Slow oscillating population activity in developing cortical networks: models and experimental results

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Baltz T, Herzog A, Voigt T. Slow oscillating population activity in developing cortical networks: models and experimental results. J Neurophysiol 106: 1500–1514, 2011. First published June 22, 2011; doi:10.1152/jn.00889.2010.—During early development neuronal networks express slow oscillating synchronized activity. The activity can be driven by several, not necessarily mutually exclusive, mechanisms. Each mechanism might have distinctive consequences for the phenomenology, formation, or sustainment of the early activity pattern. Here we study the emergence of the oscillatory activity in three computational models and multisite extracellular recordings that we obtained from developing cortical networks in vitro. The modeled networks consist of leaky integrate-and-fire neurons with adaptation coupled via depressing synapses, which were driven by neurons that are intrinsically bursting, intrinsically random spiking, or driven by spontaneous synaptic activity. The activity of model networks driven by intrinsically bursting cells best matched the phenomenology of 1-wk-old cultures, in which early oscillatory activity has just begun. Intrinsically bursting neurons were present in cortical cultures, but we found them only in those cultures that were younger than 3 wk in vitro. On the other hand, synthetically dependent random spiking was highest after 3 wk in vitro. In conclusion, model networks driven by intrinsically bursting cells showed a good approximation of the emergent recurrent population activity in young networks, whereas the activity of more mature networks seems to be better explained by spontaneous synaptic activity. Moreover, similar to previous experimental observations, distributed stimulation in the model was more effective in suppressing population bursts than repeated stimulation of the same neurons. This observation can be explained by an effective depression of a larger fraction of synapses by distributed stimulation.

DURING A LIMITED DEVELOPMENTAL period the electrical activity of neuronal networks is characterized by slow synchronous oscillatory activity, which is widely regarded to play a fundamental role in the establishment of a functional network (Ben-Ari 2001; Feller 1999; Katz and Shatz 1996; O’Donovan 1999). This activity pattern robustly emerges during the development of various neuronal tissues and in vitro preparations, including the cerebral cortex and hippocampus in vivo (Chiu and Weliky 2001; Khazipov et al. 2001, 2004; Leinekugel et al. 2002), cortical and hippocampal slices (Allêne et al. 2008; Garaschuk et al. 2000; Khazipov et al. 1997, 2001; McCabe et al. 2006), and culture preparations (Arnold et al. 2005; Baltz et al. 2010; Chiappalone et al. 2006; Feller 1999; Harris et al. 2002; O’Donovan 1999; Van Pelt et al. 2004; Streit et al. 2001; Wagenaar et al. 2005, 2006).

Immature networks are susceptible to hyperexcitability, in part due to the delayed development of γ-aminobutyric acid (GABA)ergic inhibition. GABA is the major inhibitory neurotransmitter in the adult brain, but during a transient period of early development a depolarizing and excitatory action dominates in nearly all neuronal structures investigated (for comprehensive reviews see Ben-Ari 2001, 2002; Ben-Ari et al. 2007; Le Van Quyen et al. 2006).

Experimentally, oscillatory activity can be observed as recurrent bursts of action potentials of many, if not all, cells in the network with a simultaneous strong increase of the intracellular calcium concentration (Ben-Ari 2001, 2002; Garaschuk et al. 2000; Opitz et al. 2002; Owens and Kriegstein 2002). During such population bursts cells enter the “burst state” within tens of milliseconds, whereas individual spikes during bursts are typically not synchronized across neurons (Baltz et al. 2010).

In cultures of embryonic cortical cells population bursting is highly regular and synchronized during about the first 2 wk of their development in vitro (Baltz et al. 2010; Habets et al. 1987; Kamioka et al. 1996; Marom and Shahaf 2002). During the third week, the occurrence of variable, clustered, and less synchronized bursting is dependent on GABA_ergic synaptic transmission and can be induced prematurely by a blockade of the Na⁺-K⁺-2Cl⁻ cotransporter 1 (Baltz et al. 2010). In 3-wk-old cortical cultures, GABA_ergic receptor blockade or a reduced GABA cell content leads to regular population bursts, typical for younger cultures. GABA_ergic synaptic transmission has only minor inhibitory effects on synchronized population activity during the first 2 wk in vitro (Baltz et al. 2010), and, hence, young cultured cortical networks can be considered as “purely excitatory” (see also Tsodyks et al. 2000; Wiedemann and Lüthi 2003).

Recurrent population bursts can be driven by several, not necessarily mutually exclusive, mechanisms. These include 1) rhythmically active pacemaker neurons (Le Bon-Jego and Yuste 2007; Lischalk et al. 2009; Negro et al. 2005), 2) intrinsically random spiking neurons (Faisal et al. 2008; Streit et al. 2006; Yvon et al. 2007), and 3) spontaneous synaptic activity (Bazhenov et al. 2002; Faisal et al. 2008). Each of these mechanisms might have a distinctive impact on the phenomenology, formation, or sustainment of recurrent population bursting.

Here we study the population activity in three minimalistic models of purely excitatory networks of leaky integrate-and-fire neurons with adaptation over a large volume of parameters. We qualitatively compare the activity of networks driven by intrinsically rhythmic bursting cells (IB cells), by intrinsically...
random spiking neurons (ISNs), or by spontaneous synaptic activity [i.e., spontaneous miniature excitatory postsynaptic potentials (mEPSPs)] among each other and with experimental data that we obtained from multisite extracellular recordings of young cortical networks in vitro.

We find that plausible network behavior emerged in all three models over a large parameter space, each with distinctive properties of the network dynamics. In cultured networks, we found indirect evidence that supports two of the three theoretically investigated models, namely spontaneous synaptic activity and IB cells.

