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Transition from initialization to working stage in biologically realistic networks

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Abstract. Natural cortical neurons form functional networks through a complex set of developmental steps. A key process in early development is the transition of the spontaneous network dynamics from slow synchronous activity to a mature firing profile with complex high-order patterns of spikes and bursts. In the present modeling study we investigate the required properties of the network to initialize this transition by the shift of the chloride reversal potential, which switches the effect of the GABA synapses from depolarizing to hyperpolarizing. The simulated networks are generated by a statistical first-order description of parameters for the neuron model and the network architecture.

1 Introduction

When observing the maturation process of neocortical networks, different stages with different dynamic behavior can be identified. During an early, experience-independent phase of network development, the immature networks generate slow spontaneous rhythmic activity, that stabilizes the network and prepares it for the later information processing with structural and functional consequences [1, 2, 3, 4]. The transition from this synchronous to working phase starts if sensory signals input into the network [5], the synchronous activity dissolves and the mature firing activity start with complex high-order patterns of spikes and bursts [4]. The specific mechanism behind this is unclear, but it is known that in this time period, the effect of the GABA neurotransmitter changes from depolarizing to hyperpolarizing. This "GABA shift" is due to the change of the chloride reversal potential, caused by the developmental decrease of the intracellular chloride concentration [6]. In this modeling study we discuss the question if this transition from one dynamical behavior into another can be controlled by only one parameter. With a biologically realistic model of a dissociated network with neocortical neurons under standard culture conditions generated by statistic parameters, the network properties and dynamics are analyzed.

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2 Methods

2.1 Neuron model

We use the neuron model by Izhikevich [7, 8], which reduces the biophysically accurate Hodgkin-Huxley model to a two-dimensional system of ordinary differential equations:

$$\dot{v} = 0.04v^2 + 5v + 140 - u - I_{syn} + I_{intr}, \quad (1)$$

$$\dot{u} = a\,(bv - u)\,. \quad (2)$$

Where v is the membrane potential, u is a recovery variable and a, b, c, d are the dimensionless model parameters, which allow to tune the model to different dynamics (see [7] for details). The intrinsic current I_{intr} is a stochastic component which drives the spontaneous activity of the neurons. If v reaches a threshold of 30 mV, a spike is generated and all variables are reset:

$$v \leftarrow c \quad (3)$$

$$u \leftarrow u + d \quad (4)$$

We use two different types of neurons: excitatory (glutamaergic) neurons and inhibitory (GABAergic) neurons. According to the simulations in [8], the excitatory neurons are simulated with parameters $(a, b) = (0.02, 0.2)$ and $(c, d) = (-65, 8) + (15, -6)\,r^2$, where r is uniformly distributed on the interval $[0, 1]$. Its behavior is between regular spiking (RS, $r = 0$) and intrinsically bursting (IB) and chattering (CH, $r = 1$). The square of r, (r^2), biases the distribution towards the RS cells. The parameters of the inhibitory neurons are set to $(a, b) = (0.02, 0.25) + (0.08, -0.05)\,r$ and $(c, d) = (-65, 2)$. The resulting behavior is between low-threshold spiking (LTS, $r = 0$) and fast spiking (FS, $r = 1$). The standard integration time step is 0.1 ms.

2.2 Synapse Model

To implement depression and facilitation, we use a dynamic synapse model [8], in a modified mathematical formulation, which is independent from the time step:

$$\dot{R} = (1 - R)/D, \quad (5)$$

$$\dot{w} = (U - w)/F. \quad (6)$$

with the parameters U, F and D. On each spike, which is received by the postsynaptic neuron, after the transmission delay, the variables R and w will be updated:

$$R \leftarrow R + Rw, \quad (7)$$

$$w \leftarrow w + U(1 - w). \quad (8)$$

The parameters depend on the type of presynaptic neuron: For excitatory neurons the parameters are set to $U = 0.5$, $F = 1000$ and $D = 800$ and for inhibitory neurons are set to $U = 0.2$, $F = 20$ and $D = 700$. In contrast to [8], the depression R acts as gating variable. If $R < U$, the synapse is affected by the depression, no spike will be transmitted, and the (R, w) system (eq. 7, 8) is not updated, which assumes, that a minimum of available transmitter of U is required to transmit a spike.

