Model of Neural Circuit Comparing Static and Adaptive Synapses

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Received November 2, 2004, Accepted December 14, 2004

Abstract: Replacing static synapses with the adaptive ones can affect the behaviour of neuronal network. Several network setups containing synapses modelled by alpha-functions, called here static synapses, are compared with corresponding setups containing more complex, dynamic synapses. The dynamic synapses have four state variables and the time constants are of different orders of magnitude. Response of the network to modelled stimulations was studied together with effects of neuronal interconnectivity, the axonal delays and the proportion of excitatory and inhibitory neurons on the network output. Dependency of synaptic strength on synaptic activity was also studied. We found that dynamic synapses enable network to exhibit broader spectrum of responses to given input and they make the network more sensitive to changes of network parameters. As a step towards memory modelling, retention of input sequences in the network with static and dynamic synapses was studied. The network with dynamic synapses was found to be more flexible in reducing the interference between adjacent inputs in comparison to the network containing static synapses.

Key words: Adaptive synapses – Dynamic synapses – Network dynamic – Memory

Supported by PHYSIOME, Czech Ministry of Education Research Initiative no. 1111-0000-8 and by no. 1111-0000-1.

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Introduction

Although the change of the firing rate of a single neuron shows its participation in information processing, there is evidence that temporal synchronization in the activity of groups of neurons may be an important component of neuronal code [1, 2]. A pair of neurons can be synchronized either via direct synaptic connection between them, or as a result of a common input. Because most of the synaptic contacts, which each cortical cell receives, originate from cells located in the same cortical area [3], it is reasonable to assume that much of the observed synchronization is generated locally (as a consequence of a population dynamics of neurons in the network). Many papers analyse behaviour in biologically motivated models of neuronal networks by employing static synapses with fixed conductance. However, only few papers consider more complex dynamics of synaptic transmission and its role in network dynamics [4, 5, 6]. It is interesting, since the synaptic plasticity is currently considered as one of the microscopic events underlying macroscopic brain functions, such as learning and memory. The long-term potentiation (LTP) and long-term depression (LTD) of synaptic strength are the most studied among the modifications, which a synapse can undergo after presynaptic stimulations. The change of the synaptic strength may increase the amount of information that can be stored in a network and should avoid saturation at synapses, as it was predicted theoretically [7]. In this study we try to analyse our model of cortical-like network containing dynamic synapses and compare its behaviour with the model in which the dynamic synapses are replaced by the static ones.

Materials and methods

Model

We simulated two networks with randomly connected neurons. In one of them neurons were connected by static synapses and in the other neurons were connected by dynamic synapses. All synapses were also modelled with axonal delays, reflecting the fact that action potentials (APs) have to travel between neurons. The delays were taken randomly from the uniform distribution of values ranging from 0 ms to 50 ms, with mean 25 ms and standard deviation 14.4 ms, or they were identical for all neurons within the same range. The probability of connection between neurons was set such each neuron was randomly connected with 10 other neurons in average, which hold for excitatory and inhibitory neurons, the last constituting 20% of all neurons. In simulations testing the effect of connectivity, the average number of connections between neurons varied from 1 to 50. In simulations testing the effect of the proportion of excitatory neurons, this parameter varied from 10% to 100%. The network was driven by excitatory neurons of input layer (neurons in input layer were modelled as point processes with exponential distribution of random interspike intervals; firing of input neurons was independent with the mean firing rates fixed for all neurons, distributed

randomly of uniform distribution from 0 Hz to 30 Hz, with mean 15 Hz and standard deviation 8.66 Hz; the number of input neurons was the same as the number of neurons in the network). There were no separate layers modelled or considered in the network. Each neuron in the network, except for described input neurons, was modelled using the Hodgkin-Huxley equations. All neurons in the network, except for their inhibitory V_{ISYN} and excitatory V_{ESYN} postsynaptic potentials, were identical.

