



# Is voltage-dependent synaptic transmission in NMDA receptors a robust mechanism for working memory?

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## Abstract

The voltage-dependent synaptic transmission in NMDA receptors had been demonstrated to provide persistence of a stimulated activity pattern independent of any form of synaptic plasticity (Nature Neurosci. 1 (4) (1998) 273). This possible mechanism for working memory, however, relied on some unrealistic conditions. The model requires a dominance of NMDA-mediated over AMPA-mediated currents that is unlikely. Furthermore, as we will show in this paper the mechanism is not robust against realistic amounts of noise. We propose a modified model in which short-time memory of a few hundred milliseconds is maintained by input-driven NMDA currents even in the presence of high levels of noise and AMPA currents. © 2002 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

NMDA receptor antagonists disrupt working memory, a short lasting form of memory that is maintained by sustained neuronal activity rather than synaptic modification (see for instance [1]). This experimental finding provoked speculations about the role of NMDA in working memory [5]. Lisman et al. [2] showed in a network model that NMDA-mediated EPSPs can maintain a stimulated pattern after input withdrawal. The

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underlying mechanism is a bistability of neuronal activity in a *feedback* network occurring if the NMDA conductances are strongly dominating over the AMPA conductances. The voltage dependence of the NMDA receptor leads to a second stable state of the cells (with zero synaptic current) above firing threshold.

It had been shown that the short-term memory proposed by Lisman et al. is also expressed in a refined model [4]. The refinement comprised biophysically matched Pinsky–Rinzel two-compartment neurons [3], and a diluted instead of a fully connected network. However, the refined as well as the original model was simulated under conditions with low noise levels and NMDA currents dominating strongly over AMPA currents. Because these conditions seem to be not quite realistic we tested the robustness to variations of noise levels and receptor levels. Since both the models fail under more realistic conditions we propose a more robust mechanism providing short-term memory by NMDA receptors driven by *input (feed-forward)* connections rather than by feedback connections as in the original model. We compare simulation results from the new model to those from the refined model of Lisman et al. In the following these models are referred to as “Lisman model” and “feed-forward model”, respectively.

## 2. Methods

Fig. 1 shows the two simulated models, the refined Lisman model and the feed-forward model. Both models consist of 100 two-compartment pyramidal Pinsky–Rinzel (PR) neurons [3]. The basic difference to the neurons used in [2] is that the dendritic compartment in PR-neurons includes a variable for the calcium level and calcium level-dependent ion channels. The PR cells exhibit additional slow dynamic processes

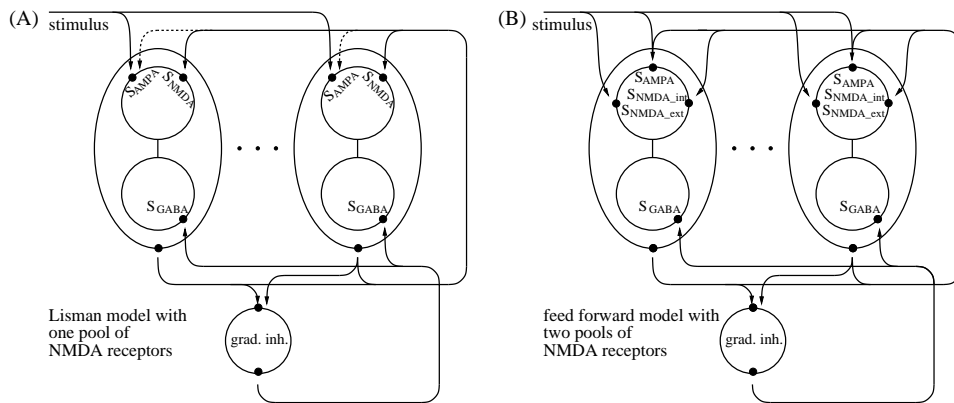


Fig. 1. Lisman model (A) and the feed-forward model (B). Both models consist of 100 excitatory two-compartment PR neurons and one gradual inhibitory neuron. Excitatory neurons make random connections ( $p = 0.3$ ) on other excitatory neurons and activate both AMPA and NMDA receptors. The inhibitory neuron is reciprocally connected with all other neurons. While in the original model of Lisman et al. only AMPA receptors are activated by the stimulus input, in the feed-forward model also a second pool of NMDA receptors ( $S_{\text{NMDA\_ext}}$ ) is activated.