The synaptic current of the neuron j is:

$$\begin{aligned} I_{syn} &= g_{AMPA}\,(v-0) \\ &\quad + g_{NMDA}\left(\frac{(v+80)/60}{1+(v+80)/60}\right)(v-0) \\ &\quad + g_{GABAa}\,(v - e_{GABAa}) \\ &\quad + g_{GABAb}\,(v - e_{GABAb}) \end{aligned} \tag{9}$$

The reversal potential of the GABAergic synapses are shifted from $e_{GABAa} = -30mV$ and $e_{GABAb} = -40mV$ to $e_{GABAa} = -70mV$ and $e_{GABAb} = -90mV$ during the simulation (see Results), thus switching the synaptic effects from excitatory to inhibitory.

The conductance changes by first-order linear kinetics. $\dot{g}_k = g_k/\tau_k$ with time constants $\tau_k = 5$, 150, 6 and 150 ms for the simulated $AMPA$, $NMDA$, $GABAa$ and $GABAb$ receptors, respectively [8]. The rising time of currents is typical short and neglected. The transmission delay depends on the Euclidean distance of neurons (velocity 0.5 m/s). All synapses have an additionally latency of 0.5 ms [9].

If a spike is received by the postsynaptic neuron j, the conductances are updated depending on the type of presynaptic neuron:

$$g_{AMPA} \leftarrow g_{AMPA} + r_{AMNM} \cdot c_{ij}, \tag{10}$$

$$g_{NMDA} \leftarrow g_{NMDA} + (1 - r_{AMNM}) \cdot c_{ij}, \tag{11}$$

$$g_{GABAa} \leftarrow g_{GABAa} + r_{gaba} \cdot c_{ij}, \tag{12}$$

$$g_{GABAb} \leftarrow g_{GABAb} + (1 - r_{gaba}) \cdot c_{ij}, \tag{13}$$

where c_{ij} is the synaptic weight, $r_{AMNM} = 0.9$ is the relation of $AMPA$ and $NMDA$ channels and $r_{gaba} = 0.9$ is the relation of $GABA_a$ and $GABA_b$ channels. The synaptic weights c_{ij} are set in respect to source and destination neuron (see table 3).

2.3 Neuron placement and connections

A *network section* of $n_{glut} = 400$ glutamatergic neurons and $n_{GABA} = 100$ GABAergic neurons was assembled, arranged on the planar area of 1 x 1 mm^2, as a simple representation of a standard neocortical culture. The neurons were connected by a set of statistical connection methods [10, 11] in such a way that each neuron has a local cluster and a displaced cluster. The local cluster

connects the cell only in the immediate neighborhood. The probability to connect a cell a on position $\mathbf{x}_a$ with a cell b on position $\mathbf{x}_b$ directly depends on the Euclidean distance $d_{ab} = |\mathbf{x}_a - \mathbf{x}_b|$ and is modulated by Gaussian function $p^l_{ab} = p_m e^{-d_{ab}/\sigma^2_{local}}$. A displaced cluster connect neurons in the neighborhood of the cluster center. An axon grows from the source neuron in a random direction $\mathbf{y}$. Anywhere in the network area (distance of l_{disp} form source neuron) a local probability map in the same way as on pure local connections is built: $p^l_{a,b} = p_m e^{-\tilde{d}_{a,b}/\sigma^2_{disp}}$ but distances are defined from the displaced cluster center: $\tilde{d}_{a,b} = |(\mathbf{x}_a + l_{disp} * \mathbf{y}) - \mathbf{x}_b|$. The cluster center approximates the branching of axons.

The parameters are specified individually for each combination of source and destination type of neurons (see table 3 in results).

3 Experiments and Results

We generate a large set of networks by different statistical parameter combinations in the possible range and run simulations on a linux-cluster (42 nodes). For each specific parameter combination five instances of the network are realized to determine the variations by the stochastic component of generation and simulation. A time window of 5 seconds (model time) is analyzed before and after the GABA switch.

One of the first results is, that synchronous activity occurs in a wide range of parameters, which confirms experimental physiological investigations [3, 12] and other modeling studies [13, 14] that have shown that network synchronous oscillatory activity does not necessarily result from the activity of pacemaker cells. For the emergence a synchronized oscillatory activity in a purely excitatory network only two conditions have to be fulfilled [15]: (i) the network needs an adequate connectivity and (ii) a damping element, as the depression of the dynamical synapses (see section 2.2).