We used standard tools: the model was written in the C under LINUX. Hardware used: an IBM type PC with the Pentium 4 at 2.4 GHz. For integrating differential equations we used a fixed time step four-order Runge-Kutta method. Different time steps for integrating fast and slow processes were used, i.e. different time steps for integrating neuronal events and synaptic events.

The Hodgkin-Huxley neuronal mechanism

The neuronal equations are based on the original equations of Hodgkin and Huxley [8], adapted for neocortical pyramidal cells by Laing and Chow [9] and Wilson [10]. The set of the equations is:

$$\tau_{MEM}\frac{dV}{dt} = (-I_{MEM} + I_{ESYN} - I_{ISYN} + I_{STIM}),$$

$$I_{MEM} = g_L(V - V_L) + g_{Na}m^3h(V - V_{Na}) + g_K n^4(V - V_K) + g_A m_A(V - V_K) + g_{Ca}m_{Ca}(V - V_{Ca})$$

$$\frac{dn}{dt} = \psi(\alpha_n(V)(1 - n) - \beta_n(V)n),$$

$$\frac{dh}{dt} = \psi(\alpha_h(V)(1 - h) - \beta_n(V)h),$$

$$\frac{d[Ca]}{dt} = -0.002g_{Ca}s(V - V_{Ca}) - [Ca]/80,$$

$$m_A = [Ca]/([Ca] + 1),$$

$$s = 1/(1 + \exp(-(V + 25)/2.5)),$$

$$m_{Ca} = 1/(1 + \exp(-(V + 50))).$$

The first equation is the net current with the membrane and synaptic currents. The second equation is the principal equation. The rest of differential equations are auxiliary equations describing the activation of individual currents for *h* and *n,* which are the standard ion channel particles of Hodgkin-Huxley voltage dependent channels**.** Equations of the voltage dependence for α and β are not shown due to the limited space, they can be found in [9]. [Ca] is calcium ion concentration. The m_A potassium after-hyper-polarization current depends on the concentration as shown, together with the *s* and m_{Ca}, which are the voltage activated calcium currents. All the variables sum up in the principal equation for the membrane current I_{MEM} and this value then sums together with excitatory synaptic input $I_{ESYN} = \sum_i y_i$ inhibitory synaptic input $I_{ISYN} = \sum_j y_j$ and stimulation $I_{STIM,}$ where y_i and y_j are effective synaptic strengths, described in the following subsection.

Other parameters: Reversal potentials are: V_L = -65 mV, V_K = -80 mV, V_{Na} = 55 mV, V_{Ca} = 120 mV, V_{ISYN} = –95 mV, V_{ISYN}= 50 mV. Channel conductances are: g_L = 0.05 nS, g_K = 40 nS, g_{Na} = 100 nS, g_{Ca} = 0.5 nS, g_A = 5 nS, the temperature factor used in the auxiliary equations is ψ = 3 and τ_{MEM} = 1 ms.

Adaptive synapse

The adaptive synapses, also called dynamic synapses, were originally described in experiments with neocortical slices [11]. We use variable names, used in [12]:

$$\tau_{syn}\frac{dy}{dt} = -y + \tau_{syn}(Dx + (1-D)z)(Fu + 1 - F)I_{INP}, \qquad \tau_{rec}\frac{dz}{dt} = -z + \frac{\tau_{rec}}{\tau_{syn}}y,$$

$$\tau_{rec}\frac{dx}{dt} = z - \tau_{rec}\,x(Fu + 1 - F)I_{INP}, \qquad \tau_{fac}\frac{du}{dt} = -u + U(1-u)I_{INP}$$

