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Synaptic model for spontaneous activity in developing networks

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Abstract

Spontaneous rhythmic activity occurs in many developing neural networks. The activity in these hyperexcitable networks is comprised of recurring "episodes" consisting of "cycles" of high activity that alternate with "silent phases" with little or no activity. We introduce a new model of synaptic dynamics that takes into account that only a fraction of the vesicles stored in a synaptic terminal is readily available for release. We show that our model can reproduce spontaneous rhythmic activity with the same general features as observed in experiments, including a positive correlation between episode length and length of the preceding silent phase.

Keywords: Synapse model; Hyperexcitable network; Synaptic vesicle pools

1. Introduction

Network-driven spontaneous activity in developing neural networks is observed in many parts of the nervous system, including the hippocampus, the retina, and the spinal cord (see O'Donovan [3] for a review). Despite the different network architectures and the different neuron types involved, the general dynamics of this

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activity is always similar: recurring *episodes* of synchronous discharge, separated by *silent phases*. In the chick spinal cord, the episode duration is 30–90 s with a rhythmic *cycle* rate of 0.1–2 Hz that decreases during the course of each episode.

All of these networks share a common feature during this stage of development: they are hyperexcitable. For example, connections that are inhibitory in the mature chick spinal cord are functionally excitatory in the embryo. This hyperexcitability in combination with limited resources within synapses are the key elements of our model. Especially the small terminals of synapses in the central nervous system (as compared to, e.g., neuromuscular junctions) have only a very limited number of readily available vesicles. Studies on hippocampal neurons indicate that only 15% of all vesicles in a synaptic terminal can be readily released [1]. The total number of vesicles in synaptic boutons of CNS neurons is estimated between 200 and 520 (see [2,5]).

In our model, we term the vesicles that can be readily released the *active pool* $\mathcal{A}$, and the vesicles that need more time to be recruited (by transition into the active pool) the *storage pool* $\mathcal{S}$. We show how the repeated depletion of $\mathcal{A}$ can produce cycles within an episode, and how the overall length of an episode is determined by the size of $\mathcal{S}$ at the onset of the episode. The start of an episode is triggered by spontaneous vesicle release at the synapses (''synaptic noise''), whereas slow postsynaptic depression reduces the excitability of the network immediately after an episode.

The spontaneous and evoked episodes in our model network share several of the qualitative features found in measurements of the developing chick spinal cord [6]: a decreasing cycling frequency during each episode, a positive correlation between episode duration and the length of the preceding silent phase, and a positive correlation between the length of the episode and the initial cycling frequency.

2. The model

We introduce a new model for presynaptic dynamics that accounts for the fact that CNS nerve terminals are very tiny and contain relatively few vesicles (usually about 200 overall). Only a fraction of about 15–20% of these vesicles can engage readily in exo-endocytotic recycling [1]. Recycling of released vesicles is a fast process, making the apparent number of readily releasable vesicles (size of the active pool $\mathcal{A}$) higher than their actual number within the synaptic terminal. For CNS neurons, recycling (and the compensation for loss of neurotransmitter) is fast enough that this small number does not seem to pose a major limitation for activity levels within the normal physiological range. Within a hyperexcitable network, however, synapses can be driven to the limit of their capacity due to the positive feedback in the network. Effectively, exhausting the active pool may be a kind of activity-dependent depression acting on a short time scale: reduced sizes of $\mathcal{A}$ will likely be accompanied by reduced probability of vesicle release [2]. We implement the averaged effect of this lowered probability by scaling the postsynaptic current by $A(t)/A_{\max}$, where $A(t)$ is the momentary size of $\mathcal{A}$ and $A_{\max}$ is its maximum capacity.

