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Neural dynamics in cortical networks — precision of joint-spiking events

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Abstract. Electrophysiological studies of cortical function on the basis of multiple single-neuron recordings reveal neuronal interactions which depend on stimulus context and behavioural events. These interactions exhibit dynamics on different time scales, with time constants down to the millisecond range. Mechanisms underlying such dynamic organization of the cortical network were investigated by experimental and theoretical approaches. We review some recent results from these studies, concentrating on the occurrence of precise joint-spiking events in cortical activity, both in physiological and in model neural networks. These findings suggest that a combinatorial neural code, based on rapid associations of groups of neurons co-ordinating their activity at the single spike level, is biologically feasible.

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Modern attempts to understand the mechanisms of higher brain function are increasingly concerned with neuronal dynamics. The task of organizing perception and behaviour in a meaningful interaction with the external world prompts the brain to recruit its resources in a properly orchestrated manner. Contributions from many elements, ranging from individual nerve cells to entire brain areas, need to be coordinated in space and time. Our principal research goal is to understand how this organization is dynamically brought about, and how the brain uses such coordinated activity in neurons. To this end, we studied the spatiotemporal organization of cortical activity recorded at many different sites at a time. The rules that govern this organization and the underlying mechanisms are brought to light by complementary approaches of neurobiological experimentation, advanced data analysis, and neural network modelling.

According to the classical view, firing rates play a central role in neuronal coding (Barlow 1972, 1992). The firing rate approach indeed led to fundamental insights into the neuronal mechanisms of brain function (e.g. Georgopoulos et al 1993, Hubel & Wiesel 1977, Newsome et al 1989). In parallel, however, a different concept was developed, according to which the temporal organization of spike discharges within functional groups of neurons, the so-called neuronal assemblies (Hebb 1949), also contribute to neural coding (von der Malsburg 1981, Abeles 1982a, 1991, Gerstein et al 1989, Palm 1990, Singer 1993). It was argued that the biophysics of synaptic integration favours coincident presynaptic events over asynchronous events (Abeles 1982b, Softky & Koch 1993). Accordingly, synchronized spikes are considered as a property of neuronal signals which can indeed be detected and propagated by other neurons (Perkel & Bullock 1968, Johannesma et al 1986). In addition, these spike correlations must be expected to be dynamic, reflecting varying affiliations of the neurons depending on the stimulus or behavioural context. Such dynamic modulations of spike correlation at various levels of precision have in fact been observed in different cortical areas, namely visual (Eckhorn et al 1988, Gray et al 1989; for reviews see Engel et al 1992, Aertsen & Arndt 1993, Singer & Gray 1995, Roelfsema et al 1996), auditory (Ahissar et al 1992, Eggermont 1994, de Charms & Merzenich 1995, Sakurai 1996), somato-sensory (Nicolelis et al 1995), motor (Murthy & Fetz 1992, Sanes & Donoghue 1993), and frontal (Aertsen et al 1991, Abeles et al 1993a,b, Vaadia et al 1995, Prut et al 1998). Little is known, however, about the functional role of the detailed temporal organization in such signals.

The first important hints about the importance of accurate spike patterns came from the work of Abeles and colleagues (Abeles et al 1993a,b, Prut et al 1998). They observed that multiple single-neuron recordings from the frontal cortex of awake behaving monkeys contained an abundance of precise spike patterns. These patterns had a total duration of up to several hundred milliseconds and repeated with a precision of ±1 ms. Moreover, these patterns occurred in systematic relation to sensory stimuli and behavioural events, indicating that these instances of precise spike timing play a functional role. Independent evidence for the possibility of precise spike timing in cortical neurons came from intracellular recordings *in vitro* (Mainen & Sejnowski 1995, Nowak et al 1997, Stevens & Zador 1998, Volgushev et al 1998) and *in vivo* (Azouz & Gray 1999).

We investigated the mechanisms underlying the dynamic organization of the cortical network by experimental and theoretical approaches. Here, we review evidence — both from experimental data and from model studies — that volleys of precisely synchronized spikes can propagate through the cortical network in a stable fashion, thereby serving as building blocks for spatiotemporal patterns of precisely timed spikes. Taken together, these findings support the hypothesis that precise synchronization of individual action potentials among groups of neurons presents an inherent mode of cortical network activity.