where *y, z, x* and *u* are state variables, called active, inactive, recovered and facilitated, respectively. The active variables are the effective synaptic strengths. Time constants are: synaptic τ_{syn} = 3 ms, recovered τ_{rec} = 100 ms and facilitated τ_{fac} = 800 ms. I_{INP} are series of input action potentials and the parameter *U* determines the increase in the value of *u* with each spike. Switches (parameters) *D* and *F* attain values of 0 or 1. With both zeros the parameters set a "static" alpha function, where the effective synaptic strength does not change. When nonzero, *D* and *F* switch on depressing and facilitating mechanisms, respectively. Depending on the history of incoming spikes, on the frequency of incoming spikes, synapses can either rest in given state, either be facilitated, or be depressed. Low frequency does not lead to synaptic strength changes, medium input frequency brings the synapse into facilitated state and when some value of high frequency is reached, the synapse is depressed, because of the lack of resources modelled by the variable *u*. Synaptic adaptive mechanisms can be compared to similar adaptive mechanisms, which broaden the range of input currents in a neuron, which is a higher computation unit. In the model presented here this type of adaptation is implemented by calcium currents, see also [12]. In Fig. 1 we show that adaptive synapses reproduce the LTP and LTD phenomena. For more extensive set of equations describing the LTP and LTD on a synapse see [13]. Adaptive synapses are a subject of further computational studies, see for example [14].

Hamming distance

To compare analytically neuronal spike trains, we used the Hamming metric; two binary spike train sequences u_i and v_i, $i \in \{1, 2, 3, \ldots, m\}$, consisting of 1 and 0, representing spike and silence within 5 ms time intervals (refractory period for AP generation), were subtracted to get the Hamming distance $H = \sum|u_i - v_i|$

In fact this parameter tells us how different are two spike trains, e.g. the spike trains belonging to two neurons or the spike trains of one neuron under various

conditions. We used Hamming metric to measure differences between network states caused by various input: the network was repeatedly stimulated with *variable input pattern* (VP), followed by silent interval – thereafter stimulated with *identical input pattern* (IP). This simulation was repeated 10 times, in order to test how the first VP input changes the network response to the IP input. The term *identical input pattern* (IP) means that spatio-temporal activity of input neurons constituting the input pattern is the same for each simulation. The term *variable input pattern* (VP) means that spatio-temporal activity of input neurons varies between simulations randomly. From binary spike train sequences corresponding to the network output during the IP stimulation, the average intersimulation Hamming distance was computed (from 50 pair-wise Hamming distances H – all pairs across 10 simulation repetitions) for each neuron. The intersimulation Hamming distances were averaged then for all neurons, producing the Hamming distances (HD) shown in fig. 5 and 6. The HD quantifies the separation of network outputs caused by varying input or stimulation arrangement. The IP stimulation lasted 200 ms in simulations where the influence of the silent interval on the HD was tested. If the influence of elapsed time on the HD was studied, the IP stimulation lasted 100 s (HD was evaluated here each second) and there was only 100 ms silent interval separating the VP and IP. To be able to compare the HD in networks with various output frequencies (smaller networks tend to have lower frequency of their neurons), we normalised the HD according to the average neuronal frequency in the network and according to the duration of analysed output sequence.

Results

First, the strength of dynamic synapse in dependence on the stimulation frequency was analysed. Fig. 1 shows the result of such stimulations with the visible depression within 0.1 – 10 Hz, representing the weakening of synaptic strength at lower frequencies. This dip, also observable on real synapses [15], indicates that within the physiological range of input frequencies the implementation of the dynamic synapse could be considered as reasonable.

In dependence on various parameters, the response of the network to stimulation is either synchronous firing, bursting, or firing with weak or no synchrony. As we can see on Fig. 2, in response to increasing relative numbers of excitatory synapses, the network started to be synchronized and burst at high proportions of excitatory synapses. With the same amount of excitatory synapses, the bursting was much more expressed in the network containing dynamic synapses (see insets in Fig. 2). To quantify and compare the network outputs, we measured the cross-correlation between binary neuronal spike trains (see Methods), depicted on Fig. 3. Evident is here the difference between the level of synchronization in static and dynamic networks. The latter synchronized with much lower proportion of excitatory neurons, compared to the former. Similar

