Analog-digital simulations of full conductance-based networks of spiking neurons with spike timing dependent plasticity

QUAN ZOU,1 YANNICK BORNAT,2 SYLVAIN SAÏGHI,2 JEAN TOMAS,2 SYLVIE RENAUD,2 & ALAIN DESTEXHE1

1Integrative and Computational Neuroscience Unit (UNIC), CNRS, Gif-sur-Yvette, France and 2IXL laboratory, CNRS, ENSEIRB-Université Bordeaux 1, France

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Abstract
We introduce and test a system for simulating networks of conductance-based neuron models using analog circuits. At the single-cell level, we use custom-designed analog circuits (ASICs) that simulate two types of spiking neurons based on Hodgkin–Huxley like dynamics: “regular spiking” excitatory neurons with spike-frequency adaptation, and “fast spiking” inhibitory neurons. Synaptic interactions are mediated by conductance-based synaptic currents described by kinetic models. Connectivity and plasticity rules are implemented digitally through a real time interface between a computer and a PCI board containing the ASICs. We show a prototype system of a few neurons interconnected with synapses undergoing spike-timing dependent plasticity (STDP), and compare this system with numerical simulations. We use this system to evaluate the effect of parameter dispersion on the behavior of small circuits of neurons. It is shown that, although the exact spike timings are not precisely emulated by the ASIC neurons, the behavior of small networks with STDP matches that of numerical simulations. Thus, this mixed analog-digital architecture provides a valuable tool for real-time simulations of networks of neurons with STDP. They should be useful for any real-time application, such as hybrid systems interfacing network models with biological neurons.

Keywords: Silicon neurons, analog integrated circuits, computational models, cerebral cortex, ASIC, Hodgkin-Huxley models

Introduction
Neurons of the central nervous system are characterized by specific intrinsic firing properties, which depend on the presence of voltage-dependent and calcium-dependent conductances in the membrane (Llinás 1988). In addition, central neurons interact electrically and chemically through various types of postsynaptic receptors operating over many time scales. Synaptic interactions are subject to short-term and long-term plasticity mechanisms, which depends on co-activity patterns in pre- and post-synaptic neurons (Buonomano & Merzenich 1998; Bi 2002; Frégnac 2002) and are responsible for various forms of computation (Destexhe & Marder 2004). Computational methods are needed to understand such complex systems, and various simulation softwares have been proposed to facilitate the design of computational
models of various levels of complexity. However, there are still difficult compromises to be made between the precision of the models and the computing speed that limits the model’s complexity, at the single neuron level as well as at the network level.

Here, we propose an alternative technical approach for simulating networks of neurons based on hardware real-time computation of conductance-based neuron models, where the timing intervals in neurons activity and in plasticity dynamics are strictly respected. Systems based on similar electronics architecture were presented in Vogelstein et al. (2003) and Carota et al. (2004), but they are based on integrate-and-fire neuron models and they are not specified for precise hardware real-time computation. One of our goals is to exploit our system in further architectures for building hybrid networks, where neuronal networks with plasticity dynamics will be interfaced with living neurons (see Le Masson et al. 2002 for single-cell hybrid systems). In that case, real-time processing together with a precise time-coding of the events dynamics are essential issues that need to be addressed by the system. We present such an approach through a system for mixed analog-digital simulation of full conductance-based analog artificial neurons and test this system for small networks of neurons. Part of this work has been published in a conference proceedings (Zou et al. 2004).

**Methods**

The choice of the type of model implemented on ASIC circuits was guided by several considerations. Our goal is to represent the “prototypical” types of neurons and synaptic interactions present in neocortex, in order to build large-scale networks. To this aim, we therefore need to (1) capture the main intrinsic firing and response properties of excitatory and inhibitory cortical neurons; and (2) capture the essential features of their synaptic interactions. These two aspects motivated the construction of numeric and analog models, which are detailed below and in the Appendix. All simulations were done under the NEURON simulation environment (Hines & Carnevale 1997), using the same parameters values for model and ASIC neurons.

**Model of intrinsic firing properties**

We have used conductance-based spiking neuron models to reproduce the two main neuronal types in neocortex, according to the classification of Connors & Gutnick (1990). First, by far the largest cell class in neocortex is the so-called “regular-spiking” (RS) neuron, which is excitatory and most often correlates with a spiny pyramidal-cell morphology. RS neurons fire trains of single spikes, which are characterized by a pronounced spike-frequency adaptation. Other cell types include the “intrinsically bursting” neurons, which fire stereotyped bursts of action potentials, the “fast rhythmic bursting” neurons (also called “chattering cells”), which fire bursts rhythmically, or the “low-threshold spike” neurons, which generate bursts of spikes in rebound to hyperpolarization. These cell classes represent a few percent of the recorded cells in primary sensory cortex, both in vivo and in vitro, so we did not include them for simplicity. To generate trains of spikes with adaptation, which is the typical response of RS cells to depolarizing current pulses (Connors & Gutnick 1990), we used a simple Hodgkin & Huxley (1952) type model consisting of three voltage-dependent conductances: two conductances for generating spikes ($I_{Na}$, $I_{K}$), and in addition, a slow potassium current activated by depolarization, which we call here “$I_{M}$”, and which is responsible for spike-frequency adaptation (see Appendix for equations and parameters). This model reproduces the typical firing characteristics of RS cells (Figure 1, top panels).