‘Unitary events’ in cortical multiple single-neuron activity

It has been proposed that cortical neurons organize dynamically into functional groups, so-called ‘cell-assemblies’ (Hebb 1949, Gerstein et al 1989). It is widely assumed that this functional organization is reflected in the temporal structure of the spike activity of the neurons involved. Thus, cortical activity would be characterized by synchronous spike volleys, travelling through the sparsely firing cortical network (‘synfire chain’ hypothesis; Abeles 1982a, 1991). To test this hypothesis, we analysed multiple single-neuron recordings from various cortical areas for the presence of excessive coincident spike events among the recorded neurons. We refer to such conspicuous coincidences as ‘unitary events’, and define them as those joint spike constellations that occur significantly more often than expected by chance (Grün et al 1994, Grün 1996). The functional significance of such unitary events was tested by investigating their occurrence and composition in relation to sensory stimuli and behavioural events.

‘Unitary event’ analysis

We developed a method that detects the presence of conspicuous spike coincidences and evaluates their statistical significance, taking into account the non-stationarities in the firing rates of the neurons involved (Grün 1996, Grün et al 2001a,b). Briefly, the detection algorithm works as follows: The simultaneous observation of spiking events from N neurons can be described mathematically by the joint process, composed of N parallel point processes. By appropriate binning, this can be transformed to an N-fold (0,1)-process, the statistics of which are described by the set of activity vectors reflecting the various (0,1)-constellations that occurred across the recorded neurons. Under the null-hypothesis of independently firing neurons, the expected number of occurrences of any activity vector and its probability distribution can be calculated analytically on the basis of the single neuron firing rates. The ‘mutual dependence’ measures the degree of deviation from independence among the neurons by comparing these theoretically derived probabilities with their empirical values. Those activity vectors that violate the null-hypothesis of independence define potentially interesting occurrences of joint events; their composition defines the set of neurons which are momentarily engaged in synchronous activity.

To test the significance of such unitary events, we developed a new statistical measure: the ‘joint-P-value’. For any particular spike activity vector, this joint-P-value measures the cumulative probability of observing the actual number of coincidences (or an even larger one) by chance. Finally, in order to account for non-stationarities in the discharge rates of the observed neurons, modulations in spike rates and coincidence rates are determined on the basis of short data segments by sliding a fixed time window (typically 100 ms wide) along the data in steps of the coincidence binwidth. This timing segmentation is applied to each trial, and the data of corresponding segments in all trials are then analysed as one quasi-stationary data set, using the appropriate rate approximation. (Further details and calibration of the unitary event analysis technique are described in Grün 1996, Grün et al 2001a,b; recent extensions of the approach are discussed in Grün et al 1999, Gütig et al 2001.)

'Unitary events' in motor cortex

In collaboration with Alexa Riehle (CNRS, Marseille, France) we tested the hypothesis that such precise synchronization of individual action potentials among groups of neurons in the monkey motor cortex is involved in dynamically organizing the cortical network during the planning and execution of voluntary movements (Riehle et al 1997).

We found that simultaneously recorded activities of neurons in monkey primary motor cortex indeed exhibited context-dependent, rapid changes in the patterns of coincident action potentials during performance of a delayed-pointing task. Accurate spike synchronization occurred in relation to external events (visual stimuli, hand movements), commonly accompanied by discharge rate modulations, however, without precise time-locking of the spikes to these external events. Accurate spike synchronization also occurred in relation to purely internal events (stimulus expectancy), where firing rate modulations were distinctly absent. These findings indicate that internally generated synchronization of individual spike discharges may subserve the cortical organization of cognitive motor processes. The clear correlation of spike coincidences with stimuli and behavioural events underlines their functional relevance (Riehle et al 1997; see also Fetz 1997).

Taken together, these findings demonstrate the existence of precise (±1–3 ms) synchronization of individual spike discharges among selected groups of neurons in the motor cortex. This synchronization is associated with distinct phases in the planning and execution of voluntary movements, indicating that it indeed plays a functional role. Moreover, these findings suggest that under behavioural conditions as investigated in this study, the brain uses different strategies in different contextual situations: in order to process a purely cognitive, i.e. an internal and behaviourally relevant event, neurons preferentially synchronize their spike occurrences without changing, at the same time, their firing rates. By contrast, when processing an external, behaviourally relevant event, neurons tend to synchronize their spikes and modulate their firing rates at the same time. Thus, precise synchronization of spike events and modulation of discharge rate may serve different and complementary functions. They act in conjunction at some times, and not others, depending on the behavioural context (Riehle et al 1997).

Conditions for stable propagation of synchronous spiking in cortical networks

In a complementary, model-oriented study we explored the mechanisms underlying these rapid synchronizations of cortical spiking activity. Specifically we focused on the explanation for the excessive occurrences of highly accurate (±1–3 ms) spike patterns (Abeles et al 1993a,b, Riehle et al 1997, Prut et al 1998), observed in frontal cortex and in motor cortex neurons of awake behaving monkeys.