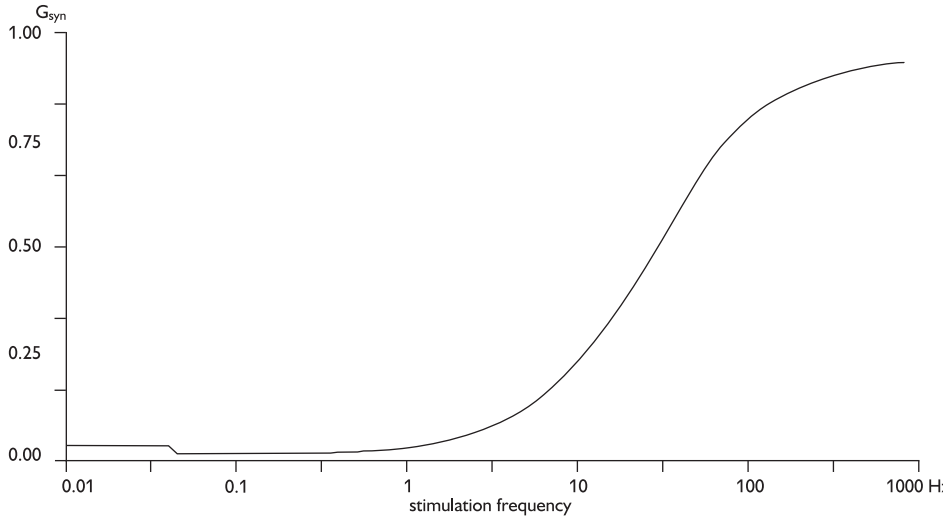

Figure 1 –The frequency dependence of dynamic synapses. On the abscissa is thea logarithm of stimulation frequency. The ordinate gives synaptic conductance G_{syn}. For the relation of this curve to the LTP/LTD phenomena, see [13].

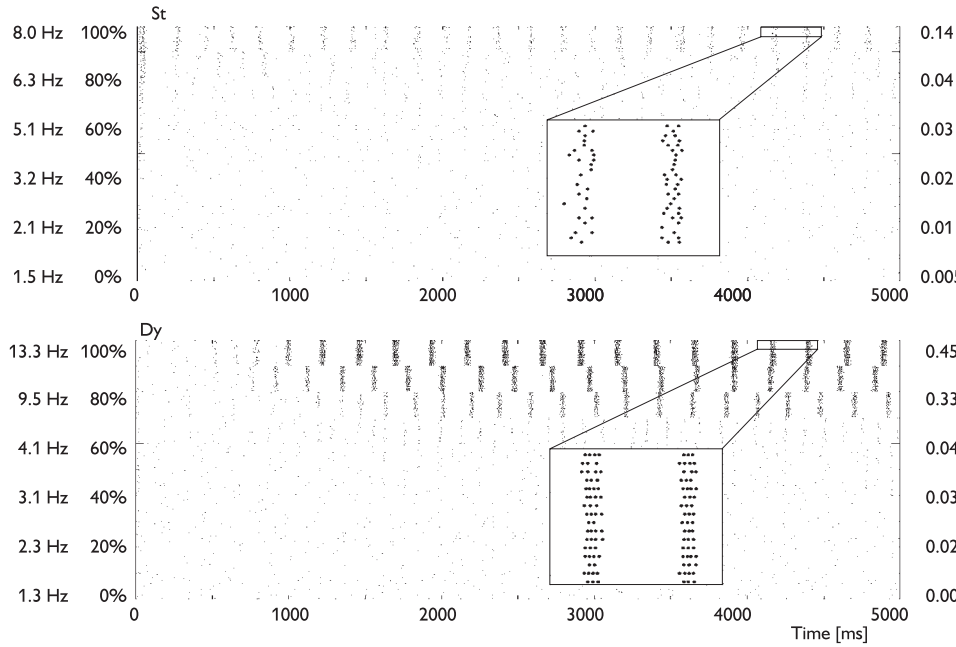

Figure 2 – Sample output spike trains. The two panels show gradual synchronization of the static (St) and adaptive (Dy) networks, when the proportion of excitatory synapses is varied. The variation of the percentage of excitatory synapses together with mean firing frequency in the network is on the y-axis left, cross-correlation Rxy is on the y-axis right. 20 sample spike trains are shown for each of the 10-parameter variations. On the x-axis is time in ms. Note the initial 1000ms period of "adaptation" in the adaptive network.