A second major cell class is the “fast-spiking” (FS) inhibitory neuron, which generally corresponds to aspiny neurons such as basket cells. FS cells respond to depolarizing pulses
Figure 1. Model of the two main classes of neurons in visual cortex. Top panels: model of “regular spiking” excitatory neuron. The model contained the currents $I_{Na}$ and $I_K$ responsible for spike generation, with an additional slow $K^+$ current ($I_M$) responsible for spike-frequency adaptation. These currents were simulated by Hodgkin–Huxley like models in NEURON. The model exhibited spike frequency adaptation following injection of depolarizing current pulses (left; 0.5 nA injected). The frequency–current (F/I) relation (right) represents the instantaneous firing rate (inverse of the interspike interval) as a function of spike number. Bottom panels: same paradigm for a model of “fast spiking” inhibitory neuron. Different colors indicate successive pairs of spikes (1st, 2nd, 3rd, … pairs are indicated in black, red, blue, green, orange, purple, brown, and yellow, respectively; note that colors are not visible in the bottom panel because the curves are nearly superimposed). This model contained only $I_{Na}$ and $I_K$ (see details in text).

by producing high-frequency trains of action potentials with little adaptation (Connors & Gutnick 1990). Many other intrinsic firing types have been described for cortical interneurons (Gupta et al. 2000), but these will not be included here. To model FS cells, the conductances for generating spikes ($I_{Na}$, $I_K$) are sufficient, in addition to a larger input resistance compared to RS cells (see details in Appendix). This model captures well the intrinsic firing characteristics of FS cells (Figure 1, bottom panels).

Models of synaptic interactions

The models for synaptic interactions are also conductance-based, and we chose a “kinetic synapse model” introduced previously (Destexhe et al. 1994; see Appendix for equations).
We considered the two main types of postsynaptic receptors in the central nervous system: the glutamate AMPA receptors, which mediate the fast type of excitatory interactions, and the GABA$_A$ receptors, which mediate the most common type of inhibition, and use gamma-aminobutyric acid (GABA) as neurotransmitter. A computationally efficient model was introduced to capture the conductance time course following activation of AMPA or GABA$_A$ receptors (Destexhe et al. 1994) and consists in a simple two-state (open-closed) kinetic scheme for the receptor, in which the opening is driven by a pulse of transmitter. This model was shown to correctly capture phenomena like saturation and summation, which are essential to synaptic transmission. The model was used in many studies in problems requiring one to take into account the exact time course of synaptic interactions.

Another reason for using this model is that it is readily extendable to hardware implementation (see below). In the original model, the receptor conductance increases as long as the transmitter is present, then it decays exponentially until further activation. The transmitter presence was represented by a brief (1 ms) pulse of high (1 mM) concentration of transmitter. In its hardware implementation, the model also uses pulses to activate the conductance, but in this case, instead of using stereotyped pulses, the length of the pulse is allowed to vary. Longer pulses will activate more conductance, and can therefore encode for stronger synapses or for multiple synaptic activations (see below).

Model of synaptic plasticity

We have used here a phenomenological model of spike-timing dependent plasticity (STDP), which was detailed in a previous contribution (Badoual et al. 2006). In this model, the synaptic weight between neurons $i$ and $j$, $w_{ij}$, evolves as a function of the respective timing of pre- and post-synaptic spikes ($t_j$ and $t_i$, respectively). Long-term potentiation (LTP) is obtained when the presynaptic spike precedes the postsynaptic spike, and long-term depression (LTD) is obtained in the opposite relative time interval between the two spikes. The model was adjusted such as to fit the phenomenology of STDP as observed experimentally (Bi & Poo 1998; Froemke & Dan 2002). The equations used, as well as their parameters, are described in the Appendix.

Hardware integration

To implement Hodgkin–Huxley type models on analog circuits, we designed specific analog integrated circuits (ASICs, for “application specific integrated circuits”) which exploit the intrinsic voltage-current relationships of individual transistors (bipolar and MOS) and passive elements to compute the mathematical functions present in the neurons membrane equations. These functions include voltage-dependent (or even calcium-dependent) conductances (Le Masson et al. 1999). These circuits were designed in 0.8 $\mu$m BiCMOS technology process from Austriamicrosystems (AMS) under Cadence environment. Each elementary analog function of the ASIC is specifically designed at the transistor level, including sizing of the transistors and layout drawing following the design rules of the fabrication process. Optimized analog layout procedures, like common-centroid, dummy devices, non minimum sizes and guard rings have been used to implement critical structures, to obtain processing precision despite the variations in the fabrication technological parameters. Integrated modules have a bandwidth over 10 MHz. As neural activity is composed of low frequency signals, we don’t consider switching noise. The circuit was dimensioned (transistor size, power supply, etc) so that the smallest representative electronic current (equivalent to a an ionic current, see below) is always significant towards the residual noise.
The model variables (state variables, conductances, ionic currents, membrane voltage) are identified to electrical variables in the circuit (currents, voltages). Each ionic conductance, source of an associated ionic current, and described by a set of nonlinear equations (Hodgkin–Huxley like formalism), is computed by a specific circuitry of transistors, resistors, and capacitors. Synaptic conductances can also be modeled using a similar representation, using kinetic models (see below). A current-mode translinear design approach has been chosen, to optimize the circuit design and minimize the silicon area. Conductance sub-circuits are organized as to sum the ionic currents on a membrane capacitance. As the integrated circuit dynamics strictly replicate the model’s ones, and due to the analog mode of computation, the circuit processes the model’s variables continuously and in real-time. The Hodgkin–Huxley like equations of the conductance-based models integrated on ASICs were as described in the Appendix for the currents $I_{Na}$, $I_K$, and $I_M$. Figure 2 describes the ASIC implementation of RS and FS cells, which correctly simulate the basic electrophysiological properties outlined above (see details in Saighi et al. 2005).