METHODS

Simulations

Basic neuron model. If not stated otherwise, the model neurons were of the regular spiking type, as most neurons in the neocortex belong to this class (Connors and Gutnick 1990; Steriade 2004). These neurons can show an adaptation to prolonged input currents and are modeled here as follows. The membrane potential ($V_m$) evolves according to:

$$C_m \frac{dV_m}{dt} = g_L (E_L - V_m) + g_{\text{ref}} (E_{\text{ref}} - V_m) + g_{sra} (E_{sra} - V_m) + I_{\text{syn}}$$

where $C_m = 1 \mu F/cm^2$ is the specific membrane capacitance, $g_L = 50 \mu S/cm^2$ is the leak conductance, $E_L$ is the reversal potential of the leak current, and $I_{\text{syn}}$ summarizes the synaptic currents (see below). Two additional potassium conductances were added: a strong conductance $g_{sra}$ with a short time constant and a weaker conductance $g_{sra}$ with a longer time constant to account for a postsynaptic refractory period and for a weak spike rate adaptation, respectively. The reversal potential of the potassium currents was $E_{sra} = -75$ mV. After reaching the firing threshold $V_{\text{thres}}$, the membrane potential $V_m$ was reset to $-60$ mV, and $g_{\text{ref}}$ and $g_{sra}$ were increased by an amount of $\Delta g_{\text{ref}}$ and $\Delta g_{sra}$ respectively. These conductances exponentially relaxed with time constants of $\tau_{\text{ref}}$ and $\tau_{sra}$. The parameters $\Delta g_{\text{ref}}$ and $\tau_{\text{ref}}$ were set to $\Delta g_{\text{ref}} = 1 \mu S/cm^2$ and $\tau_{\text{ref}} = 5$ ms. To introduce heterogeneity, the parameters $\tau_{sra}$ and $V_{\text{thres}}$ were random numbers for each neuron, drawn from a Gaussian normal distribution with a mean and standard deviation of 1,000 ms and 300 ms and $-50$ mV and 1.5 mV, respectively. Furthermore, the variable $\Delta g_{sra}$ was drawn from a log-logistic distribution with $\alpha = 1.0$ and $\beta = 2.0$ and cutoff at 15 (in units of $\mu S/cm^2$), resulting in a small mean with only some neurons being affected more strongly by spike rate adaptation.

A small amount of uniformly distributed “thermal noise current” was added to allow slight random fluctuations of the membrane potential ($\pm 0.5$ mV). The general firing behavior of an adapting model neuron is exemplified in Fig. 1, A–C.

Synaptic conductances. Each neuron received synaptic input $I_{\text{syn}}$:

$$A \cdot I_{\text{syn}} = g_{\text{AMPA}} (E_{\text{exc}} - V_m) + g_{\text{NMDA}} (V_m) (E_{\text{exc}} - V_m)$$

where $E_{\text{exc}} = 0$ mV is the reversal potential of excitatory currents, $A$ is the total membrane area, and $g_{\text{NMDA}}(V_m)$ is the voltage-dependent NMDA conductance. The membrane area was $A = 4,000 \mu m^2$, thereby giving a total membrane resistance of the modeled cultured neurons of 500 M$\Omega$ (Opitz et al. 2002). Maximum AMPA conductivity of a single synapse was varied between 0.3 and 0.7 nS (see RESULTS). Synaptic delays were random and uniformly distributed between 0 and 3 ms. Although NMDA receptors are not mandatory for the occurrence of synchronous population bursts, a NMDA conductance was included, as it leads to more realistic burst duration and rise and descent of the firing rate during population bursts (see RESULTS). Maximum NMDA conductance was set to a fixed AMPA-NMDA ratio of 1:0.3. Voltage dependence of the NMDA receptor was idealized according to the following equation (Izhikevich et al. 2004):

$$g_{\text{NMDA}}(V_m) = g_{\text{NMDA}} \left[ \frac{(V_m + 80)/60}{1 + [(V_m + 80)/60]^2} \right]$$

Both synaptic conductances $g_x$ ($x = \text{AMPA/NMDA}$) had first-order linear kinetics:

$$\frac{dg_x}{dt} = g_x \frac{g_x}{\tau_{AMPA}}$$

with $\tau_{AMPA} = 5$ ms and $\tau_{NMDA} = 180$ ms.

Short-term synaptic depression. In the developing neocortex, most synapses exhibit synaptic depression (Reyes and Sakmann 1999).
phenomenological model for short-term synaptic depression was used, based on the concept of a limited pool of synaptic resources (Fuhrmann et al. 2002; Tsodyks and Markram 1997):

\[
\frac{dR}{dt} = \frac{1 - R}{\tau_{rec}} - R \cdot U_{SE} \cdot \delta(t - t_{spk})
\]

The synaptic resource \( R \) of a given synapse is decreased by a fraction of \( U_{SE} = 0.15 \) (Fuhrmann et al. 2002; Markram 1997) every time the corresponding neuron emits a spike \( (t_{spk}) \), with \( \delta(t) \) being the dirac delta function. The time constant \( \tau_{rec} \) determines the recovery rate of the available pool and was a Gaussian normal distributed random number for each synapse with a mean and standard deviation of 1,200 ms and 300 ms, respectively (Fuhrmann et al. 2002; Markram 1997). The maximum amplitude of each postsynaptic potential, then, is modulated by the magnitude of \( R \).

Intrinsically bursting neurons. In a subset of simulations (detailed in RESULTS), the networks were supplemented with a number of neurons capable of firing rhythmic bursts of action potentials without external input. Rather than adding a complex set of interacting currents to model bursting behavior, neurons were considered as black boxes that show a certain firing pattern. To implement the intrinsic bursting behavior, a transient “calcium” current \( I_T \) was added to the basic integrate-and-fire model (Smith et al. 2000):

\[
I_T = g_T m h (V_m - V_T)
\]

where \( V_T = 120 \) mV and \( g_T = 40 \mu S/cm^2 \). The variable \( h \) represents the inactivation of the low-threshold conductance. It relaxes to zero with the time constant \( \tau_h = 90 \) ms and relaxes back to unity with \( \tau_h = 150 \) ms:

\[
\frac{dh}{dt} = \begin{cases} 
- h/\tau_h & \text{if } V_m > V_h \\
(1 - h)/\tau_h & \text{if } V_m < V_h 
\end{cases}
\]

For \( V_m \) below \( V_h = -70.5 \) mV, the current \( I_T \) is “deinactivated,” and it is inactivated for \( V_m \) greater than \( V_T \). The function \( m = H(V_m - V_T) \) is the activation function, with \( H(\cdot) \) being the Heaviside step function. To enable low-frequency spontaneous bursting, the membrane equation of IB cells also contains the negative feedback conductance \( g_{sra} \). The burst frequency, then, mainly depends on the time constant \( \tau_{sra} \), which is a random number for each IB cell drawn from a Gaussian normal distribution with a mean of 4,000 ms and a standard deviation of 800 ms. This gives an average burst frequency of \( \sim 0.1 \) Hz. Leak reversal was set to \( E_L = -70 \) mV, and \( \Delta V_{sra} \) was 15 \( \mu S/cm^2 \). All other parameters and equations were similar to the basic neuron model described above. The resulting behavior of the model cell is exemplified in Fig. 1, D–G.