outputs were generated by increasing the connectivity in the network (by increasing the number of synapses connecting neurons, Fig. 3), causing bursting at high level of connectivity in dynamic network (not shown). At low proportions of excitatory neurons, or at weak connectivity in the network, the firing desynchronised.

Because axonal delays certainly play very important role in the network dynamics [16], we tested how they influence the network activity, and how the mechanisms of adaptive synapses could interfere with delays. We found very strong dependence between the degrees of neuronal synchronization and mean axonal delays in network with dynamic synapses (Fig. 4). Different behaviours resulted when the delays were random and when they were fixed, both with the same mean. In the first case synchronization decreased with the increasing delay, whereas the fixed delays acted contrary-wise and initiated bursting when prolonged. Only weak dependence was found between delays and degree of synchronization in the network with static synapses (Fig. 4).

Testing the effects of some other parameters on the firing regime, e.g. the influence of synaptic strength of input neurons or the effect of their number, we found they have small influence on the network behaviour (not shown).

As the first attempt in studying memory in the network, we tried to measure retention of the presented input in the network (by the term retention we mean effects of previous inputs on the current input). As described in Methods, the network was stimulated by two input sequences, with the variable input pattern (VP) followed by the identical input pattern (IP), which was separated from the VP by silent period – absence of any input. Using the Hamming metric, we analysed differences between network outputs for various VP to get separation HD between network outputs during the second stimulation sequence IP. The extent to which are network outputs separated when responding to the identical IP stimulations indicates how the VP input is retained in the network. First, we tested how the length of the silent period following the VP input affects its retention, what is depicted in Fig. 5. If the silent interval separating the VP and IP input was shorter then 1800 ms, the network response to the IP input was influenced by the VP input. If it was longer, the network did not retain any traces of the initial VP input, and responded identically (with the 100% reproducibility) to the IP input. This holds even in the network containing 1000 neurons (Fig. 5, graphs with stars) and for 1000 ms or 10000 ms lasting VP sequence (not shown). Retention (Fig. 5) was also influenced by the size of the network – as the networks gets smaller, the retention curves reached zero level earlier (Fig 5 shows this relationship for 10, 100 and 1000 neurons, both for static and dynamic synapses). Remarkable is the difference between the retention in static and dynamic network. The retention curve in the network with static synapses is close to linear shape, whereas for the network containing adaptive synapses it is close to the exponential.