Synaptic conductances were described using the same open–closed kinetic scheme as outlined above (see also Appendix for equations). The main difference was that the pulse was used to encode synaptic strength as follows. First, the duration of the pulse was kept to the shortest value as possible, which was compensated by a much faster time constant for its rise time. Therefore, the synaptic conductance approached an instantaneously rising conductance, followed by an exponential decay (which would correspond to replace the term $T$ by a delta function in Equation 1). The advantage of this scheme is that doubling the duration
of the pulse in $T$ will double the peak conductance without affecting its decay, therefore performing a quasi-instantaneous summation. Using such a scheme, one can therefore implement “multisynapses” using a very compact circuit, in which presynaptic spike events are collected, and the duration of the pulse of $T$ is calculated accordingly at each time.

Networks were implemented by using a mixed analog-digital architecture in which all membrane equations including synaptic integration are solved by analog ASIC circuits, while the connectivity is managed by a digital interface (Bornat et al. 2006; see data flow chart in Figure 3). The neural activity and the presynaptic information are digitally coded; the digital interface reads the neuron’s activity (spikes), and dispatches it as inputs to other neurons according to the programmable connection matrix. This scheme was implemented through a PCI board that support the ASIC circuits, and runs through a fixed-period loop ($<100 \mu s$) during which digital signals are updated. This loop was implemented as follows: first, the computer reads the binary output signals from the PCI board, giving which presynaptic neurons fired; second, it determines which postsynaptic neurons (according to the connection matrix) must receive a presynaptic event; third, it computes the transmitter pulse durations according to plasticity rules and respective spike times; fourth, it writes the binary input signals to the PCI board according to pulse durations; fifth, it waits for an interrupt signal from the PCI board to start the next cycle. This circuitry has been dimensioned to process a 8-bit resolution in the pulse width. The quantum ($1/256$ of the $100 \mu s$ clock period) in the pulse width corresponds to the synaptic conductance quantum (minimum conductance step). When processed as a current in the analog circuit, this quantum is still significant when compared to the estimated signal-to-noise ratio.

Figure 4 illustrates a simple case of three presynaptic neurons connected to a single postsynaptic cell (Figure 4A). The connections were managed by the digital interface as described...
Figure 4. Synaptic interactions in the analog–digital simulator. A. Scheme of the connections realized in a simple network with 3 presynaptic RS cells (top), connected to a postsynaptic RS cell (bottom) via excitatory synapses (arrows). B. Simulation showing the excitatory postsynaptic potential (EPSP) generated by the three presynaptic RS neurons (top traces) on the postsynaptic RS neuron (bottom trace). The simulation shows the EPSP generated either by a single presynaptic spike (1), or by the summation of two presynaptic spikes (2). Both were subthreshold for generating action potentials in the postsynaptic neuron. C. Similar arrangement, but in this case the summation of three nearly-simultaneous action potentials in the presynaptic neurons generated a spike in the postsynaptic neuron (3). All traces were measured directly in the circuit using an oscilloscope (voltage values indicated are real voltage on the ASIC circuit).

above, and the circuit could simulate the summation of EPSPs arising from presynaptic cell firing (Figure 4B–C).

Thus, this analog-digital system can manage in real time networks of Hodgkin–Huxley like spiking neurons, connected with conductance-based excitatory and inhibitory synapses. These synapses can be subject to complex (spike-timing dependent) plasticity rules (see
Results). The main advantage of this analog-digital system is flexibility: different types of connectivity can be tested, as well as different types of plasticity rules, which are all managed by the digital interface. The system can also be used to implement probabilistic release and short-term plasticity (not shown). All the operations performed by the digital interface are elementary and can be optimized, for example by reporting it (completely or partially) on digital hardware. Therefore, we expect that large networks of neurons can be managed by such a system, depending on the processor speed, and the capacity of producing and assembling large numbers of neurons in hardware. We report here the results obtained using a prototype system of 8 neurons.

Results

As detailed in the Methods, the ASIC circuits implemented Hodgkin–Huxley like models of RS and FS cells (see Figure 1 for models, and Figure 2 for direct measurements on the ASICs). The synaptic interactions were handled by a digital interface which can be used for managing synaptic inputs in neurons, either arising from external inputs, or from other neurons (see Figure 4). We tested the analog-digital ASIC system by successively considering single neurons, or circuits consisting of 2-neurons, 3-neurons or 8-neurons interconnected with plastic synapses (Figure 5). In each case, we compared numerical simulations with the ASIC neuron implementations. We describe these different experiments below.