Synfire chains and pulse packets

On the basis of the characteristic anatomy and physiology of the cortex, Abeles (1982a, 1991) proposed that 'synfire' activity, which propagates in volleys through the sparsely firing cortical neural network, presents a natural explanation for this phenomenon. We have investigated the conditions under which such synchronous volleys of action potentials can propagate reliably through the cortical network (Diesmann et al 1996, 1999, Aertsen et al 1996). Our theoretical approach combined analytical calculations and extensive simulations of single-neuron responses and network dynamics (Diesmann et al 1995, Gewaltig 1999).

Existing measures for the efficacy of synaptic transmission concentrate on two limiting cases: full synchrony and random arrival of spikes. Intermediate cases with a realistic degree of temporal dispersion are hardly addressed. To overcome these restrictions and to quantify the degree of temporal synchrony in propagating volleys of spike activity we introduced the concept of 'pulse packets' (Diesmann et al 1996). A pulse packet is a probabilistic description of the spiking activity of a group of neurons, represented by a pulse density function. This density function is characterized by two parameters: the 'activity', defining the number of spikes in the volley, and the 'width', defining their temporal dispersion. For a single realisation of a pulse packet, the activity is measured by counting the number of spikes in the volley, and its width is measured by the standard deviation of the spike distribution.

Neural transfer function and synchronization dynamics

Adopting this approach, we studied the response behaviour of a model cortical neuron to input activity with varying degrees of synchrony by presenting pulse packets with different choices of the 'activity' and 'width' parameters as stimuli.

From the model neuron we recorded the response (time of first spike), collected in a peri-stimulus time (PST) histogram over many trials. After normalization for the number of trials, the resulting output distribution was again described as a pulse packet, and the associated pulse density, along with the values of the activity and width were determined. The resulting neural transfer function, which describes the input–output relation between incoming and outgoing pulse packets, was visualized in an iterative map. This map yields a compact characterization of the neuron's response to transient input. In contrast to earlier approaches where the neuron's firing probability is measured quasi-statically as a function of DC current, this new transmission function takes full account of the dynamic properties of the input distribution (Aertsen et al 1996).

The temporal evolution of a pulse packet as it travels through the network can be traced by iterating the transfer function. Keeping the width of the chain fixed at a value in the order of 100, the dynamics of the two-dimensional iterated system is characterized by three fix points: two attractors and a saddle point. These fix points partition the state space in two domains, with stable propagation of the synchronous pulse packet in the first and extinction of the synchronous activity in the second. For increasing numbers of neurons per group, the fix points move further apart, increasing the basin of attraction, i.e. the range over which synchronous spiking can survive in the network. By contrast, for too few neurons per group, the fix points disappear, and all trajectories lead to extinction. Synchronous spiking then is no longer a viable option for the network. We found that under physiological conditions, pools of 100 neurons can easily sustain stable synchronous transmission through the network (Diesmann et al 1999).

This state space portrait describes the evolution of synchronous activity 'in the mean', i.e. by subsequent values of the expectation of the pulse packet parameters across trials with different background activity realizations. On the basis of network simulations we could confirm that the results of such analysis in the mean also hold for single-trial realizations (Gewaltig et al 2000, 2001). Around each point of a trajectory, these realizations form a distribution with a width determined by the pulse packet parameters, the group size and inter-group connectivity. This width becomes more important near the separatrix, due to the increased probability — even for trajectories which are stable in the mean — that individual realizations leave the basin of attraction (and vice versa). Thus, it is possible to assess the survival probability at each point in the state space, by computing which fraction of the trajectories crossing a small area around that point reaches the attractor. We found that there is a wide range of stimulus parameters for which the pulse packet is likely to evolve towards the attractor. If the pulse packet is moved away from the fix point, it is able to re-synchronize and to re-gain activity. Important aspects of these synchronization dynamics could be dissected and understood with the help of a continuous, probabilistic description of propagating synfire activity: the 'pulse-density model' (Gewaltig et al 1997, Gewaltig 1999).

Synchronization dynamics in recurrent networks

We also studied the spatiotemporal dynamics of spiking activity in cortical network models with recurrent synaptic architecture (Rotter & Aertsen 2000). The dynamics in such networks provide clues to the interplay that may result from the simultaneous activity of many pulse packets travelling through the cortical network.