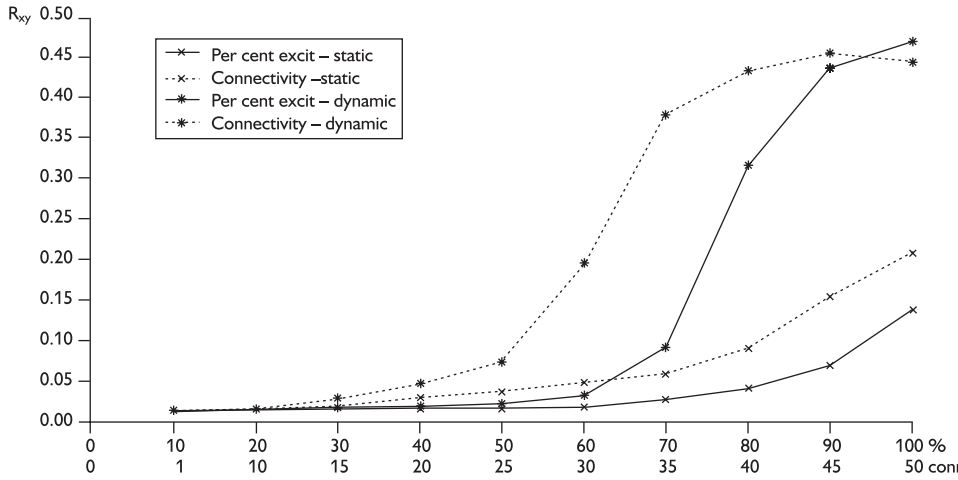

Figure 3 – Cross-correlation in dependence on connectivity and power of excitation. The observation from Fig. 2 is shown quantitatively here, using the cross-correlation R_{xy}. On the x-axis is percentage of excitatory synapses (solid line) and number of connections of one neuron (dotted line). Static synapses are shown by crosses (x), dynamic synapses are shown by stars (*). Both parameters make the cross-correlation R_{xy} rise. Number of neurons was 100. Axonal delays were random and ranged between 0–30 ms.

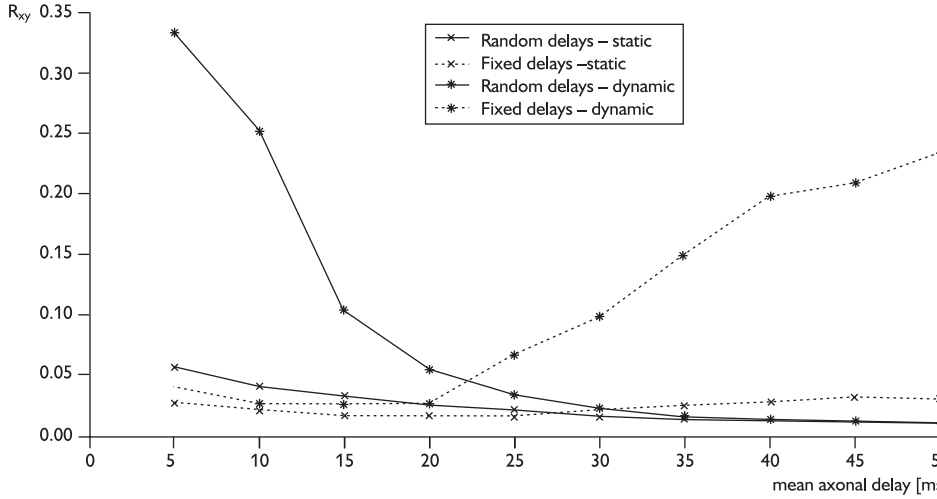

Figure 4 – Cross-correlation in dependence on delays. Delays are not captured by ordinary differential equations (DE's), they have to be implemented as extra features. The dependence of cross-correlation R_{xy} on all combinations of random (solid line) and fixed (doted line) delays in static and adaptive synapses is shown here. Number of neurons was 100 with 80% of excitatory neurons.

Whereas the previous stimulation arrangement analysed principally the fading of network activity, studying responses of the network exposed to the IP input for much longer than 200 ms produced retention curves with another meaning. Here, the course of the HD represents the extent to which the initial input interferes with ongoing network activity. The silent interval was 100 ms and the response of the network at the end of the 100 s lasting IP stimulation could be as variable as at the beginning of the IP stimulation (see Fig. 6A). This holds mainly in larger networks containing static synapses. As the networks get smaller or static synapses are replaced by dynamic ones, the retention of the initial VP input fades out and the reproducibility of network responses to the IP stimulation improves. E.g. for the network containing 20 neurons, the retention of the initial VP after the 100s stimulation with IP is at the 25% of its initial value, see Fig. 6a. In the network composed of 100 neurons, the retention after the 100s IP stimulation is still 98%, the same as for the network with 20 neurons connected by static synapses (Fig. 6a). However the insertion of the 1s silent period into ongoing IP input decreases this retention by 40%, but not in the networks with static synapses – the retention here is still 100% (see Fig. 6b).

