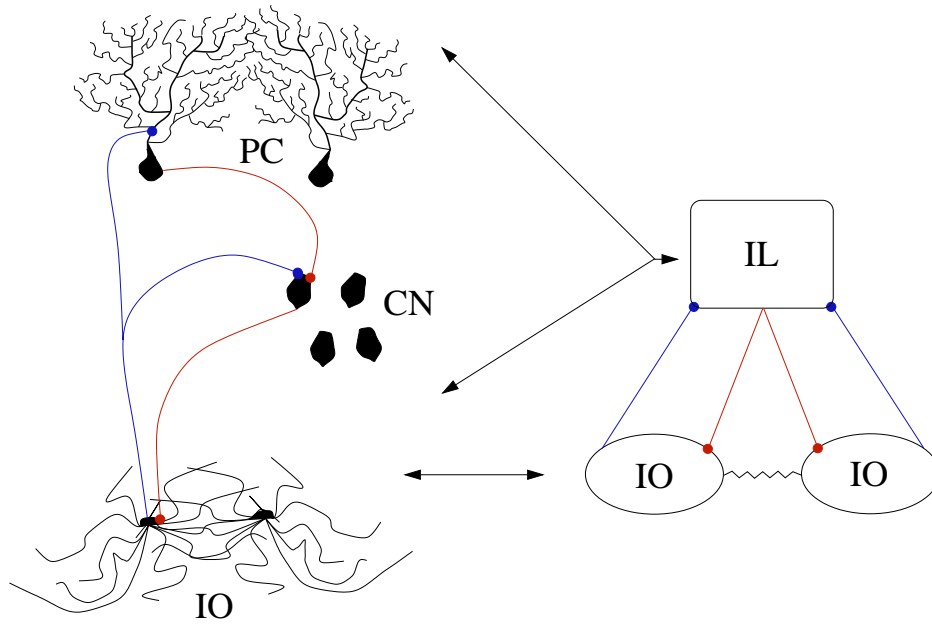
Fig. 15.   Left: Representation of the cerebellar inhibitory loop. IO: inferior olive neuron; CN: cerebellar nuclei; PC: Purkinje cell. Dark connections are excitatory, light ones are inhibitory. Right: schematic simplification of the inhibitory loop (IL) used in our model.
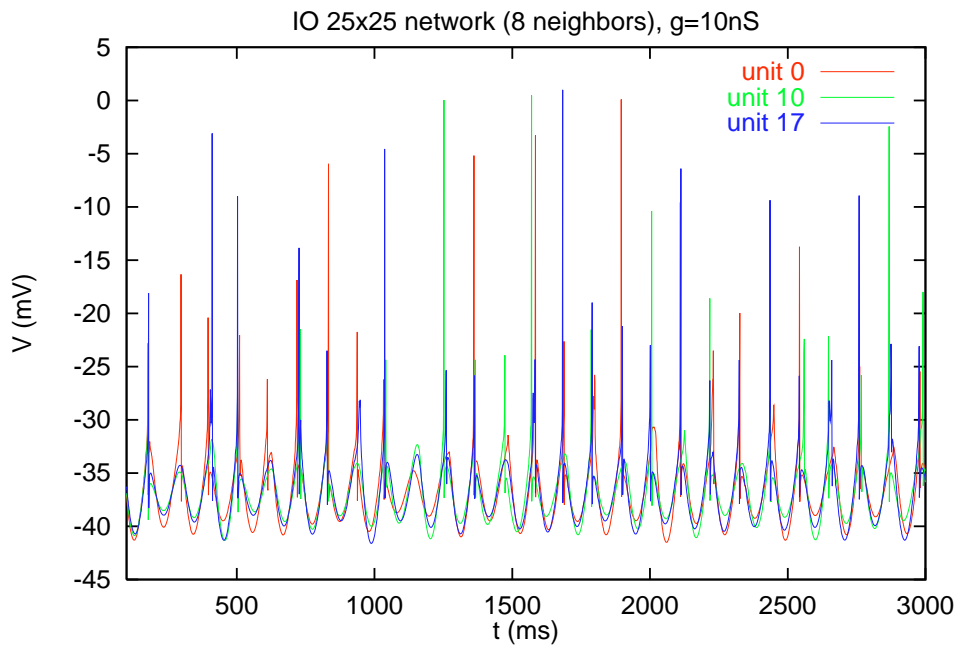

Fig. 16.   Time series of the subthreshold and spiking activity in a model of the inferior olive. The membrane potential of three different neuron members of an ensemble electrically coupled is shown. There is a high degree of synchronization caused by the gap junctions.

of spiking activity that can remain bounded in a region of the network.