Intrinsically random spiking neurons. In another set of simulations, a fraction (5–30%) of the neurons stochastically emit a single spike. Generally, these neurons were governed by the same equations and parameters as the basic neuron model. However, to have a fine control over ISN firing rate and to avoid the need for additional synapses, biophysical mechanisms of spike generation were neglected and membrane potentials of ISNs were set above its firing threshold according to Poisson processes with an average frequency of 0.1–20 Hz (see RESULTS) and a 3-ms refractory period.

Spontaneous synaptic activity. In a final set of simulations, the effect of subthreshold spontaneous synaptic activity on population activity was studied. To this end, spontaneous synaptic activity was modeled as spontaneous mEPSPs, which followed the same equations as the regular postsynaptic potentials. Their arrival times at the synapses were modeled by Poisson processes with mean rates varied between 0.1 and 5 Hz (see RESULTS).

General properties and data analysis. Plausible population bursts can emerge in relatively small networks \(~20\) model neurons (Bazhenov et al. 2002). Here, the impact of synaptic coupling (0.4–1 nS) and connectivity (5–25%) for each input scenario in a network of 100 randomly connected neurons was studied. In addition, the number of IB cells, the number of ISNs and their average spontaneous firing frequency, as well as the average frequency of spontaneous mEPSPs were varied (see above and RESULTS for parameter ranges). In total, the occurrence of population bursting in \( >3,000 \) different parameter configurations was analyzed.

In biological networks, the frequencies and durations of population bursts are variable, depending on the experimental settings and the developmental stage of the network (Kamioka et al. 1996; Marom and Shahaf 2002; Robinson et al. 1993; Wagenaar et al. 2006). Therefore, we did not aim to model any particular network type but to qualitatively reproduce population behavior to compare different input scenarios. The frequencies and durations of population bursts were, however, always in the physiological range that was experimentally observed in the studies cited above.

The detection of bursts was based on the entropy of spike occurrence. When the entropy for a sequence of at least three spikes exceeded a threshold of five, they constituted a burst. If bursting of at least 10% of the neurons overlapped in time, a population burst was defined. Detected population bursts were checked by visual inspection for plausibility.

To investigate the evolution of the firing rate during population bursts, spike times of all neurons \([\text{or electrodes in case of microelectrode array (MEA) recordings}]\) were collected in 5-ms-wide bins and smoothed with a Gaussian with a standard deviation of 20 ms.

All simulations were implemented in the neuronal network simulator Brian v1.21 (Goodman and Brette 2009) with an integration time step of 0.2 ms. The simulated time was 60 s for each run, of which the first 10 s were not considered in the analysis.

Cell Culture

For cultivation of cortical neurons plasma-cleaned (Herrick Plasma, Ithaca, NY) MEAs [Multi Channel Systems (MCS, Reutlingen, Germany)] were treated overnight with poly-D-lysine (0.1 mg/ml in borate buffer, pH 8.5, 36°C). To suppress cell proliferation and to support neuronal survival (de Lima and Voigt 1999; Schmalfenbach and Müller 1993), a feeder layer of purified astroglial cells was prepared from cerebral hemispheres of P0–P3 Sprague-Dawley rats as reported in detail previously (de Lima and Voigt 1999). The astroglial cells were plated onto the MEA substrate with a density of 500 cells/mm² 5 days before the neurons. Young neurons were prepared from cerebral cortices of embryonic Sprague-Dawley rats at embryonic day (E)16 (day after insemination was E1; birth = E22). The cortical tissue was obtained from the lateral parts of the telencephalic vesicles (excluding hippocampal and basal telencephalic anlagen). The cells were dissociated with trypsin-EDTA and seeded at a density of 1,200 cells/mm² onto the feeder layer. All cultures were maintained in N2 medium (75% DMEM, 25% Ham’s F-12, and N2 supplement; Invitrogen, Carlsbad, CA) in a humidified 5% CO₂-95% air atmosphere at 36°C. The culture chamber was sealed by a screw cap to prevent infection and evaporation. Within the incubator, the cap was loosened to allow gas circulation. Some MEA cultures were purchased (→bicuculline methiodide (bicuculline) from RBI (RBI/ Sigma, Deisenhofen, Germany) and D-2-amino-5-phosphonopentanoic acid (D-AP5), 6-imino-3-(4-methoxyphenyl)-1(6H)-pyridazinethione acid hydrobromide (gabazine), and 6-cyano-7-nitroquinoline-2,3-dione disodium (CNQX)
from Tocris Cookson (Biotrend, Cologne, Germany). Drugs were applied directly from the stocks, and cultures were allowed to equilibrate for at least 20 min before recording started to avoid a putative interference of transient changes in the network activity that might have been induced by culture handling (Wagenaar et al. 2006).

**MEA recordings and data processing.** Recording of electrical activity was carried out with MEAs with 59 substrate-embedded titanium nitride recording electrodes, arranged in a $10 \times 6$ rectangular array with 1 electrode missing in the first column (MCS). However, because of immaturity, in only a fraction of the electrodes (typically 5–15) can electrical activity be recorded in very young cultures (Wagenaar et al. 2006). The electrodes, $30 \, \mu m$ in diameter, had an interelectrode distance (center to center) of $500 \, \mu m$. Signals were amplified $1,100 \times$ and sampled at 25 kHz with a preamplifier (MEA1060-Inv-BC) and data acquisition card (both MCS). The spontaneous activity of individual cultures was monitored at $36^\circ C$ with MC_Rack software (MCS). Recordings for different culture conditions were always age matched. Spikes were detected online on the band-pass filtered ($0.15–3.5 \, kHz$) signal, using a threshold of $–5 \times$ standard deviation from background noise, and were considered if their peak-to-peak amplitude exceeded $15 \, \mu V$. Custom-written MATLAB (version 2007b, Mathworks, Natick, MA) programs were used for off-line analysis. Overlapping spike waveforms were commonly seen during bursts, supposedly due to high action potential firing of several cells near a particular electrode. Given that the cells rarely fired between bursts, automatic spike sorting procedures are less reliable. Thus sorting was not attempted, and results are based on multiunit data.

**RESULTS**

Here the population activity of purely excitatory networks of leaky integrate-and-fire neurons coupled via depressing synapses is studied over a large volume of parameters in three minimalistic models. The activity of networks driven by intrinsically rhythmic bursting neurons (IB neurons), by intrinsically random spiking neurons (ISNs), or by spontaneous synaptic activity (i.e., spontaneous mEPSPs) were qualitatively compared with each other and with experimental data that were obtained from multisite extracellular recordings of young cortical networks in vitro.