Single-neuron experiments

We first tested the frequency response of single neurons submitted to random background noise. An RS neuron (Figure 5A) was submitted to random (Poisson-distributed) excitatory synaptic inputs according to defined mean input rates. The neuron occasionally fired, as shown by the raster plots in Figure 6. The ASIC circuits behaved remarkably similar to the model (ASIC in Figure 6). The mean firing frequency was estimated for different input rates. Comparing the model and the ASIC circuits shows that the two can match remarkably well in some cases (Figure 6A), whereas in other cases the model tended to fire at lower...
Figure 6. Firing properties of a single neuron bombarded by random synaptic inputs. A. Neuron 4 on board was bombarded by Poisson-distributed random excitatory (AMPA) synaptic inputs at different firing rates, with maximal conductance of 100 nS. Neuron 4 was setup as a “weakly adapting” RS cell ($g_M = 45.5 \mu S/cm^2$; MD00 on board). Both ASIC (left) and model (middle) simulation were run for 10 seconds under each bombardment, and split into 10 traces to form a raster plot against time. Right panel: firing frequency as a function of input rate. The firing frequency was averaged by spike counting during the simulations, and represented as a function of the mean input rate of the synaptic bombardment. The frequency response of ASIC (circles) was very close to that of the model (squares). B. Same simulation as A, with Neuron 4 set as a “strongly adapting” RS cell ($g_M = 181.8 \mu S/cm^2$; MD11 on board). In this case, the frequency response of the ASICs (right panel, circles) was higher than that of model (squares).

frequencies (Figure 6B). This is most likely caused by the adaptation conductance ($g_M$), which is preset on the board, and which was probably smaller than the value used in the model.

Figure 6 also shows that the exact timing of spikes is not identical between model and ASIC neurons. An example of spike train is given in Figure 7A, comparing the numeric model with its ASIC implementation, using the same random synaptic background activity. To further quantify this difference, we have computed the cross-correlograms between similar traces for different values of the rate of AMPA inputs (Figure 7B). The correlations peaked at 0.02–0.03, demonstrating that although their mean firing rate was similar, ASIC and model neurons did not produce spikes at the same time, which is presumably due to the dispersion of parameter values implemented in the ASICs (see below). Note that this evaluation concerns the strict replication of digital simulation by analog simulations and not the precise timing capabilities of the system. As explained in Methods, events are precisely timed in this system, which allows one to use spike-timing dependent plasticity (STDP) paradigms, as investigated below.
Figure 7. The precise timings of spikes is not emulated by analog neurons. A. Two example spike trains from a simulated RS neuron (top) and an analog RS neuron (bottom), submitted to the same random background activity (same settings as in Figure 6A; 5 Hz). Although they received the same random synaptic conductances, the exact spike timings was different in numeric and analog models. B. Cross-correlograms calculated from numeric and ASIC RS neurons, shown for different rates of Poisson-distributed random synaptic (AMPA) inputs (1 Hz to 10 Hz, from bottom to top). Both ASIC and model simulations were run for 10 seconds under each bombardment, and used the same pre-generated random inputs. Pearson cross-correlations were calculated using a time bin of 50 ms. The maximal amplitude was of about 0.02–0.03, indicating that the precise timings of spikes was in general different in ASIC and model simulations.
2-neuron circuit experiments

Next, we considered two-neuron circuits with synapses subject to STDP, as illustrated in Figure 5B. First, we investigated a circuit consisting of two excitatory (RS) neurons, receiving random synaptic bombardment as above, and inter-connected with excitatory synapses subject to STDP. The spiking activity in this circuit induced changes of synaptic weights, according to the STDP rule, such that synaptic weights converged to a steady-state independent of the initial conditions given to synaptic weights (Figure 8, Model). This convergence dynamic was well reproduced by the 2-neuron system simulated on ASIC circuits (Figure 8, ASIC). Variations of different parameters such as the average frequency of the random excitatory drive did not affect this matching of model and ASIC circuits (not shown). On the other hand, varying the dynamic range of STDP (parameter $\omega_{LTP}$) revealed differences between the two implementations (Figure 9). In the ASIC circuit, the synaptic weights converged to different values for $\omega_{LTP} > 80$ nS (Figure 9A, left), which was paralleled by differences in average firing frequency of the two ASIC neurons (Figure 9A, right). Such a difference was not present in the model when the two neurons were identical (Figure 9B). However, if variations in parameters (emulated here by choosing slightly different values of the voltage-dependent currents) were introduced in the model, such as to match the difference in firing frequency (Figure 9C, right), the synaptic weights converged towards similar values as in the ASIC circuit (Figure 9C, left). These simulations show that dispersion of the values implemented on analog circuits may have an impact on the synaptic weights, and that this can be captured by introducing dispersion in the model.

Second, we considered a circuit consisting of one excitatory (RS) and inhibitory (FS), interconnected with excitatory and inhibitory synapses (see Figure 5B, right). In this case, only the excitatory synapse was subject to STDP. We used the same paradigm as above and found a similar agreement between ASIC and model circuits. Figure 10 shows that, in this case, the effect of dispersion of parameters was minimal on the final value of synaptic weights. The matching between model and ASIC circuits was excellent (compare left panels in Figure 10A, B), although there were differences in the mean firing rate (Figure 10A, B, right panels). Inclusion of dispersion in the model to match the values of firing rates of the
Figure 9. Effect of dispersion of parameters on the final value of synaptic weights. A. Left: final value of synaptic weights obtained for different maximal values of the maximal synaptic weight. Same simulation as in Figure 8 with $\omega_{\text{LTP}}$ of 40, 80, 120, 160 and 200 nS. The initial weight was half that value. Right: mean discharge frequency of the two neurons during these simulations. B. Same arrangement and parameters using the model with 2 identical RS neurons. C. Same simulation as in B, but the parameters were adjusted to match the differences found in the circuit (A, right). In the latter case, the final synaptic weight (left) matched that of the ASIC simulations.