Spatiotemporal patterns of precisely timed spikes

We used a network model, which is based on interacting stochastic point processes (Rotter 1994, 1996). Such systems can be formally described in terms of a Markov process, the dynamic state of which at a given point in time is the spatiotemporal pattern of previously generated spikes. The transition probabilities specify how the pattern gradually evolves in time. A generalized type of integrate-and-fire dynamics thereby emerges as a mathematical consequence of the assumption that neurons communicate by action potentials. Assuming the existence of infinitesimal spike probabilities, which is in fact a very mild condition for physical systems, the corresponding dynamic equations could be completely solved.

The solutions for special cases have been used to identify some important model parameters from electrophysiological recordings of real neurons. A simple parametric characterization of single neuron function is in fact achieved by fitting the model to the discharge behaviour of various types of cortical pyramidal cells. Some fundamental properties of recurrent cortex-like networks assembled from such neurons can be readily predicted, most notably their ability to maintain stable low rates of activity without the help of inhibitory neurons (Rotter & Aertsen 1997). Furthermore, computer simulations of random-topology, but otherwise realistic cortical networks indicate that high precision spatiotemporal patterns, embedded in periods of enhanced cooperative group activity, may play a role in coding and computation in such networks. This is true, even if neither the anatomy of the network nor the physiology of its neurons are in any sense specifically designed for that purpose.

Plasticity of precise time structure

Plasticity of the temporal structure of patterns of precisely timed spikes is achieved by introducing Hebb-like synaptic plasticity into the network. The phenomena observed in a number of experiments concerning the influence of local synaptic modification on the spatiotemporal dynamics in recurrent networks allow a number of conclusions (Rotter & Aertsen 1995, Rotter 1996). Learning rules can be formulated which only use local information, without the necessity for explicit renormalization of total synaptic transmission (cf. Song et al 2000, Rubin et al 2001). Evidence for temporally asymmetric plasticity, very much in line with such learning rules, has recently come from electrophysiological studies (Markram et al 1997, Bi & Poo 1998). Using such rules, rapid convergence of synaptic strengths can be achieved, while stable global activity is maintained. Convergence can be extremely fast, within a few presynaptic action potentials. The reason is that the pre-existing (random) patterns of activity are 're-used' or only slightly modified until the correlation structure of the stimulus input is matched. Learning affects only the microscopic time scale, i.e. there is plasticity of time structure in the millisecond range. In fact, the Hebbian time window defining temporal coherence is determined both by the dynamics of after-hyperpolarization in the post-synaptic neuron and by the low-pass properties of the synapse. Modification of a synapse can be enabled and disabled by controlling the rate of the presynaptic neuron. Thereby, a more global strategy of supervised learning is achieved by letting pools of dedicated instructor neurons control firing rates within the network, depending on some reward condition. The learning of input–output associations may take place in terms of a stochastic exploration of error gradients. Again, this amounts to a completely local processing of global information.

Conclusions and outlook

Assuming realistic values for the anatomical and physiological parameters, our model work predicts that the cortical network is able to sustain stable propagation of synchronous spike volleys consisting of spikes from groups of about 100 neurons, interconnected in feedforward fashion, with a temporal precision of about 1 ms. We are currently investigating to what extent the cortical architecture supports the existence of such structures, and how they are spatially embedded in the cortical network (Hehl et al 2001).

Evidence from recent computer simulations suggests that the observed synchronization dynamics are strongly influenced by the activity climate in the surrounding network. In particular, the robustness and propagation velocity of the synchronous spike volleys exhibit a non-monotonic dependence on the level (Diesmann et al 2000) and temporal structure (Mohns et al 1999) of the background activity. With increasing membrane potential fluctuations, the basin of attraction first increases and then decreases again (see also Boven & Aertsen 1990, Aertsen et al 1994), a phenomenon reminiscent of stochastic resonance (Collins et al 1996).

These results have interesting consequences in view of recent findings regarding the relation between ongoing network activity and the variability of evoked responses, both in cortical activity and in behavioural responses (Arieli et al 1996a,b, Azouz & Gray 1999).

Our findings on the synchronization dynamics in recurrent networks indicate that the degree of irregularity of neuronal spike trains is primarily a reflection of the network dynamics. Spatiotemporal patterns of precisely timed spikes are a consequence of these network dynamics. The introduction of Hebb-like synaptic learning rules (cf. Song et al 2000, Rubin et al 2001, Gütig et al 2001) induces a plasticity of the precise spike patterns. Possible scenarios for the functional relevance of such precisely timed spike patterns and their plasticity are the subject of current investigation.

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This report summarizes results from a number of ongoing collaborations, and extends an earlier review by two of the authors (Rotter & Aertsen 2000). Contributions by and stimulating discussions with Moshe Abeles, George Gerstein, Alexa Riehle and Eilon Vaadia are gratefully acknowledged. Partial funding was received from the Deutsche Forschungsgemeinschaft (DFG), the Human Frontier Science Program (HFSP) and the German-Israeli Foundation for Research and Development (GIF).