Generally, the “thermal noise” added in the model (see METHODS) was not capable of pushing neurons significantly away from their resting membrane potentials. Hence, without any additional input the model networks were completely silent. Resulting network behavior is discussed in separate sections below.

In all three scenarios studied, the network exhibited intervals of synchronous population bursts during which virtually all neurons entered a “burst state” within tens of milliseconds. During these population bursts, neurons typically fired a train of action potentials with a duration roughly ranging between 100 and 1,000 ms. Although differences between the distinct input types existed, population bursting always occurred under a large space of parameter settings (see below), indicating that it is an inherent property of neurons coupled via depressing synapses (see also Tsodyks et al. 2000).

**Networks Driven by Intrinsically Bursting Neurons**

One mechanism for inducing recurrent population bursts into a neuronal network is the introduction of dedicated pacemaker cells. In this section, networks consisting of slowly adapting integrate-and-fire neurons, supplemented with a number of bursting pacemaker cells (Fig. 1, D–G) are considered. These pacemaker cells are capable of firing recurrent bursts of action potentials without synaptic input (Fig. 1E). The burst frequency of single IB cells is determined mainly by their time constant $\tau_{rsa}$ (see METHODS) and was a Gaussian normal distributed random number for each IB cell (mean 4,000 ms, standard deviation 800 ms). This results in a burst frequency of $\pm 0.1 \, Hz$ for individual IB cells.

Coupling strengths between the neurons (0.4–1 nS), their connectivity (5–25%), and the fraction of IB cells in the network (2–30%) were systematically varied, and the resulting population activity was investigated.

In simulations with 5% connectivity, IB cells fire mostly independently at their individual burst frequency (Fig. 2A). In contrast, at 25% connectivity and sufficient synaptic coupling strength, each action potential is part of a population burst, with 100% of the neurons being recruited (Fig. 2E and Fig. 3C). With these parameter settings, population bursts occur in an all-or-none manner, i.e., the network is either in a burst or in a silent state with no spikes during interburst intervals (IBIs) (Fig. 2E). If population bursts are present, typically most of the spikes are clustered in these bursts. Consequently, the total spike frequency increases with the frequency of population bursts in a trivial manner. The grayscale in the graphs of Fig. 3, therefore, codes the frequency of spikes during IBIs. Showing the spike frequency when the network is not in a burst state, rather than the total spike frequency, gives a more detailed overview of the network dynamics.

The variability of the IBI was low for most parameter ranges, as indicated by the coefficient of variation (CV) of the IBI (Fig. 3, insets). In 93.20% of all simulations, the CV IBI falls in the range between 0.03 and 0.5, with highest values at the transitions from independent bursting of individual IB cells to population bursting. These values of the CV IBI are typically observed in young cortical networks in vitro, as well as in mature networks when fast GABAergic transmission is blocked (see Baltz et al. 2010).

With intermediate parameter settings, the population activity comprised partially synchronized and fully synchronized bursts with little or no activity during IBIs (Fig. 2B). Partially synchronized bursts are triggered by the subpopulation of IB cells with a high intrinsic burst frequency (Fig. 2C). In some cases, IB cells do not recruit the whole network because of incomplete recovery from synaptic depression (Fig. 2C).

A quite similar phenomenology of population activity was observed in 1-wk-old cortical cultures, when dendritic and synaptic maturation is not fully completed yet and hence connectivity and synaptic coupling strength are relatively low (Fig. 4, A and B). To investigate whether cortical networks in culture contain rhythmically bursting cells that are independent from fast glutamatergic and GABAergic synaptic transmission, the synaptic blockers CNQX (50 $\mu M$), D-AP5 (50 $\mu M$), and bicuculline (10 $\mu M$) were applied to the bathing solution of 6- to 7-DIV (days in vitro) old cultures to block AMPA, NMDA, and GABA$_A$ receptors, respectively. In all cases, synaptic blockade reversibly abolished population bursting ($n = 5$). In three of five cultures recurrent bursting persisted at single sites (2.7–14% of the initial active electrodes; mean spike rate $0.13 \pm 0.03 \, Hz$) (Fig. 4C), and in two of five cultures only random single spikes persisted at very low rates ($5.04 \pm 3.10\%$ of the...
At 15–16 DIV synaptically independent bursting cells were still present in three of three cultures investigated. In older cultures (21–34 DIV, mean 24 DIV), however, synaptically independent bursting cells were not detected ($n = 9$ cultures) (not shown).

Taken together, the dynamics of the network activity of simulated networks driven by IB cells share the phenomenology of young cortical cultures. Furthermore, cells that are rhythmically bursting independent from fast GABAergic and glutamatergic synaptic transmissions are present in young cortical networks. Given that the average spike rate of rhythmic bursting cells in the presence of synaptic blockers is considerably higher than that of remaining spikes that were not clustered in bursts and that bursts are ideally suited to overcome the spike threshold in postsynaptic targets, intrinsically...
Networks Driven by Intrinsically Spiking Neurons

In this section, networks driven by a fraction of neurons that emit a single spike stochastically (i.e., not clustered in bursts) independent of synaptic input are investigated. The fraction of ISNs in the network (5–30%) as well as their average firing frequency (0.1–20 Hz) were varied. Additionally, the coupling strength and the connectivity were systematically varied at similar ranges as in the previous section. The resulting network behavior is summarized in Figs. 5 and 6. When the fraction of ISNs was 5%, 15%, or 30% no recurrent population bursting was observed at 5% connectivity (Fig. 6). At high synaptic coupling strengths and 15% connectivity, population bursting first appears when 15% of the neurons are ISNs and fire with an average frequency of at least ~2 Hz (Fig. 6B). The maximum burst frequency in this model (~0.7 Hz) was reached at moderate synaptic coupling strengths, when the fraction of ISNs was increased to 30% and their average firing rates were ~20 Hz (Fig. 6C). At higher synaptic coupling strengths (>0.8 nS), the frequency of population bursts decreases (Fig. 6C) and the network activity ultimately makes a transition from regular bursting to continuous spiking (not shown). Such behavior was never observed in developing cortical cultures under normal culturing conditions.

Similarly to simulations with IB cells, the variability of the IBIs was relatively low, with CV IBIs mostly much smaller than one (Fig. 6, insets).

To maintain population bursts at moderate frequencies (i.e., >0.1 Hz), the fraction of ISNs and their firing rates had to be relatively high (Figs. 5 and 6). In cultures of cortical cells, the frequency of random spiking is typically low and observed only at a few electrodes (see below).