Because the synchronous activity occurs in a wide range of connectivity, young networks can start a slow synchronous activity by a few connections and evolve very specific connections by activity driven self organizing mechanisms (e.g. STDP) without dramatic changes in dynamics over the whole synchronous stage, as a homeostatic behavior. During this time, the inter burst interval falls with rising connectivity [1]. Since here only the network at the end of the synchronous stage is of interest, we focus on networks with a high connectivity (see table 3). The large GABAergic neurons have a higher number of connections and dominate the dynamics in the synchronous stage [3].

To get a realistic behavior of the network after the transition to working stage, a fine tuning of the balance of inhibitory and excitatory synaptic weights is necessary. Resulting parameters for the simulation are listed in table 3. The realized networks based on these parameters produce in the synchronous phase network a burst with a frequency of about 2 Hz, which is plausible from a biological point of view [1]. In the working phase they show a complex pattern with some low frequent and weak network bursts. Figure 1 shows a typical activity

	glu → glu	glu → GA	GA → glu	GA → GA
$\sigma_{local}/\mu m$	75	150	150	150
$\sigma_{disp}/\mu m$	37.5	37.5	75	75
c_{ij}	0.025	0.04	0.04	0.02

Table 1: Size of connection cluster and initialization value of synaptic weights between glutamatergic neurons (glu) and GABAergic neurons (GA).

pattern from the realized simulations. The basic properties [16] of the resulting networks are analyzed: mean output degree (number of output connections) 28 (glut.), 70 (GABA) and 36 (all); mean cluster coefficient is 0.36 (glut.), 0.19 (GABA) and 0.32 (all); average path length 2.2. This properties are typical of well connected networks with local and long range connections.

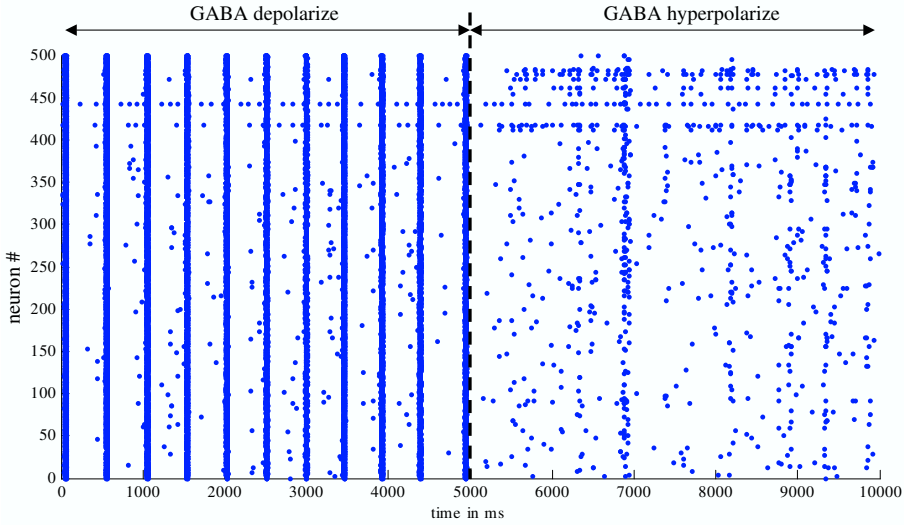

Fig. 1: A typical activity pattern of a network with parameters of table 3. Reversal potential switch at 5000 ms; neuron #: 1 to 400 glutamergic, 401 to 500 GABAergic.

4 Discussion

Artificial neuronal networks with some hundred to some thousands spiking neurons can be simulated effectively on parallel computers [17, 8]. For real engineering applications of spiking neural networks, there is often a lack of knowledge in the set-up of network architecture, neuron connections and synaptic weights and in the parameter adjustments in different scaled networks, which is the motivation to look closer to the maturation process of biological networks.

We have shown by simulation experiments, that the switching of only one parameter is sufficient for the transition from the synchronous to the working stage during the network development. However, a fine tuning of all other parameters is necessary and of critical importance. In real biological networks, this fine tuning is the result of self organizing mechanisms, which we will focus in further studies.

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