References

Abeles M 1982a Local cortical circuits. Springer-Verlag, Berlin

Abeles M 1982b The role of the cortical neuron: integrator or coincidence detector? Isr J Med Sci 18:83–92

Abeles M 1991 Corticonics. Cambridge University Press, Cambridge

Abeles M, Bergman H, Margalit E, Vaadia E 1993a Spatiotemporal firing patterns in the frontal cortex of behaving monkeys. J Neurophysiol 70:1629–1643

Abeles M, Prut Y, Bergman H, Vaadia E, Aertsen A 1993b Integration, synchronicity and periodicity. In: Aertsen A (ed) Brain theory: Spatio-temporal aspects of brain function. Elsevier Science Publishers, Amsterdam, p 149–181

Aertsen A, Arndt M 1993 Response synchronization in the visual cortex. Curr Opin Neurobiol 3:586–594

Aertsen A, Vaadia E, Abeles M et al 1991 Neural interactions in the frontal cortex of a behaving monkey: signs of dependence on stimulus context and behavioral state. J Hirnforsch 32: 735–743

Aertsen A, Erb M, Palm G 1994 Dynamics of functional coupling in the cerebral cortex: an attempt at a model-based interpretation. Physica D 75:103–128

Aertsen A, Diesmann M, Gewaltig MO 1996 Propagation of synchronous spiking activity in feedforward neural networks. J Physiol Paris 90:243–247

Ahissar M, Ahissar E, Bergman H, Vaadia E 1992, Encoding of sound-source location and movement: activity of single neurons and interactions between adjacent neurons in the monkey auditory cortex. J Neurophysiol 67:203–215

Arieli A, Sterkin A, Grinvald A, Aertsen A 1996a Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. Science 273:1868–1871

Arieli A, Donchin O, Aertsen A et al 1996b The impact of ongoing cortical activity on evoked potentials and behavioral responses in the awake behaving monkey. Soc Neurosci Abstr 22:2022

Azouz R, Gray CM 1999 Cellular mechanisms contributing to response variability of cortical neurons *in vivo*. J Neurosci 19:2209–2223

Barlow HB 1972 Single units and sensation: a neuron doctrine for perceptual psychology? Perception 1:371–394

Barlow HB 1992 Single cells versus neuronal assemblies. In: Aertsen A, Braitenberg VB (eds) Information processing in the cortex. Springer-Verlag, Berlin, p 169–174

Bi GQ, Poo MM 1998 Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. J Neurosci 18:10464–10472

Boven KH, Aertsen A 1990 Dynamics of activity in neuronal networks give rise to fast modulations of functional connectivity. In: Eckmiller R, Hartmann G, Hauske G (eds) Parallel processing in neural systems and computers. Elsevier Science Publishers, Amsterdam, p 53–56

Collins JJ, Chow CC, Capela AC, Imhoff TT 1996 Aperiodic stochastic resonance. Phys Rev E 54:5575–5584

de Charms RC, Merzenich MM 1995 Primary cortical representation by the coordination of action potential timing. Nature 381:610–613

Diesmann M, Gewaltig MO, Aertsen A 1995 SYNOD: An environment for neural systems simulations — language interface and tutorial. Technical Report GC-AA/95–3. The Weizmann Institute of Science, Rehovot, Israel (see also: http//www.synod.uni-freiburg.de)

Diesmann M, Gewaltig MO, Aertsen A 1996 Characterization of synfire activity by propagating “pulse packets”. In: Bower J (ed) Computational Neuroscience–Trends in Research 1995. Academic Press, San Diego, p 59–64

Diesmann M, Gewaltig MO, Aertsen A 1999 Stable propagation of synchronous spiking in cortical neural networks. Nature 402:529–533

Diesmann M, Gewaltig MO, Aertsen A 2000 Analysis of spike synchronization in feed-forward cortical neural networks. Soc Neurosci Abstr 26:2201

Eckhorn R, Bauer R, Jordan W et al 1988 Coherent oscillations: a mechanism of feature linking in the visual cortex? Multiple electrode and correlation analysis in the cat. Biol Cybern 60: 121–130

Eggermont JJ 1994 Neural interaction in cat primary auditory cortex II. Effects of sound stimulation. J Neurophysiol 71:246–270

Engel AK, König P, Kreiter AK, Schillen TB, Singer W 1992 Temporal coding in the visual cortex: new vistas on integration in the nervous system. Trends Neurosci 15: 218–226