If this model is consistent with developing cortical networks in vitro, spontaneous firing at sufficient rates should be observed in cultured networks. Furthermore, a blockade of excitatory synapses would abolish spontaneous bursting but should have little or no impact on the activity of ISNs, since their firing is independent from synaptic input.

To study this issue, we first investigated whether random spiking is present in developing cortical networks by recording spontaneous electrical activity of 5- to 22-DIV-old cultures. To compare random spiking of networks across different developmental periods, fast GABAergic synaptic transmission was blocked with 20 μM gabazine to obtain “purely excitatory” networks throughout the development (see also Baltz et al. 2010). In these cultures, the frequency of random firing during the IBIs increased with development (Fig. 7). Highest rates were observed after 3 wk in vitro. In 20- to 22-DIV-old cultures, on average, at 10.45 ± 1.35% of the total active electrodes spike frequencies above 0.1 Hz were detected during IBIs (average spike frequency during IBIs was 0.7 Hz; maximum was 4.85 Hz in a 21-DIV-old culture; 10 recordings of 4 cultures between 20 and 22 DIV). Second, in a 15-day-old culture, it was tested whether spiking during IBIs is of synaptic origin. Application of the glutamate receptor blockers CNQX (50 μM) and D-AP5 (50 μM) led to a disappearance of spiking on all but one electrode, on which rhythmic bursting persisted (Fig. 8). Furthermore, after glutamatergic synaptic transmission was blocked in 21- to 34-DIV-old control cultures, spikes could be detected, on average, on <1% (range 0–3%) of the initially active electrodes, with an average spike frequency below 0.02 Hz (range 0–0.015 Hz) [control firing rate, averaged over all active sites, was 1.02 ± 0.61 Hz (range 0.01–12 Hz); n = 9]. In sum, random spiking during IBIs in cultured cortical networks seems to be mainly a result of spontaneous glutamatergic synaptic activity. Thus these experiments suggest that synaptically independent neuronal firing plays only a minor role in burst generation, although population activity with plausible properties was generated in simulated networks.
before, maximum coupling strength (0.4–1 nS) and connectiv-
ity (5–25%) were varied and the resulting population activity
was investigated. The results are summarized in Figs. 9 and 10.
At low connectivity (5%), the neurons do not fire or fire at
low rates (on average <1 Hz) and population bursts hardly
emerge (Fig. 9A and Fig. 10A). When the connectivity is
increased to 15%, population bursts robustly appear at suffi-
cient coupling strengths and mEPSP frequencies (Fig. 10B).
When the coupling strength at a given mEPSP frequency is
continuously increased, spike frequency during the IBIs first
increases and then decreases, with highest IB firing rates
occurring at the transition from stochastic spiking to population
bursting (Fig. 10B).
Reduced firing frequency after each burst (Fig. 9C) is
typically observed in biological networks that show population
bursting (see also Fig. 7, D and E, and Fig. 8A) and is
suggestive of a networkwide refractory period (Opitz et al.
2002; Sanchez-Vives and McCormick 2000; Staley et al.
1998). In the model, the reduced firing is mainly a consequence
of an exhaustion of the synaptic reserves after repetitive action
potential firing (Fig. 9C).
When the connectivity is increased to 25%, bursting is
observed at lower mEPSP frequencies and lower coupling
strengths (Fig. 10C). Similarly to the model networks driven by
ISNs, the burst frequency drops and the network activity makes
a transition to sustained firing when coupling strength and
mEPSP frequencies take high values (Fig. 10C). As above and
in line with experimental observations in purely excitatory
biological networks, there was relatively little variation of the
IBI in the simulations (see histograms in Fig. 10). In this
scenario, all spike activity is glutamate receptor dependent, and
population bursts, as well as random spiking during IBIs, will
be abolished when glutamate receptors are not functional.
Consequently, this model is compatible with culture experi-
ments (see Fig. 8).

General Features of Modeled Networks

Network firing during bursts. The rise and decay of the firing
rate during population bursts is dependent on the developmen-
tal stage of the network (Chiappalone et al. 2006; van Pelt et al.
2004; Wagenaar et al. 2006) and thus correlated with important
network parameters, such as the connectivity, number of func-
tional synapses, and mode of GABA action, and might addi-
tionally depend on the given experimental configuration. Typ-
ically, the time range to reach the peak firing rate of a
population burst is considerably shorter than the decay back to
the baseline firing rate.

The evolution of the firing rate of “purely excitatory” net-
works (i.e., GABAergic transmission chronically blocked)
and control networks under the present experimental condi-
tions is shown for different developmental stages in Fig. 11.
Marked differences between the two conditions emerge after
~2 wk in vitro, when bursting becomes heterogeneous in
control networks and remains stereotyped in blocked networks
(see also Baltz et al. 2010).

In model networks driven by IB cells, the variation of the IB
cell fraction had relatively little impact on the evolution of the
firing rate during bursts at a fixed synaptic coupling strength
(Fig. 12A). A higher fraction of IB cells led to a slight
reduction of the firing rate during the decay and a higher
“peak,” since IB cells in the model typically fire short bursts
upon depolarization (see also Fig. 1, D–G). Moreover, in

Networks Driven by Spontaneous Synaptic Activity

In the last section, it was shown that synaptically indepen-
dent spiking of a sufficient number of neurons led to plausible
population bursts in the model, but the frequency of synapti-
cally independent spikes was extremely low in cultured cortical
networks. In this section, a synaptically dependent mechanism
for the generation of recurrent population bursts is considered.
In this set of simulations, network activity was driven by
spontaneous synaptic activity, which was modeled by the
occurrence of mEPSPs at various frequencies (see below). In
contrast to ISNs, which, once activated, are likely to produce
postsynaptic potentials in most of their target cells, spontane-
ous mEPSPs occur without a presynaptic action potential and
independently from each other.

Each model synapse is capable of inducing a mEPSP in its
postsynaptic cell independent from presynaptic activity. As
before, maximum coupling strength (0.4–1 nS) and connectiv-

Fig. 5. Example activity of modeled networks driven by intrinsically random
spiking neurons (ISNs). A: population firing rate (top) and raster plot of
the network activity (bottom) of a network driven by ISNs (see asterisk in Fig. 6B
for parameters used). B, top: network activity with a higher number of ISNs
(asterisk in Fig. 6C). Bottom: average synaptic resources in the network.
C: membrane potential trace of a single randomly chosen non-ISN (top) with
its synaptic currents (bottom) (black: AMPA, gray: NMDA component).