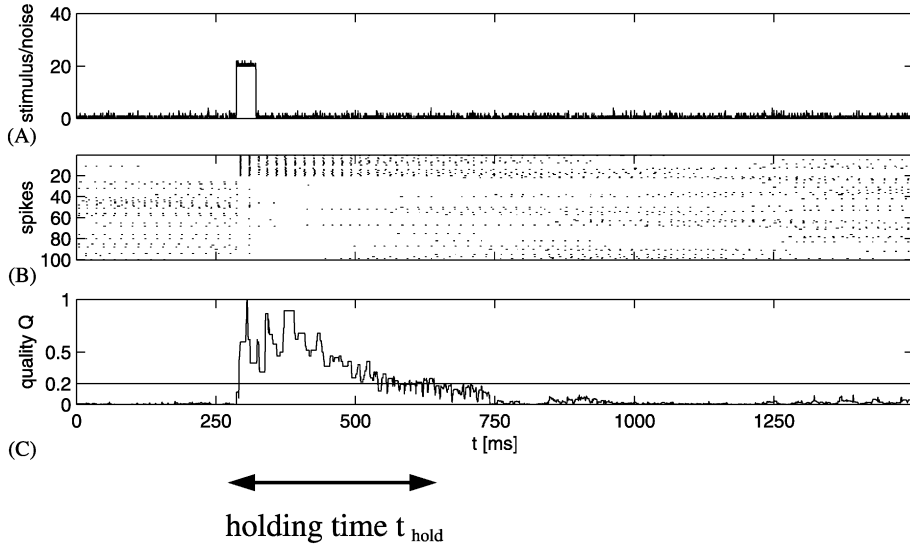


Fig. 2. Example of the stimulation protocol (experiment with Lisman model,  $\text{SNR} = 200:1$ ,  $Q_{\text{th}} = 0.2$ ,  $t_{\text{hold}} = 350$  ms). (A) Total number of input spikes over time due to noise and stimulation. After around 300 ms the pattern neurons are stimulated by a short pulse (35 ms) of high-frequency input. (B) Raster plot of the 100 PR neurons over time. After around 300 ms the neurons 1–20 are activated due to stimulation. The stimulated neurons continue firing after stimulus offset, but the pattern disappears gradually due to noise. (C) Quality  $Q$  over time as (normalized) transinformation between stimulated and active neurons. Holding time  $t_{\text{hold}}$  is time interval where  $Q$  is greater than threshold  $Q_{\text{th}}$ .

like an increase of firing threshold after several hundred milliseconds of firing, often paraphrased as neuronal fatigue. The PR neurons were coupled by a binary random connectivity matrix with probability of a connection between two neurons of  $p = 0.3$ . All PR neurons are connected to a single gradual neuron network mediating inhibition via GABA-A receptors.

In the *Lisman model* (Fig. 1A) the “memory” relies entirely on the effect of neuronal bistability [2] requiring all NMDA receptors in the network to be saturated by internal feedback (variable  $S_{\text{NMDA}}$ ). AMPA receptors are activated by external input and by internal feedback. However, internal AMPA feedback is practically eliminated in the original model (dashed lines). By AMPA stimulation a subpopulation of neurons can be brought in the active stable state. Other neurons being accidentally in the active state (e.g. by ongoing activity) are suppressed by inhibitory feedback and fatigue. Since excitatory feedback is unspecific, the NMDA receptors of all neurons get activated equally. Therefore, the short-term memory is vulnerable to noise once the stimulation has been switched off.

In the *feed-forward model* (Fig. 1B) we drop another unrealistic assumption of the Lisman model, namely that the NMDA occupation of all synapses on a dendrite can be described by one single variable ( $S_{\text{NMDA}}$ ). Though we do not treat every synapse individually, we introduce a second variable  $S_{\text{NMDA\_ext}}$  describing a pool of NMDA synapses that can be activated by external input. When a subpopulation of the neurons

receives external input a memory effect can be expected due to the second NMDA pools activated more strongly for stimulated neurons. However, the lasting of this memory effect should be restricted by the decay time constant of NMDA-mediated currents (about 150 ms).

A typical *stimulation protocol* employed in our simulation experiments is shown in Fig. 2. It describes stimulation of 20 neurons with a short pulse (35 ms) of high-frequency input spikes. The strength of the input pulse was chosen as weak as possible to reliably activate the stimulated neurons. All neurons receive Poisson input spikes at all time according to the base noise level. The memory quality  $Q$  (over time) is defined as (normalized) transinformation between stimulated and active pattern. The holding time  $t_{\text{hold}}$  is determined as the time interval where  $Q$  is greater than threshold  $Q_{\text{th}} = 0.2$ .

### 3. Results

Fig. 3 shows the simulation results of the Lisman model and the feed-forward model under different noise and receptor conditions. Arbitrarily long holding times for a stimulated pattern as reported for the original Lisman model [2] are only achieved in the absence of any noise and with NMDA conductances dominating strongly over the AMPA conductances (Fig. 3A). For increasing noise levels the holding time decreases rapidly to values near zero. With more realistic NMDA/AMPA ratios the memory effect is absent even without noise (Fig. 3B).