ASIC circuits (Figure 10C, right) resulted in values of synaptic weights which were in equally good match with the ASICs (Figure 10, left). Thus, in this case, the effect of dispersion was not so critical, presumably due to the presence of inhibition, and the matching of the model with the ASICs was also excellent.
Figure 10. Convergence between model and ASIC circuits for a RS-FS 2-neuron circuit. Same description as for Figure 9, but for a circuit consisting of one RS cell connected to one FS cell (Figure 5B, right). Only the RS-to-FS excitatory synapse was subject to STDP. A. Left: final value of the synaptic weight obtained for different maximal values of the maximal synaptic weight ($\omega_{LTP}$ of 40, 80, 120, 160 and 200 nS; initial weight was half that value). Right: mean discharge frequency of the two neurons during these simulations. B. Same arrangement and parameters using the model. C. Same simulation as in B, but the parameters were adjusted to match the differences found in the circuit (A, right).

3-neuron circuit experiments

Next, we considered a three-neuron circuit consisting of two RS neurons connected with one FS neuron (see scheme in Figure 5C). In a first set of simulations, we investigated this circuit when only the RS–RS excitatory synapses were subject to STDP (Figure 11). The results
Figure 11. 3-neuron circuit with plasticity on excitatory synapses between RS neurons. Two excitatory (RS) neurons and one inhibitory (FS) neuron were connected according to the scheme of Figure 5C. All neurons were bombarded by independent excitatory and inhibitory Poisson random background activities at an input rate of 20 Hz, with maximal conductance of 100 nS and 50 nS, respectively. Only the excitatory synapses between RS neurons were subject to STDP. The dynamic range of all synaptic weights was changed by changing the maximal value of synaptic weight ($\omega_{\text{LTP}}$; values used here: 40, 80, 120, 160 and 200 nS; $\omega_{\text{LTD}} = 0$). The initial weight was half that value. A. Left: final value of the two synaptic weights obtained for different maximal values of the maximal synaptic weight ($\omega_{\text{LTP}}$; values used here: 40, 80, 120, 160 and 200 nS; $\omega_{\text{LTD}} = 0$). Right: mean discharge frequency of the two neurons during these simulations. B. Same arrangement and parameters using the model in which the 2 RS neurons were identical. C. Same simulation as in B, but the parameters were adjusted to match the differences found in the circuit (A, right). In the latter case, the final synaptic weight (left) matched that of the ASIC simulations.
obtained were qualitatively similar to the 2-neuron RS–RS circuit of Figure 9. Differences between the model and ASIC circuits were paralleled with differences of mean discharge activity (Figure 11A,B). These differences were minimized when dispersion was taken into account (Figure 11C).

In a second set of simulations, we considered the same circuit in which only the excitatory synapses from RS to FS were subject to STDP (Figure 12). In this case, the final synaptic weight was weakly sensitive to the activity and dispersion of individual neurons.

Figure 12. 3-neuron circuit with plasticity on excitatory synapses between RS and FS neurons. Same arrangement as Figure 11, except that the excitatory synapses from RS to FS were subject to STDP, while the RS–RS synapses were fixed. In this case, the final value of synaptic weight was weakly sensitive to the activity and dispersion of individual neurons.
weight were similar between ASIC and model circuits (Figure 12A, B, left panels) despite strong differences in mean firing activity (Figure 12A, B, right panels). Including dispersion to match this activity (Figure 12C, right) resulted in a slightly better matching between the two implementations (Figure 12C, left). These results are very similar to the RS–FS circuit investigated in Figure 10, and suggest that the value of synaptic weight at RS-to-FS synapses is robust to variations of mean level of activity in the network. This dynamics and its difference with RS–RS synapses, are well captured by ASIC circuits.

8-neuron circuit experiments
Finally, we investigated the behavior of the 8-neuron circuit, with 6 RS and 2 FS cells, as displayed in Figure 5D. We used a paradigm similar as above, in which neurons were subject to random synaptic inputs in addition to recurrent synapses from other neurons in the network. STDP was applied to the excitatory synapses from RS to FS cells, and their steady-state synaptic weight is represented in Figure 13 as a function of the input rate. The agreement between the ASIC and model neurons was remarkable, for the whole range of inputs considered. Figure 13A (right) indicates the mean firing rate of the different neurons during these simulations. The 8 neurons in the ASIC circuit displayed a considerable variability in their frequency response, presumably due to dispersion in their parameters. In a model with identical neurons, the frequency responses were stereotyped for RS and FS cells (Figure 13B, right). Despite these differences, the synaptic weights converged to similar values (compare left panels in Figure 13A and B), although the ASIC circuits displayed more variability. We attempted to reproduce this variability in the model (Figure 13C, right), which resulted in a slight increase of variability in the synaptic weights (Figure 13C, left). However, we could not fully emulate the variability found in the ASIC circuits, in particular for the two neurons displaying non-monotonic behavior. Despite these differences, the behavior of the 8-neuron ASIC circuit was remarkably similar to that of the model.