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contrast to the other two models, the recovery of the overall synaptic reserves during IBIs is not hindered that much by random neuronal and synaptic activity, which supports higher peak firing rates during population bursts.

In networks driven by ISNs, the peak firing rate during population bursts decreases as a function of ISN firing rate (Fig. 12B) when the duration of the IBIs is so low that it approaches the average time constant for the recovery from synaptic depression (not shown). Under these conditions, synapses can only partially recover, resulting in smaller amplitudes of postsynaptic potentials and ultimately in reduced firing rates during population events.

In networks driven by spontaneous synaptic activity, the peak firing rate during population bursts decreases as a function of the mEPSP frequency (Fig. 12C) when the IBIs approach the time constant for the recovery from synaptic depression. This decrease of the peak intraburst firing rate is further amplified at higher mEPSP frequencies, because high mEPSP rates only allow a partial recovery of the overall synaptic resources in the network from depression, even at low burst frequencies (see, for example, Fig. 9, B and C).

Generally, differences between the models were not so striking to clearly refer to a specific input mechanism based on the intraburst firing characteristics.

Spike train correlations. In cortical cultures, peaks in cross correlograms emerge as soon as bursting starts at about the end of the first week in vitro (see Fig. 11 and Chiappalone et al. 2006). Cross correlation analysis for the three models is exemplified in Fig. 12. Similar to what is observed in young cultured cortical networks (Chiappalone et al. 2006), when the synaptic density and neuritic outgrowth are expected to be low and to increase with development, spike train correlations in the models were initially flat and a single peak emerged and became broader when the synaptic coupling strength and connectivity were increased.

Higher peak firing rates during bursts in model networks driven by IB cells (see above) led to slightly higher peaks in cross correlograms (Fig. 12A). In models driven by ISNs or spontaneous synaptic activity, spike probability in cross correlation graphs was generally high in some simulations, because the network activity made a transition from regular bursting to high-frequency spiking (not shown).

In summary, cross correlation peaks emerge as a result of synchronous population activity, and major differences between networks driven by IB cells and the other two models arise when the network dynamics make a transition from regular bursting to high-frequency spontaneous firing. This overexcitation cannot occur in networks driven by IB cells, because non-IB cells cannot maintain spiking after population bursts due to synaptic depression and because, after synaptic recovery, no random sources of excitation (spontaneous synaptic activity or ISNs) exist.

Lack of NMDA conductance decreases burst duration. In previous simulations (Gritsun et al. 2010; Tsodyks et al. 2000; Wiedemann and Lüthi 2003), synchronous population events were typically very short (down to ~1 spike per neuron). This might be in part due to the lack of a long time constant from the NMDA conductance in these simulations. In developing cortical networks in vitro, the firing rate of population bursts typically has a fast rise and a slower descent (Fig. 11; see also van Pelt et al. 2004; Wagenaar et al. 2006). To investigate the contribution of NMDA recep-
tors on the burst duration in young cultured cortical cells, electrical activity of 10-DIV-old cultures was monitored. Compared with controls, the firing rate during population bursts decayed much faster back to zero in the presence of the NMDA receptor blocker D-AP5 (50 μM) (Fig. 13), leading to a reduction of burst duration of 47.43 ± 13.48%. A reduction of the NMDA conductance in the models also leads to significantly shorter bursts (see Fig. 13C for an example for the mEPSP model). Furthermore, shortening the time constant of the NMDA conductance from 180 ms to 50 ms or increasing the AMPA conductance in NMDA receptor-devoided networks also led to short population bursts with a fast decay (not shown), indicating that it is mainly the long time constant of NMDA receptors that determines the slower decay of the firing rate, rather than the additional depolarizing current through NMDA receptors per se.

Burst suppression by distributed stimulation. Previous data showed that bursting can be suppressed by distributed electrical stimulation in cultured cortical networks (Wagenaar et al. 2005). The mechanisms of burst suppression are, however, not yet understood.

Distributed electrical stimulation could lead to continuous exhaustion of synaptic reserves, thereby preventing a recovery necessary for synchronized bursting. In line with this idea, bursting was suppressed in simulated networks when a fraction of network activity was stimulated for a short time (Fig. 8).
Fig. 9. Example activity of modeled networks driven by spontaneous synaptic activity. A: raster plot of a network driven by action potential-independent synaptic activity (see white asterisk in Fig. 10B for parameters used). Neurons typically fire single action potentials at low frequencies (<1 Hz). However, neurons with an exceptionally high amount of presynaptic activity can continuously fire at higher rates (neuron 50). Dashed line denotes the time range, which is shown expanded in B. B, top: membrane voltage trace of neuron 50 for the time range indicated by dashed line in A. Middle: synaptic currents of neuron 50 (black: AMPA, gray: NMDA component). Bottom: average available synaptic resources in the network. Because of spontaneous synaptic activity, which led to miniature excitatory postsynaptic potentials (mEPSPs), the synaptic resources in the network fluctuate around 75%. C: with higher synaptic coupling (see gray asterisk in Fig. 10B), population bursts emerge. Top: networkwide firing rate. Middle: raster plot of the network activity (neurons are sorted by their firing rate). Bottom: synaptic resources available in the network, which are strongly reduced after each population event. Note the transient period with low spiking after each burst due to depressed synapses (see also E1 in Fig. 8A and Fig. 7, D and E). D: raster plot of the network activity with further increased synaptic coupling strength (black asterisk in Fig. 10B).

Fig. 10. Summary plots of simulated networks driven by mEPSPs. A, top: axis labeling and grayscale denotation of the plots below. Bottom: burst frequency as function of synaptic coupling strength and the frequency of mEPSPs. Grayscale indicates the average spike frequency of neurons during IBIs. Inset: histogram of the CV of the IBIs. B: same as A except for 15% connectivity. Asterisks indicate parameters for which the network activity is exemplified in Fig. 9. C: same as B except for 25% connectivity. Inset: top graph is a rotated version of the graph on the left (note the different grayscale). of neurons was stimulated every 20 ms (Fig. 14). Similar to previous observations (Wagenaar et al. 2005), low-frequency “single-site stimulation” (i.e., exciting the same neurons with each stimulus) can enhance bursting, whereas high-frequency “multisite stimulation” (i.e., randomly changing stimulated neurons) suppresses bursting (Fig. 14).

This can be easily understood in terms of synaptic depression, since distributed stimulation in the model mainly leads to an effective reduction of overall synaptic reserves available in the network and thus prevents a recovery from depression necessary for recurrent bursting.