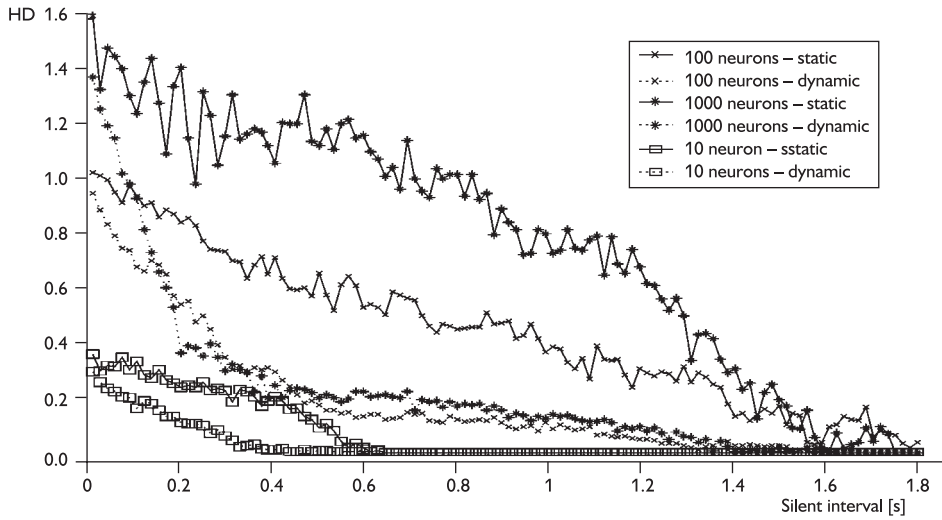

Figure 5 – Retention and fading of activity for static and adaptive networks. The hamming distance (HD) between network outputs is depicted here in dependence on the duration of silent interval separating the VP and IP input. The HD indicates the retention of the VP input after silent intervals following the VP input. After 2s, exactly 1800 ms, even the network containing 1000 neurons forgets completely its input. Elapsed time – "silence interval" – epoch of input silence after the VP input is on the x-axis and fraction of the VP retention is on the y-axis. The values on the ordinate are normalised with respect to firing frequency and duration of analysed output sequence and represent HD referred to one AP.

Discussion

What is the advantage for neuronal networks to use dynamic synapses changing their strength within milliseconds or seconds over the usage of static ones? We tried to answer this question and built a computer model of network containing neurons connected by static or dynamic (adaptive) synapses. Considering transitions between output regimes – bursting, synchronous firing, firing with weak or no synchrony – we found that dynamic synapses enable networks to be more sensitive to the changes in their input in comparison to the static networks requiring broader spectrum of inputs to produce similar outputs. Moreover, dynamic synapses endowed networks more sensitivity to changes involving neuronal connectivity, delays or ratio between excitatory and inhibitory neurons.

As a step towards studying memory in modelled network, we tried to estimate the retention (fading) of the input after the silent period or during the ongoing input. In the first case we obtained the exponential curves for dynamic synapses,