We have investigated several ingredients that modulate the frequency of the spiking behavior in the network. Three major factors have been identified:

- The electrical coupling conductance; higher values of the coupling strength increase the synchronization level and diminish the frequency of the spiking behavior.
- The number of electrically coupled neighbors also decreases the frequency of the spiking behavior,
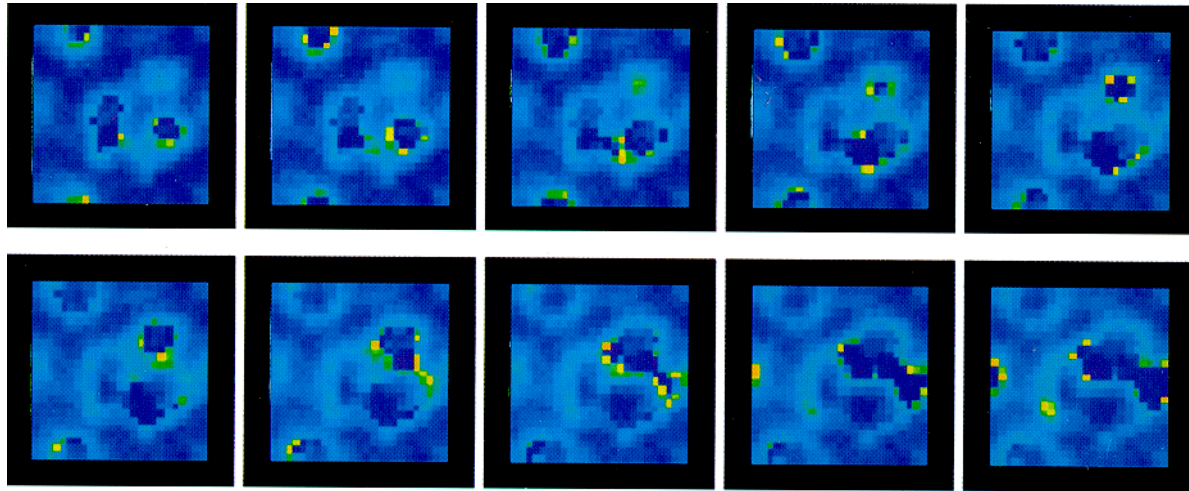
Fig. 17. Spatiotemporal patterns generated with a network of 30×30 inferior olive neurons electrically coupled to their nearest neighbors. Sequence goes from left to right and from top to bottom. Regions with the same color have synchronous behavior. Light colors mean depolarized potential.

but only for a strong enough coupling. In this case the degree of synchrony among cells is higher although the frequency of the subthreshold oscillations remains constant under all these changes.

- The presence of inhibitory chemical synapses coming from the cerebellar nuclei changes both the spiking frequency and the frequency of the subthreshold oscillations. For a given value of the coupling conductance and a fixed number of nearest neighbors, the inhibition usually decreases the frequency of the spiking activity. Some simulations show that the frequency can also increase depending on the time constant used to implement the inhibitory synapses.

We use this model to understand how the IO oscillations can encode and control several simultaneous rhythms. The intrinsic modulation of the input on the system activity, the importance of the coexistence of the synchronization induced by the electrical coupling, and the competition caused by the inhibitory loop have been identified out by the use of this model. Realistic models such as this can also explain the role of some of the subcellular processes and the particular neural physiology in the generation of observed rhythms.

7. Discussion

We have illustrated how neural circuits on different levels use synchronization and competition mechanisms for the production of rhythms and for in-

formation processing. Several important questions come to mind when we want to understand how general these mechanisms can be.

- What morphological and physiological characteristics of individual neurons and their interconnections are essential to perform a specific cooperative function?
- What is the significance for the generation of a rhythm or for information processing of the dynamical heterogeneity of neurons?
- Do different circuit architectures underlie different processing functions?

We briefly discuss these questions.

In the last few years many neuroscientists have agreed that "the traditional views of the significance of single neurons are fading in power" and "there are signs from experimental and theoretical work on the neocortex that we are on the threshold of a revolution in which the hegemony of the single neuron will be replaced by much more circuit-oriented concepts" [Douglas & Martin, 1991].

Do we agree with this viewpoint? Well, yes and no! "Yes", because in fact many experiments show that very often groups of neurons organized in microcircuits behave as a dynamical unit. However, neurons are individually complex, capacitive and nonlinear devices that transform streams of neurochemical packets into electrical waveforms. Their modes of operation are intrinsically time dependent, and, therefore, their functions or role in a circuit cannot be limited by their position in the circuit architecture. In particular, there are many examples

that suggest the importance of the details of individual neural dynamics: in stimulus representation the neural activity of learning and storage requires neurons with specific features such as subthreshold oscillations; coding of the time delay between several inputs, etc. However, in general, the microcircuit concept is very useful and powerful [Rolls & Treves, 1998].

Of course, all neurons are different, but as we showed above both the synchronization and competition phenomena are structurally stable. This observation implies that variation of individual neuron parameters inside the group that produces cooperative behavior can be large, yet the functional requirements of the assembly are well met as a result of the architecture. Real neural systems may achieve some of this stability as the result of some redundancy as well [Rabinovich & Abarbanel, 1999c].

Does a neural circuit have to possess a unique architecture to achieve a specific function? If so, strict rules are presently unknown. Circuits with different architectures are able to do the same job [Getting, 1989; Ullstrom *et al.*, 1998]. Conversely, circuits with fixed structure may play different roles when receiving different inputs. Even for the same input arriving at different times, the outcome may differ as the responses of neural circuits may be quite state dependent.

Our view of neural assemblies as input/output dynamical systems has led us to uncover some quite general principles of neural activity. In the examples presented in this paper, these include the essential role of inhibitory connections among individual, often complex, nonlinear neural oscillators. In our discussion much of the averaged or coarse grained behavior of an assembly occurs with a simplified model for the individuals when they are coupled with a global set of inhibitory connections. At the same time we see an essential and important role for the details of spiking/bursting neurons in achieving functional goals for these networks. The critical role of subthreshold oscillations in the inferior olive and in the olfactory processing as well as the importance of particular patterns of inhibitory coupling among these neurons join to produce accurate, robust and reliable functional networks.

Acknowledgments

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