DISCUSSION

Recurrent synchronized activity is ubiquitous in developing neuronal networks (Ben-Ari 2001; Feller 1999). In the present
study, different input mechanisms that can lead to rhythmic and stable collective patterns of activity in purely excitatory networks were considered. The consistency of the models was investigated in cultured cortical networks. The modeled networks comprised randomly coupled excitatory leaky integrate-and-fire neurons with first-order synaptic kinetics and slow synaptic depression. Network activity was driven by bursting pacemaker neurons (IB neurons), by intrinsically random spiking neurons (ISNs), or by spontaneous synaptic activity (i.e., mEPSPs).

Numerical simulations showed that the phenomenology of the population activity of purely excitatory networks was adequately reproduced for a large volume of parameter settings and for the different input scenarios. Specifically, the burst duration (~100–1,000 ms), the range of burst frequencies (<1 Hz), the onset and decay of the firing rate during bursts, as well as the variation of the IBIs were previously observed in developing biological networks (Kamioka et al. 1996; Maeda et al. 1995; Robinson et al. 1993; Wagenaar et al. 2006). The evolution of firing rates during population bursts of simulated networks best matched cultured networks younger than 2 wk in vitro. This is expected, since beyond this developmental period the GABAergic inhibition evolves and cultured networks cannot be considered as purely excitatory any more (see below and Baltz et al. 2010). In cultured networks, indirect evidence was found that supports two of the three theoretically investigated models, namely spontaneous synaptic activity and IB cells.

Intrinsically Bursting Neurons

In theoretical studies, the need for IB cells represents a relatively strong constraint and might, therefore, often be replaced by weaker assumptions, such as membrane noise or synaptic noise. Providing experimental evidence for the presence of pacemaker mechanisms of IB cells turned out to be difficult (Opitz et al. 2002; Robinson et al. 1993). When traditional approaches are used, such as single-cell intracellular recordings, putative pacemaker cells are likely to be overlooked, since their incidence might generally be low or restricted to certain developmental periods. Even in multisite extracellular recordings of cortical cultures, IB cells were found only on a few sites and only in cultures younger than 3 wk in vitro.

Cortical neurons for the present cultures were obtained very early during embryonic development (E16) (de Lima and Voigt 1997), that is, typically 2–6 days earlier than in other studies (Chiappalone et al. 2006; Eytan and Marom 2006; Maeda et al. 1995; van Pelt et al. 2004; Potter and DeMarse 2001; Robinson et al. 1993; Shahaf and Marom 2001; Stegenga et al. 2009). A systematic study of such cultures shows that they undergo the typical developmental changes of immature neuronal networks.

Fig. 11. Change of firing characteristics in cultures during development. A and B: evolution of the firing rate during population bursts of a cultured cortical network without (A) and with (B) chronically GABA<sub>A</sub> receptor blockade obtained from 20-min recording sessions at the indicated DIV (gray: single burst; black: average). Scale bar is 1,000 spikes/s in all graphs and scaled so that the peaks of 10- to 20-DIV-old blocked networks are approximately at the same height; same scale bars in A and B for better comparison. C and D: typical shape of the averaged spike train correlogram of 1 electrode with all others from the recordings in A and B. Zero in x-axes is indicated in D.

Fig. 12. Evolution of the firing rate during population bursts and spike train correlations. A, top: each line represents the evolution of the firing rate for 1 simulation with 25% connectivity, averaged for all population bursts during a given simulation. Line color indicates fraction of IB cells (see grayscale; $g_{exc} = 0.74$ nS). Bottom: spike train correlation for simulations in A. Black bar indicates zero in the x-axes. B: same as A except for networks driven by ISNs. C: same as A except for networks driven by spontaneous synaptic activity.
including the GABA shift (see Baltz et al. 2010). Several facts point to a functional role of an IB cell type in triggering synchronized activity during the early phase of network development. First, IB cells are present in cultures obtained very early during embryonic development. Second, IB cells are active during the development, at ages when rhythmic population activity emerges (around 6 DIV). Third, bursts of action potentials generated by these types of cells are ideally suited to overcome the spike threshold of their postsynaptic targets, and, finally, IB cells were not found in cultures aged 3 wk and older in vitro.

In the model, networks with relatively weak synaptic coupling and driven by IB cells, but not networks driven by ISNs or spontaneous synaptic activity, generated population activity that was qualitatively similar to that of young (~1 wk in vitro old) cortical cultures. Higher coupling strengths and connectivity in the model networks led to very synchronized bursts with little variation. Similarly, during the development in vitro, when dendritic and synaptic maturation progresses, bursting tends to become very synchronized and stereotyped (Marom and Shahaf 2002; see also Baltz et al. 2010).

Since the incidence of IB cells was generally low, their absence in recordings from older cultures, however, does not exclude the possibility that they are still present. IB cells might lose their ability to fire recurrent burst when synaptically isolated, because intrinsic conductances that lead to rhythmic bursting in young neurons might not sufficiently compensate the decreased membrane resistance of older neurons (see, for example, Klueva et al. 2008). In older networks, then, the increased spontaneous synaptic activity could provide the depolarization necessary to reinitiate recurrent bursting in IB cells. In this scenario, IB cells are still present in older networks but do not fire recurrent bursts of action potentials when glutamatergic synaptic activity is blocked. This is compatible with the idea of “privileged neurons” (Eytan and Marom 2006).

The number of IB cells necessary to drive rhythmic network activity is expected to be lower in older cultures than in younger cultures, since dendritic and synaptic maturation increases the connectivity and coupling strength. Homeostatic regulatory mechanisms could also actively downregulate the molecular machinery leading to intrinsically rhythmic bursting of individual cells. Whether such downregulation is a consequence of rhythmic activity itself [e.g., due to high intracellular calcium (Owens and Kriegstein 2002)] or of genes that are developmentally regulated independently of electrical activity remains to be explored.

In slices of the mouse cerebral cortex, Le Bon-Jego and Yuste (2007) recently identified neurons that are regularly active in the absence of fast synaptic transmission. These cells
belonged to either a class of pyramidal neurons with a thin apical dendritic tree or a class of interneurons with ascending axons, traditionally classified as Martinotti cells (Le Bon-Jego and Yuste 2007). It is reasonable to assume that similar cell types are present in cultures of the rat cerebral cortex. The fact that putative pacemaker cells were present in the absence of fast GABAergic synaptic transmission (see Fig. 7C, inset), then, suggests that pyramidal neurons partly contribute in triggering bursting.