Fetz EE 1997 Temporal coding in neural populations? Science 278:1901–1902

Georgopoulos AP, Taira M, Lukashin A 1993 Cognitive neurophysiology of the motor cortex. Science 260:47–52

Gerstein GL, Bedenbaugh P, Aertsen A 1989 Neuronal assemblies. IEEE (Inst Electr Electron Eng) Trans Biomed Eng 36:4–14

Gewaltig MO 1999 Evolution of synchronous spike volleys in cortical networks — Network simulations and continuous probabilistic methods. Shaker Verlag, Aachen

Gewaltig MO, Rotter S, Diesmann M, Aertsen A 1997 Cortical synfire activity — Stability in an analytical model. In: Elsner N, Wässle H (eds) From membrane to mind: proceedings of the 25th Göttingen neurobiology meeting 1997. Thieme Verlag, Stuttgart, p 620

Gewaltig MO, Diesmann M, Aertsen A 2000 Cortical synfire activity: Configuration space and survival probability. Neurocomputing, in press

Gewaltig MO, Diesmann M, Aertsen A 2001 Propagation of cortical synfire activity — survival probability in single trials and stability in the mean. Neural Netw, in press

Gray CM, König P, Engel AK, Singer W 1989 Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus patterns. Nature 338:334–337

Grün S 1996 Unitary joint-events in multiple neuron spiking activity — Detection, significance, and interpretation. Verlag Harri Deutsch, Frankfurt

Grün S, Aertsen A, Abeles M, Gerstein G, Palm G 1994 Behavior-related neuron group activity in the cortex. In: Proc 17th Ann Meeting Europ Neurosci Assoc. Oxford Univ Press, Oxford, p 11

Grün S, Diesmann M, Grammont F, Riehle A, Aertsen A 1999 Detecting unitary events without discretization of time. J Neurosci Meth 94:67–79

Grün S, Diesmann M, Aertsen A 2001a 'Unitary events' in multiple single-neuron spiking activity I: detection and significance. Neural Comput

Grün S, Diesmann M, Aertsen A 2001b 'Unitary events' in multiple single-neuron spiking activity II: non-stationary data. Neural Comput, in press

Gütig R, Rotter A, Aertsen A 2001 Statistical significance of coincident spikes: count-based versus rate-based statistics. Neural Comput, in press

Gütig R, Aharonov-Barki R, Rotter A, Aertsen A, Sompolinsky H 2001 Generalized synaptic updating in temporally asymmetric Hebbian learning. In: Göttingen Neurobiology Report 2001, Proc 28th Göttingen Neurobiology Conf, in press

Hebb D 1949 The organization of behavior. A neuropsychological theory. Wiley, New York

Hehl U, Hellwig B, Rotter S, Diesmann M, Aertsen 2001 Anatomical constraints on stable propagation of synchronous spiking in cortical networks. In: Göttingen Neurobiology Report 2001, Proc 28th Göttingen Neurobiology Conf, in press

Hubel DH, Wiesel TN 1977 Farrier lecture. Functional architecture of macaque monkey visual cortex. Proc R Soc Lond B Biol Sci 198:1–59

Johannesma P, Aertsen A, van den Boogaard H, Eggermont J, Epping W 1986 From synchrony to harmony: Ideas on the function of neural assemblies and on the interpretation of neural synchrony. In: Palm G, Aertsen A (eds) Brain Theory. Springer, Berlin, p 25–47

Mainen ZF, Sejnowski TJ 1995 Reliability of spike timing in neocortical neurons. Science 268:1503–1506

Markram H, Lübke J, Frotscher M, Sakmann B 1997 Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 275:213–215

Mohns M, Diesmann M, Grün S, Aertsen A 1999 Interaction of synchronous input activity and subthreshold oscillations of membrane potential. In: Elsner N, Eysel U (eds) From molecular neurobiology to clinical neuroscience. Thieme Verlag, Stuttgart, p 100

Murthy VN, Fetz EE 1992 Coherent 25- to 35-Hz oscillations in the sensorimotor cortex of awake behaving monkeys. Proc Natl Acad Sci USA 89:5670–5674

Newsome WT, Britten KH, Movshon JA 1989 Neuronal correlates of a perceptual decision. Nature 341:52–54

Nicolelis MA, Baccala LA, Lin RC, Chapin JK 1995 Sensorimotor encoding by synchronous neural ensemble activity at multiple levels of the somatosensory system. Science 268: 1353–1358

Nowak LG, Sanchez-Vives MV, McCormick DA 1997 Influence of low and high frequency inputs on spike timing in visual cortical neurons. Cereb Cortex 7:487–501