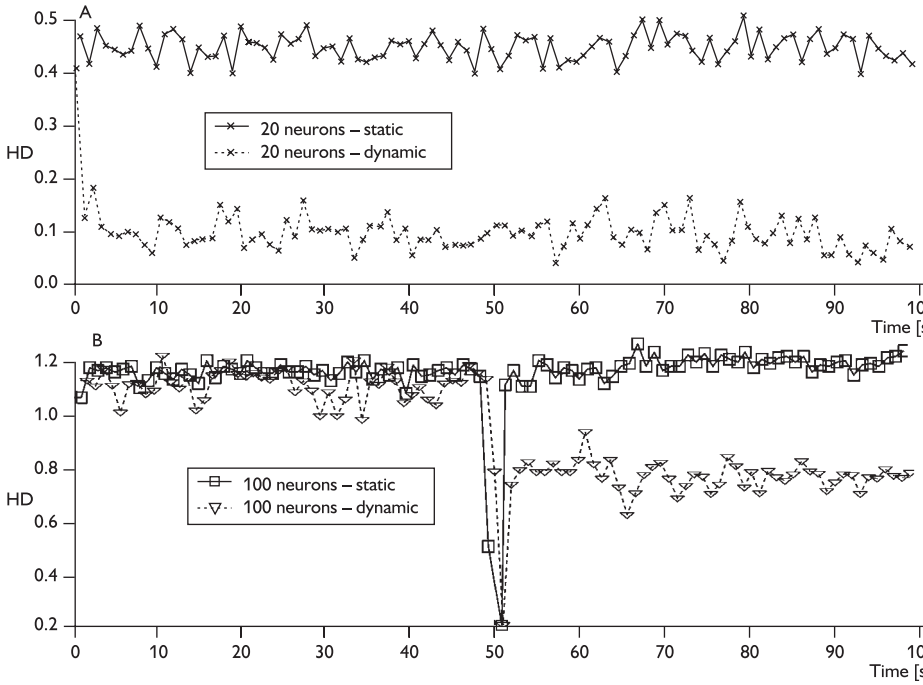

Figure 6 – Retention upon ongoing network activity. This two graphs show how is the 100s lasting IP input pattern influenced by the first 100ms lasting VP input. The IP and VP inputs are separated by 100ms silent interval. Panel A shows the retention (evaluated by Hamming distance, HD) of the VP input in the 20 neuronal networks with static (solid line) and dynamic synapses (dashed line). Panel B represents the same stimulation arrangement but in the network containing 100 neurons and with the 1s lasting silent interval inserted into the middle of the IP input (after 50 seconds). The values on the ordinate are normalised with respect to firing frequency and duration of analysed output sequence and represent HD referred to one AP.

and linear curves for static synapses. This means that networks with dynamic synapses reach their readiness for new input more quickly after the end of previous input than do networks with static synapses. In the network containing dynamic synapses, with its longest synaptic time constant τ_{fac} = 800 ms, the reason of such behaviour could be the fading of synaptic facilitation during the silent interval. However in the network with static synapses, the longest time constant is only τ_{syn} = 3 ms what do not explain such long fading in static network. The only possible cause is the calcium dynamics implemented in neurons of static and dynamic networks (see Methods), with the level of intracellular Ca^{2+} changed in dependence on neuronal activity [17]. Type of the synaptic transition changes the retention from linear to exponential, however without prolonging it significantly. Two seconds after any input followed by silent period, the network was not able to remember it and responded to the second input without interference with the first one. This means that events arriving into the network separated by period of network inactivity lasting few seconds could not be integrated together. The network or neuronal tissue deprived of the input for such time certainly possesses other mechanisms responsible for integrating events separated by longer intervals. We did not consider these mechanisms here [18]. Probably, the average spontaneous firing frequency in the CNS (2 – 5 Hz) and extensive interconnectivity among neurons prevent neuronal networks form such long silent periods anyway.

If the silent period between inputs is less than two seconds, what is the most common situation, the fist input influences network output even after the hundreds seconds lasting second input (fig. 6). The reason is the bifurcation in the network [19] induced by a first input. We found that fading of the effect of bifurcation depends on network size, interval of silent period and on the type of the synapse. As showed in Results, in small networks containing tens or hundreds of neurons (e.g. smaller than number of neurons in cortical columns, where the mutual connectivity is higher than the connectivity to outside), the dynamic synapses may speed up this fading and cause the processing of new input is being better eliminated from the undesired interference of already processed input. Thus the network with dynamic synapses could have advantage over the networks with static synapses – the processing of streamed input is more efficiently filtered from the interference of past network activity.

Omitting here other mechanisms supporting the memory storage like other types of synaptic plasticity, structural changes at synapses or the connectivity pattern [20], it is possible one type of memory is maintained by the sustained network activity, revived by multiple inputs from different CNS regions. Such input could provide the network with meaningful stimuli or drive it with random input, with background noise [21]. In the first case input is modified in the network, resulting in the very complex storage code and dynamics. In the second case, there should be mechanisms filtering out the meaningless input from meaningful information.

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