Random Spike Activity

In line with Gritsun et al. (2010), random spiking during IBIs was observed on a fraction of the recording electrodes. Highest rates of random spiking occurred in 3-wk-old cultures (Fig. 7). However, random spiking vanished after blockade of glutamatergic synaptic transmission (Fig. 8), suggesting that spontaneous synaptic activity is the source of excitation rather than ISNs. Spikes that persisted in the presence of synaptic blockers were either clustered in bursts (in younger cultures; Fig. 4 and Fig. 8) or occurred at very low rates (<0.1 Hz). The increasing frequency of random spiking during development would be in accordance with a developmental increase of the number of synapses and sizes of the readily releasable pools of neurotransmitter. When the neurons in a network are predominantly connected via synapses with relatively large releasable pools, the total release probability is higher compared with networks containing synapses with smaller pool sizes (Dobrunz and Stevens 1997; Dobrunz 2002; Murthy et al. 1997).

In simulated networks that were driven by spontaneous mEPSPs, all synapses were potential sources of excitation. In biological networks, however, the emergence of synapses with a high spontaneous release rate, which lead to spontaneous mEPSPs, might be guided by molecular cues limited to certain neuronal subtypes or pacemaker regions (Feinerman et al. 2007; Ham et al. 2008; Koester and Johnston 2005; Lischalk et al. 2009; Sanchez-Vives et al. 2008; Staley et al. 1998). This can lead to single “pacemaker” neurons, which fire at relatively high rates, whereas all other neurons in the network fire at very low rates (see also Fig. 8A and Fig. 9A).

Firing During Population Bursts

Using numerical simulations, Gritsun et al. (2010) recently concluded that neurons that rhythmically emit a single spike independently of synaptic transmission (termed pacemaker-like cells) best explain the evolution of the intraburst firing rates. In the present study, however, in young cortical cultures cells were found that were rhythmically active in the absence of glutamatergic and fast GABAergic synaptic transmission and typically fired in bursts, rather than single spikes. Moreover, parameters other than the input type had a severe impact on the rise and descent of the firing rate during population bursts, making it difficult to infer to the input type based on the intraburst firing properties. On the other hand, when considering the network dynamics as a whole, alternating partially and fully synchronized bursts in young (i.e., “purely excitatory”) neuronal networks, with little or no activity between burst events might be indicative of a network driven by IB cells (Fig. 2C and Fig. 4, A and B).

The relatively slower descent of the intraburst firing rate, compared with the rise, was mainly dependent on the amount of synaptic depression (see below) and the slow time constant of NMDA receptors (not considered in Gritsun et al. 2010) (see Fig. 13). In cultured networks, the decay of neuronal firing during population bursts was strongly reduced when NMDA receptors were blocked, leading to almost a 50% reduction of the burst duration (Fig. 13B). Similarly, the duration of population bursts decreased in the model when the NMDA conductance was reduced (Fig. 13B). This impact of the NMDA conductance on the burst duration was generally independent from the input mechanism.

In the theoretical studies of Tsodyks et al. (2000) and Wiedemann and Lüthi (2003), synchronized population activity was brief, with typically each neuron contributing one spike to a population event. In modeled networks, the duration of population bursts mainly depends on the amount of synaptic depression and the NMDA conductance. Synaptic depression, which may be caused by transmitter depletion (Jones et al. 2007; Staley et al. 1998), developed more slowly in the present models, resulting in population bursts with longer durations.

Regardless of the parameter settings, a clear exponential dependence between the frequency of population events and their durations was not observed. This is in line with the findings in cortical slices where such an “avalanche-like” behavior, in the case of such dependence, disappears when GABAergic inhibition is blocked (Beggs and Plenz 2003; Shew et al. 2009).

A depolarization blockade for spike generation was not explicitly introduced in the model (see Yvon et al. 2007). Yvon et al. (2007) suggested that a depolarization blockade might be a candidate mechanism for the oscillatory discharges during population bursts (see also below). Such oscillatory discharges or afterdischarges often follow an initial burst discharge within tens of milliseconds during developmental periods when bursting is already robustly established (i.e., after ~3 wk in vitro) in networks with blocked fast GABAergic transmission (Fig. 11B, 20 DIV), or, at similar ages, in networks with reduced GABA cell density (Baltz et al. 2010). In these cultures, strongest depolarization is expected, since synaptic development progressed and fast GABAergic inhibition is largely absent. A depolarization block in a number of neurons, then, might explain the “kink” in the evolution of the firing rate during population bursts (Fig. 11, A and B) after the initial discharge in extracellular recordings of older cultures with blocked GABAergic transmission, rather than a smooth decay.

External Input and Bursting Networks

It has been shown that bursting can be suppressed by distributed electrical stimulation in cortical cultures (Wagenaar et al. 2005). In simulated networks, bursting was suppressed when a significant fraction of the neurons fired at high rates (Fig. 14), as a consequence of maintained depression of a large number of the synapses. The tendency of cortical networks to burst, therefore, could be partly a result of the absent external input (see also Wagenaar et al. 2005), which, if present, could maintain a sufficient amount of depression in a large number of the synapses. This idea is compatible with the observation that rhythmic bursting preferentially is observed under conditions where external input is reduced, as in developing networks (Ben-Ari 2001), in ferret visual cortex in vivo after optic nerve transection (Chiu and Weliky 2001), and in the cortex of the...
Models for Synchronized Activity

A simple spiking neuronal network model is provided that reproduces key features of synchronized population activity of developing cortical networks. The dynamics of simulated networks driven by IB cells best matched the activity of young cortical networks (~1 wk in vitro old) and might, therefore, be a good approximation when studying the first emergence of recurrent population activity. On the other hand, in older networks synaptically dependent spikes occurred at higher rates and the network dynamics might be better explained by spontaneous synaptic activity, or a combination of spontaneous synaptic activity and IB cells. On the basis of the present data, it might be tempting to speculate that the mechanisms of synchronized network activity generation change with development in vitro from networks predominantly driven by IB cells to networks driven to a greater extent by spontaneous synaptic activity.

Slow recurrent population burst activity (<1 Hz) has also been studied beyond the context of development (Bazhenov et al. 2002; Beggs and Plenz 2003; Sanchez-Vives and McCormick 2000; Sanchez-Vives et al. 2008; Steriade et al. 1993; Timofeev et al. 2000; Tsodyks et al. 2000; Wiedemann and Lüthi 2003). The results presented here might therefore have potential relevance for more complex networks and scenarios.

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DISCLOSURES

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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