Palm G 1990 Cell assemblies as a guideline for brain research. Conc Neurosci 1:133–147

Perkel DH, Bullock TH 1968 Neural Coding. Neurosci Res Program Bull, Vol. 6, Nr. 3. MIT, Brookline, MA

Prut Y, Vaadia E, Bergman H, Haalman I, Slovin H, Abeles M 1998 Spatiotemporal structure of cortical activity: properties and behavioral relevance. J Neurophysiol 79:2857–2874

Riehle A, Grün S, Diesmann M, Aertsen A 1997 Spike synchronization and rate modulation differentially involved in motor cortical function. Science 278:1950–1953

Roelfsema PR, Engel AK, König P, Singer W 1996 The role of neuronal synchronization in response selection: A biologically plausible theory of structured representations in the visual cortex. J Cogn Neurosci 8:603–625

Rotter S 1994 Wechselwirkende stochastische Punktprozesse als Modell für neuronale Aktivität im Neocortex der Säugetiere. Harri Deutsch, Frankfurt

Rotter S 1996 Biophysical aspects of cortical networks. In: Torre V, Conti F (eds) Neurobiology: ionic channels, neurons, and the brain. Plenum Press, New York, p 355–369

Rotter S, Aertsen A 1995 Hebb's rule in networks of spiking neurons. In: Elsner N, Menzel R (eds) Learning and memory. Thieme Verlag, Stuttgart, p 69

Rotter S, Aertsen A 1997 Current balance and neuronal assemblies. In: Elsner N, Wässle H (eds) From membrane to mind: proceedings of the 25th Göttingen neurobiology meeting 1997. Thieme Verlag, Stuttgart, p 622

Rotter S, Aertsen A 2000 Cortical dynamics — Experiments and models. In: Lehnertz K, Arnhold J, Grassberger P, Elger CE (eds) Chaos in brain? World Scientific Publishing, Singapore, p 3–12

Rubin J, Lee D, Sompolinsky H 2001 Equilibrium properties of temporally asymmetric Hebbian plasticity. Phys Rev Lett 86:364–367

Sakurai Y 1996 Population coding by cell assemblies — What it really is in the brain. Neurosci Res 26:1–16

Sanes JN, Donoghue JP 1993 Oscillations in local field potentials of the primate motor cortex during voluntary movement. Proc Natl Acad Sci USA 90:4470–4474

Singer W 1993 Synchronization of cortical activity and its putative role in information processing and learning. Annu Rev Physiol 55:349–374

Singer W, Gray CM 1995 Visual feature integration and the temporal correlation hypothesis. Annu Rev Neurosci 18:555–586

Softky WR, Koch C 1993 The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. J Neurosci 13:334–350

Song S, Miller KD, Abbott LF 2000 Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nat Neurosci 3:919–926

Stevens C, Zador AM 1998 Input synchrony and the irregular firing of cortical neurons. Nat Neurosci 1:210–217

Vaadia E, Haalman I, Abeles M et al 1995 Dynamics of neuronal interactions in monkey cortex in relation to behavioral events. Nature 373:515–518

Volgushev M, Christiakova M, Singer W 1998 Modification of discharge patterns of neocortical neurons by induced oscillations of the membrane potential. Neuroscience 83:15–25

von der Malsburg C 1981 The correlation theory of brain function. Internal Report. MPI Biophys Chem, Göttingen, p 81–82

DISCUSSION

Sejnowski: There is a problem that has to do with the probability of transmission at synapses. Several groups have now used various techniques to look at the reliability of transmission at a single synapse between, for example, two pyramidal cells. It varies. The peak of the distribution is at one tenth: every 10 times that you stimulate the axon, on average you only get the release of a single vesicle on one of those trials. That is a typical synapse. There are some that have a probability of a third or a half, and there are a few that are silent. How does this degree of unreliability at the synapse fit into a model like yours that requires recovery of precision at every stage.

Aertsen: The actual values for the synaptic strengths used in our model were taken from the experimental literature. As these numbers are based on spike-triggered averaging, they of course represent an average picture. As I have shown, the stability is very much governed by the size of the neuron groups in the network. You can compensate for lower synaptic strength by up-scaling this group size. Essentially, it is the product of the two that determines what arrives at the next stage. So, if you bring the synaptic connectivity down, you will need more neurons per group. If, by contrast, you manage to increase the strength of the synaptic connections — through learning or some other means — this will bring the necessary group size down. Another issue is how this scaling interacts with background activity. In additional simulations (Diesmann et al 2000) we found that if you consider the level of background activity, this introduces a third axis, in addition to the two I showed here. As a result, the phase portrait is re-shaped in a rather complex way, because it depends in a non-monotonic way on this third dimension. Yet, there are interesting trade-offs that can be made between the level of background activity and the numbers for the necessary group size and synaptic connectivity.