Discussion
We have shown here the first results from a prototype analog–digital system for simulating networks of conductance-based neuronal models. The rationale for building such a system is that real-time simulation of networks of conductance-based models is difficult to achieve using conventional workstations. Real-time simulations are needed in various paradigms, for example to perform real-time analysis of natural environment (such as vision, audition, etc.), or for building hybrid systems involving the interaction between a network of artificial neurons and real neurons (see for example Le Masson et al. 2002).

Characteristics of the system
The system investigated here was based on specific analog integrated circuits (ASICs) which design principles were previously validated for the simulation of Hodgkin–Huxley like models (Le Masson et al. 1999). These ASIC circuits were modified to incorporate conductance-based synaptic inputs inspired from a previous pulse-based model of synaptic conductances (Destexhe et al. 1994), and which can handle the integration of multiple convergent inputs as well as modulations of their synaptic weight. The system was conceived such as its inputs and outputs can be digitally coded (time-stamped spike events) and can be managed by a computer interfaced with the ASICs. Thus, a PCI board containing the ASICs can be interfaced easily with a conventional PC computer to form the analog-digital network simulator investigated here.
Figure 13. Steady-state synaptic weights and firing rates in ASIC and model 8-neuron circuits. 8 neurons were connected as in Figure 5D, using weakly-adapting RS cells and STDP at excitatory synapses from RS to FS cells. Each cell was subject to random synaptic activity, with a mean excitatory input rate which was varied from 10 to 100 Hz, while the inhibitory input rate was fixed at 20 Hz. The STDP rule was applied at 12 AMPA synapses during 50 seconds simulation time. After transients, the steady-state synaptic weight and firing rate was calculated at each synapse by averaging over the last 30 seconds. A. Steady-state synaptic weight (left) and rate (right) exhibited by ASIC circuits, for different values of the excitatory input rate $\gamma_{\text{AMP}}$. B. Same description for a model circuit with the same values of parameters, and in which all RS neurons were identical. C. Model in which the properties of RS and FS neurons were dispersed in order to create cell-to-cell variability comparable to ASIC circuits.
Similar strategies are currently developed in other laboratories. Simoni et al. (2004) recently developed a multi-conductance silicon neuron (6-conductances, fixed parameters), as stand-alone units. They plan to use it to build hybrid networks to study the role of central pattern generators in rhythmic motor patterns. Oster et al. (2005) currently develop neuromorphic VLSI, organized as reconfigurable networks of spiking neurons. The general principle is that large arrays of imprecise processing elements can cooperate to provide robust real-time computation in complex problems. Concerning the mixed analog–digital simulation platform, systems with a closed architecture were developed, exploiting analog neuron model as a computational core inserted in digitally computed neural networks (Vogelstein et al. 2003; Carota et al. 2004). The hardware and software characteristics, as well as the goal of those systems are different from ours: (1) the neuron models are integrate-and-fire models; (2) most of those systems use address-event representation to code the network activity, with priority encoding; (3) the simulated networks are large networks with internal hierarchy, and plasticity is limited to pre-defined synaptic connections; (4) real-time processing in not a specification of those systems; real-time is eventually attained on the global simulation duration, but not ensured at the spike level. As we discuss below, the system we designed has different features: it computes conductance-based models, codes the network activity by time-stamped events, allows all-to-all plastic connectivity, and simulations run in real-time even for the smallest dynamics (100 μs).

In the prototype system investigated here, all the network connectivity is software computed: the connectivity (detect pre-synaptic spikes and apply it on the post-synaptic neurons inputs) and plasticity mechanisms (modification of synaptic weights). As described above, the hardware circuits compute the synaptic conductances and the neurons membrane voltage. Each spike of a neuron is an event, which results in an automatic update by the software of the related synaptic weights, via the PCI interface. The spiking events are sampled at high frequency (here 10 kHz), and time-stamped to ensure hard real-time for the simulation. The system cannot process more than one event per synapse during each sampling period. Two simultaneous events (in the same time window) are processed serially. This principle (communication between software and hardware each 100 μs) limits the size of the network, i.e., the number of neurons combined with the number of synaptic connections. In the present (non optimized) configuration, using a Pentium-4 2.6 GHz processor, connectivity and plasticity are both calculated by the processor, and the limit is between 20–40 plastic synapses with STDP (depending on the complexity of the STDP algorithm). If no plasticity is to be computed by the processor, the limit of number of synapses that can be handled in real time is about 1000. We are presently working on optimizing the system such that both STDP and connectivity are calculated on the board (by FPGA or embedded dedicated processor). In this case, one expects that much larger (probably two orders of magnitude) plastic synapses can be calculated in real time, depending on the level of activity of the system. In addition, the input signals to the synapses could be more elaborate than one bit, for example sending to each synapse from 1 to 8 “quanta”, so that several events could be processed simultaneously. We are presently studying these different alternatives for a second generation system. In any case, the software part will always be necessary to provide a user interface, store the data and supervise the whole system.

Applications of the system

As outlined above, one of the main advantage of building real-time networks of conductance-based neurons is that any real-time paradigm can be simulated with no need to simplify the
model network in order to match the requirements of real time. Conductance-based models provide a greater biophysical realism compared to simplified representations (such as the integrate and fire model), and they capture the dynamics of spike threshold, threshold variations, refractory period, etc. Combined with conductance-based synapses, these properties may be important for spike selectivity and timing (Azouz & Gray 2000; Wilent & Contreras 2005), therefore this system could be used in principle for relatively complex paradigms where these properties would be important. In addition, conductance-based models are required for interfacing real neurons through intracellular recordings (dynamic-clamp), which is another possible applications of such a system.