In contrast, the feed-forward model shows a memory effect also for higher noise levels and more realistic receptor conditions. With dominating NMDA conductances, the model shows arbitrarily long holding for zero noise similar as in the original model (Fig. 3C). For increasing noise levels the holding time decreases much more slowly (note the different noise scales) and reaches a plateau where still holding times of several hundred milliseconds are possible. For more realistic receptor conditions the component of long holding times is absent even without any noise (Fig. 3D). Over a large range of noise the holding time seems to be rather independent of noise and stays in a range between 200 and 300 ms. We repeated the simulations using different activation strengths “extNMDA” of the NMDA input pool. While increasing the strength of the external NMDA connections shows little influence on the model variant with dominating NMDA conductances (Fig. 3E), the holding time grows for the variant with more realistic receptor conditions, at least for smaller noise levels (Fig. 3F). For higher noise levels the NMDA input variable  $S_{\text{NMDA\_ext}}$  is driven into saturation by the noise itself and therefore no information about the input is preserved in the activity pattern. Noise-driven saturation occurs the earlier the higher the strength “extNMDA” is. However, this may be an artefact of our simple model. By modelling NMDA conductances for *individual synapses* (instead of two synapse pools per neuron) we would expect even stronger noise not driving the NMDA activation into saturation and therefore holding times should still remain high. In a control simulation experiment we eliminated the feedback NMDA receptor pool ( $S_{\text{NMDA\_int}}$ , see Fig. 1). The holding times were still several hundred milliseconds over a large range of noise levels (data

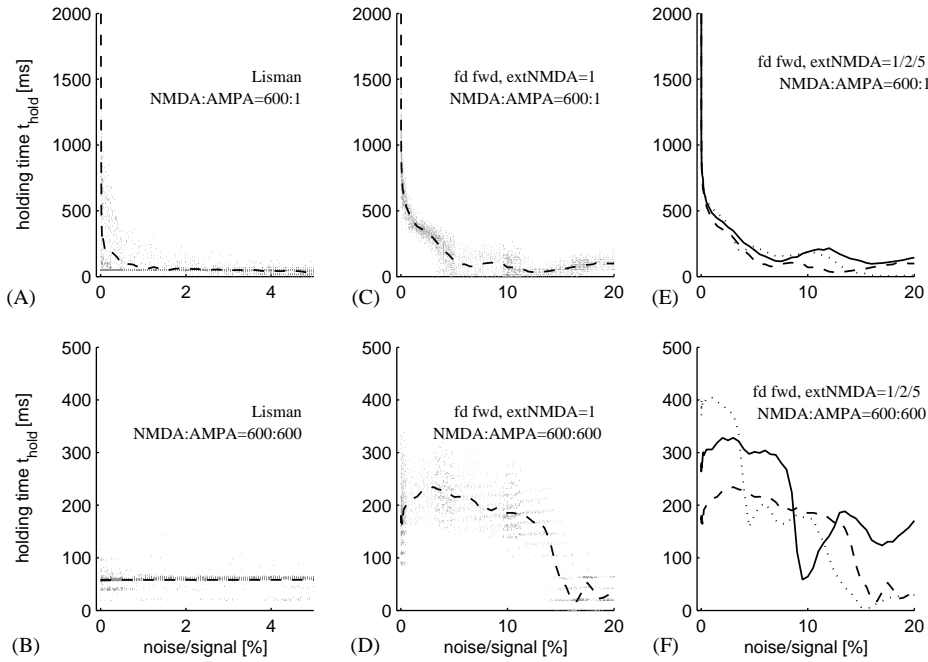


Fig. 3. Simulation results for the Lisman model (A,B) and the feed-forward model (C–F) for strongly dominating NMDA receptors (top row,  $g_{\text{NMDA}}:g_{\text{AMPA}} = 600:1$ ) and more realistic conditions (bottom row,  $g_{\text{NMDA}}:g_{\text{AMPA}} = 600:600$ ). The plots show the holding time over noise level (noise-to-signal ratio in percent). Each grey dot indicates one stimulation as shown in Fig. 2, while black lines represent mean values. The feed-forward model was tested for different activation strength of the NMDA input pool: extNMDA = 1 (dashed line, C–F), extNMDA = 2 (solid), extNMDA = 5 (dotted).

not shown). This indicates that the described memory effect is mainly due to the feed-forward connections activating NMDA receptors.

#### 4. Conclusion

Our simulation experiments show that the memory effect by neuronal bistability as proposed by the original model of Lisman et al. [2] is not robust against noise. Moreover, the effect breaks down with more realistic levels of AMPA conductances. Therefore, we believe that the Lisman model in its original form cannot explain NMDA-based short-term memory. We proposed an alternative model where the information about a stimulus is maintained by differences in saturation of NMDA receptors driven by input (feed-forward) connections. The proposed NMDA short-term memory has three advantages over the earlier proposed model by Lisman. (1) It does not require unrealistically low AMPA conductances. (2) It is not assumed that NMDA receptor occupation is equal for all synapses on the dendrite of a neuron. (3) The memory effect survives much larger amounts of noise. In conclusion, our model suggests that NMDA receptor

properties support a short-term memory of up to several hundred milliseconds duration. For longer durations, however, additional effects such as short-term plasticity of synapses are required.

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