Berridge: When considering Terry Sejnowski's comment about failures in synaptic transmission, it is reasonable to ask whether there are any data on how many synapses are formed between interacting neurons. Perhaps you get around the failure rate by having more synapses.

Aertsen: There are numbers on this from various sources. Braitenberg was one of the first who looked into this (reviewed in Braitenberg & Schüz 1991), later several others also studied it. The number of synapses between any two neurons in the neo-cortex depends strongly on the distance between the two cells. If they are very close, there is a high probability that they will have multiple (up to 10) synapses between them; if they are further apart (100 μm or more), this probability goes down rapidly (e.g. Hellwig 2000). So, neurons that are some 500 μm apart will typically have at most one synapse between them.

Berridge: Then this probability of failure really matters.

Aertsen: Yes. For a story like this to hold under such circumstances, by necessity we need to increase the size of the assembly. Also, it imposes interesting constraints on the amount of cortical space such an assembly can live in (Hehl et al 2001). I would like to point out that if this doesn't work, nothing does. This is the only viable type of activity in such networks.

Iyengar: I am still thinking what your boundary conditions mean. To achieve that, one has to increase reliability at each synapse, so there is no potentiation but the synapse becomes reliable enough that all of them work, and if this is not achieved in a few cases it fails. If you go back and record at single synapses will they become more reliable?

Sejnowski: That has been done. It is much easier to potentiate a low probability synapse than a high probability synapse. Conversely, it is much easier to depress a high probability synapse. I think there is a close relationship between the two. One idea of LTP is that you are just converting a synapse from a low probability state to a high probability state. This can be deceiving. The beauty of having a contact of a low probability is that you can recruit it if you need it, and you can reorganize your network. There is yet another degree of complexity that underlies synapses that has to do with short-term dynamics. For example, if you stimulate a synapse at high frequency, some synapses will depress, that is each subsequent signal will produce a smaller output, and there are some synapses where the probability of release will go up.

Iyengar: This scares me, because then I wonder how is it that these biochemical events in each of these get coordinated to produce these results.

Aertsen: I agree that the combinatorial complexity increases with each new axis that you open up. On the other hand, part of the good news is that this sort of construction creates robustness.

Sejnowski: There may be a principle for self-repair of a network with many unreliable components, which collectively produces a reliable state.

Iyengar: So you pre-select biochemically for those that are working, and when you reach a critical number the system becomes reliable.

Eichele: However, there are organisms that have very few neurons, yet they still work.

Aertsen: This isn't a theory for all brains of all animals. It is just a theory for the neo-cortex of the mammalian brain. Moreover, it critically depends on the spike rates in the network: it works nicely for low to moderate rates (typical for cortex), but at high spike rates, this theory breaks down.

Sejnowski: Even in humans there are synapses that are highly reliable, such as the neuromuscular junction, which releases so many vesicles that a contraction is bound to occur, regardless of the fluctuation. Where reliability is called for, nature usually achieves this with an anatomical specialization. This is not found in the cortex, except in a few specialized places such as the mossy fibre terminals in CA3.

Laughlin: I would put a slightly different gloss on it. We found that the single synapse, which is just a small synapse, $0.5 \times 0.1\,\mu\mathrm{m}$, was transmitting 55 bits per second. It is achieving a good transmission rate without any failure. It is not just a question of using large numbers of synapses or big synapses. You can engineer small synapses to be reliable or unreliable, presumably by adjusting vesicle release mechanisms.

Sejnowski: The distinction there is that it is a graded or drip synapse, working over a wide range of potentials, whereas in the cortex it is an all-or-none event.

Laughlin: I would say that these synapses have been deliberately engineered to be unreliable and to have their probability of release depend on other events.

References

Braitenberg V, Schüz A 1991 Anatomy of the cortex. Springer, Berlin

Diesmann M, Gewaltig M-O, Aertsen A 2000 Analysis of spike synchronization in feed-forward cortical neural networks. Soc Neurosci Abstr 26:2201

Hehl U, Hellwig B, Rotter S, Diesmann M, Aertsen 2001 Anatomical constraints on stable propagation of synchronous spiking in cortical networks. In: Göttingen Neurobiology Report 2001. Thieme, Stuttgart, in press

Hellwig B 2000 A quantitative analysis of the local connectivity between pyramidal neurons in layers 2/3 of the rat visual cortex. Biol Cybernetics 82:111–121