Before starting such applications, however, it is necessary to test the system, which was the primary goal of this paper. We tested the system by considering models of increasing complexity, starting with single-neuron experiments. Single ASIC neurons, stimulated with either current pulses (Figure 2) or random conductance-based synaptic inputs (Figure 6), behaved very similarly to computer simulations of the corresponding numerical simulations. Simple circuits were then constructed by incorporating a relatively complex form of plasticity, which depends on the respective timing of the spike in pre- and post-synaptic neurons (STDP). An excellent match was found both for the general behavior of the circuit, as well as for the values of synaptic weights after convergence (see Figures 8–13). In particular, we found that the values of synaptic weights depended on the activity, and could be sensitive to differences of activity due to the dispersion of parameters on the ASIC circuits (see Figures 9 and 11). Incorporating a similar dispersion in the models led to values consistent with those obtained in the analog-digital system. On the other hand, excitatory synapses on inhibitory neurons show a larger robustness to the dispersion of activity in the network (Figures 10, 12 and 13). In this case, as expected, the agreement with the numeric model was excellent even if no dispersion was taken into account. Finally, we found that the values to which synaptic weights converged were robust although the ASIC circuits did not precisely replicate the spike timings of the model. This interesting result constitutes another indication supporting the relevance of such analog circuits to spike-timing based computation.

We conclude that the prototype system presented here can successfully simulate relatively complex paradigms involving conductance-based models of neurons and synapses, as well as spike timing-dependent plasticity mechanisms. Future work should investigate to what extent the dispersion of values in the circuit can predict population activity in larger networks, and perhaps even be exploited to simulate the diversity of neuronal properties found experimentally (for example, see Gupta et al. 2000). We are presently conceiving a system capable of handling larger numbers of neurons, still based on the same analog–digital strategy, for which the goal is to simulate in real time large networks of neurons of up to several hundred neurons.

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References

Appendix: Model equations

Models of voltage-dependent currents

The voltage-dependent ionic currents were implemented on ASIC circuits following a formalism very similar to the model of Hodgkin & Huxley (1952). Ionic currents depend on activation and inactivation variables, each described by a first-order differential equation with voltage-dependent rate constants. The steady-state activation and inactivation functions are
described by sigmoidal functions of voltage, identically to the Hodgkin–Huxley (HH) equations. The difference with the HH equations is that the time constants of these activation variables are either constant, or vary as step-like functions of voltage. Although this represents an approximation of HH equations, this type of model shows several fundamental properties typical of HH models: Na$^+$ and K$^+$ conductance changes associated to spikes, spike threshold variations, refractoriness, repetitive firing, etc. The reason is that the time constants do not vary much before the spike, so the HH dynamics is pretty well approximated by a model with fixed (or step-like) time constants (if they are chosen within the appropriate range of values). However, during the spike, time constants experience drastic changes, which will not be correctly captured by this model, resulting in unrealistic spike shapes. Thus, this HH-like model will be appropriate to capture any type of single-cell or network interaction where spike shapes are not critical.

The model equations implemented in both numerical simulation and analog circuits were as follows:

$$C \frac{dV}{dt} = -\sum(I_{ion}) + \sum(I_{ext}),$$

where $I_{ion}$ are the ionic currents, $I_{ext}$ the synaptic and stimulation currents. These currents were described by:

$$I_{ion} = \bar{g}_{ion} m^\alpha h^\beta (V - V_{EQ})$$

$$\tau_m(V) \frac{dm}{dt} = m_\infty(V) - m$$

$$m_\infty(V) = \frac{1}{1 + \exp\left(-\frac{V - V_{OFFSETm}}{V_{SLOPEm}}\right)}$$

$$\tau_h(V) \frac{dh}{dt} = h_\infty(V) - h$$

$$h_\infty(V) = \frac{1}{1 + \exp\left(\frac{V - V_{OFFSETh}}{V_{SLOPEh}}\right)}$$

Due to electronics technical constraints, the area of the integrated cells is 0.00022 cm$^2$, which corresponds a value for the membrane capacitance of $C_{MEM} = 1 \mu F/cm^2$.

The membrane equation of excitatory (RS) neuron models is given by:

$$C_{MEM} \frac{dV}{dt} = -I_{Na} - I_K - I_M - I_{STIM} - I_{SYN}$$

with the following parameters:

$I_{LEAK} = g_{LEAK}(V - V_L)$:

$$g_{LEAK} = 0.00015 S/cm^2, \quad C_{CMDL} = '1' \to V_L = -80 mV$$

$I_{Na} = g_{Na} m^3 h (V - V_{Na})$:

$$g_{Na} = 0.05 S/cm^2, \quad V_{Na} = 50 mV$$

$$m: V_{OFFSET} = -37 mV, \quad V_{SLOPE} = 7.2 mV$$

$$h: V_{OFFSET} = -42 mV, \quad V_{SLOPE} = -4.6 mV$$

$$\tau_m = 0.03 ms, \quad \tau_h \begin{cases} V > 0 \to \tau_h = 3 ms \\ V < 0 \to \tau_h = 0.25 ms \end{cases}$$
\[ I_K = g_K n^4 (V - V_K) : \]
\[ g_K = 0.005 \text{ S/cm}^2, \quad V_K = -100 \text{ mV} \]
\[ n : V_{OFFSET} = -37 \text{ mV}, \quad V_{SLOPE} = 11.38 \text{ mV} \]
\[ h : V_{OFFSET} = -42 \text{ mV}, \quad V_{SLOPE} = -4.6 \text{ mV} \]
\[ \tau_n = 3 \text{ ms}, \]
\[ I_M = g_M m (V - V_K) : \]
\[ g_M : \]
\[ \begin{align*}
'00' & \rightarrow 45.5 \mu \text{S/cm}^2 \\
'01' & \rightarrow 90.9 \mu \text{S/cm}^2 \\
'10' & \rightarrow 136.8 \mu \text{S/cm}^2 \\
'11' & \rightarrow 181.8 \mu \text{S/cm}^2 \\
\end{align*} \]
\[ m : V_{OFFSET} = -35 \text{ mV}, \quad V_{SLOPE} = 11.4 \text{ mV} \]
\[ \tau_m : \]
\[ \begin{align*}
V > 0 & \rightarrow \tau_m = 300 \text{ ms} \\
V < 0 & \rightarrow \tau_m = 8 \text{ ms} \\
\end{align*} \]

The membrane equation of inhibitory (FS) neuron models is given by:
\[ C_{MEM} \frac{dV}{dt} = -I_{Na} - I_K - I_{STIM} - I_{SYN} \]

with the same parameters as for the RS model, except for:
\[ I_{LEAK} = g_{LEAK} (V - V_L) : \]
\[ g_{LEAK} = 0.0001 \text{ S/cm}^2, \quad C_{CMDL} = '0' \rightarrow V_L = -70 \text{ mV} \]
\[ I_K = g_K n^4 (V - V_K) : \]
\[ g_K = 0.001 \text{ S/cm}^2 \]

Models of synaptic currents

Synaptic currents were are described by a simple open-closed kinetic scheme for synaptic receptors (Destexhe et al. 1994). The postsynaptic current is given by:
\[ I_{SYN} = g_{MAX} r (V - E_{SYN}) \]
\[ \frac{dr}{dt} = \alpha [T] (1 - r) - \beta r, \]

where \( g_{MAX} \) is the maximal conductance, \( E_{SYN} \) the reversal potential, \( V \) the post-synaptic membrane potential, \( r \) the fraction of receptors in open state, \( \alpha \) and \( \beta \) voltage-independent forward and backward rate constants, \([T]\) the transmitter concentration. When a spike occurred in the presynaptic neuron, a pulse of transmitter was triggered such that \([T] = 1 \text{ mM}\) during 1 ms.

The integrated values were as follows:

excitatory synapse: \( \alpha = 1.1 e^6 \text{ M}^{-1}\text{s}^{-1}, \beta = 190\text{s}^{-1}, E_{SYN} = 0 \text{ V}, g_{MAX} = 0.1 \text{ mS}; \)
inhibitory synapse: \( \alpha = 5 e^6 \text{ M}^{-1}\text{s}^{-1}, \beta = 180\text{s}^{-1}, E_{SYN} = -80 \text{ V}, g_{MAX} = 0.05 \text{ mS}. \)
The synaptic weight of excitatory synapses from RS to FS was 0.01 mS, and for inhibitory synapses from FS to RS, it was 0.005 mS. During the simulation, input background noise for each neuron was loaded from a set of pre-calculated independent Poisson random processes.

**Models of synaptic plasticity**

The time evolution of the synaptic weight between neurons $i$ and $j$, $w_{ij}$, is given by:

$$\frac{dw_{ji}}{dt} = -\varepsilon^\text{pre}_j \varepsilon^\text{post}_i \sum_{t_i} P\left(t - t^\text{last}_j(t)\right) \delta(t - t_i) + (w_{ji} - w_{LTP}) \times \sum_{t_j} Q\left(t - t^\text{last}_i(t)\right) \delta(t - t_j),$$  \hspace{1cm} (2)

where the functions $P$, $Q$ and $\varepsilon$ express the potentiation or depression as a function of the respective timing of pre- and post-synaptic spikes ($t_j$ and $t_i$, respectively). These functions are given by:

$$P(t) = \exp\left[-\frac{t(t)}{\tau_p}\right], \quad Q(t) = \exp\left[-\frac{t(t)}{\tau_q}\right]$$

$$\varepsilon(t) = 1 - \exp\left[-\frac{t(t) - t^\text{last}_i(t)}{\tau_s}\right]$$

in which, $\tau_p = 14.8$ ms, $\tau_p = 33.8$ ms, $\tau_i^\text{pre} = 28$ ms, $\tau_i^\text{post} = 88$ ms, $w_{LTD} = 0$, $w_{LTD} = 2 \times \bar{g}_{max}$. The function $t^\text{last}_i(t)$ gives the time of the last spike that occurred in neuron $i$ at time $t$ (see details in Badoual et al. 2006).

This type of STDP rule, characterized by “soft bounds” (terms $w_{ji} - w_{LTP}$ and $w_{ji} - w_{LTD}$), contrasts with the “hard bounds” proposed in previous models (Song et al. 2000).