Unless $\mathcal{A}$ is filled up to its maximum, it gets constantly, but slowly, replenished by transition of vesicles from the storage pool $\mathcal{S}$ into $\mathcal{A}$. We define a gating variable $\alpha_{\mathrm{tr}} \in [0,1]$ that triggers the transfer of a vesicle when it reaches 1, after which it is reset to 0:

$$\tau_A \frac{\mathrm{d}\alpha_{\mathrm{tr}}(t)}{\mathrm{d}t} = \begin{cases} S(t) + S_{\max} & \text{if } (A(t) < A_{\max}) \wedge (S(t) > 0), \\ 0 & \text{else,} \end{cases} \tag{1}$$

where $S(t)$ is the momentary size and $S_{\max}$ the maximum capacity of $\mathcal{S}$. The storage pool, in turn, gets replenished with "new" vesicles via a metabolic process that is much slower than the transition rate from $\mathcal{S}$ to $\mathcal{A}$. Similar to the transition process, we define a gating variable $\alpha_{\mathrm{gen}} \in [0,1]$ that obeys

$$\tau_S \frac{\mathrm{d}\alpha_{\mathrm{gen}}(t)}{\mathrm{d}t} = \begin{cases} \text{const.} & \text{if } S(t) < S_{\max}, \\ 0 & \text{if } S(t) = S_{\max}, \end{cases} \tag{2}$$

with a time constant $\tau_S \gg \tau_A$. A new vesicle is added to $\mathcal{S}$ whenever α_{gen} exceeds 1, followed by a reset of α_{gen} to 0.

Experimentally, a slow time-delayed depression is observed between episodes, which reaches its maximum 1–1.5 min after the end of the episode and decays slowly during the entire silent phase [4]. We model this depression by a homeostatic mechanism that regulates the postsynaptic *sensitivity* $s(t)$ to inputs. The average firing activity of the postsynaptic neuron within a time window of 10 s is compared to a *neutral range* of activity. The sensitivity is decreased (increased) if the average activity is above (below) the neutral range, and kept constant if the activity is within the neutral range. The change in sensitivity takes effect with a delay of 15 s.

Within episodes, the network sustains a state of low activity between the cycle peaks. In the current form of the model, this activity is simulated by random neuronal firing at a low rate for a limited time after each cycle.

Finally, we account for observed spontaneous synaptic events that become more frequent and stronger throughout the silent phase, peaking before the spontaneous start of an episode [3]. We model these events as spontaneous vesicle release (Poisson noise) that increases in frequency during the course of the silent phase.

The synaptic model outlined above is used to connect leaky integrate-and-fire neurons randomly to create an all-excitatory recurrent network without external input. The subthreshold equation of motion for the membrane potential of neuron i obeys

$$\frac{\mathrm{d}u_i(t)}{\mathrm{d}t} = -\frac{u_i(t)}{\tau} + \sum_{j=1}^{N} J_{ij} s_i(t) \frac{A_j(t)}{A_{\max}} \tilde{S}_j(t), \tag{3}$$

where τ is the membrane time constant and $s_i(t)$ is the sensitivity of neuron i. The connection strength J_{ij} between presynaptic neuron j and neuron i is chosen to be $2/\sqrt{kN}$ with connection probability k (existing connection) and 0 otherwise. The

synaptically filtered spike train $\tilde{S}_j(t)$ of neuron j is given by

$$\tilde{S}_j(t) = \int_{-\infty}^{t} \mathrm{d}t' K(t-t') S_j(t'), \tag{4}$$

where $S_j(t) = \sum_s \delta(t - t_j^s)$ is the spike train and $K(t)$ is the filter kernel.

3. Results

The following results were obtained with a network size of $N = 300$ neurons, randomly connected with connection probability $k = 0.4$. We found the same qualitative behavior with bigger network sizes (we tried up to thousands of neurons) and different connection probabilities.

The top panel of Fig. 1 shows the average network activity plotted as a function of time. The network activity was obtained by averaging the total number of spikes per millisecond (ms) over a sliding time window of 20 ms. With the absolute refractory period of 3 ms chosen in our simulations, the maximum average activity is 0.25 kHz. The figure shows the episodic nature of the activity, where three episodes of cycling activity can be seen. The first episode was evoked at the beginning of the simulation. The second episode started spontaneously, while the third one was evoked by driving the membrane potential of all neurons above threshold for a few milliseconds at time $t = 215$ s. It can be seen that the cycling frequency decreases during the course of each episode. The prematurely evoked episode is shorter in length and starts with a lower cycling frequency.

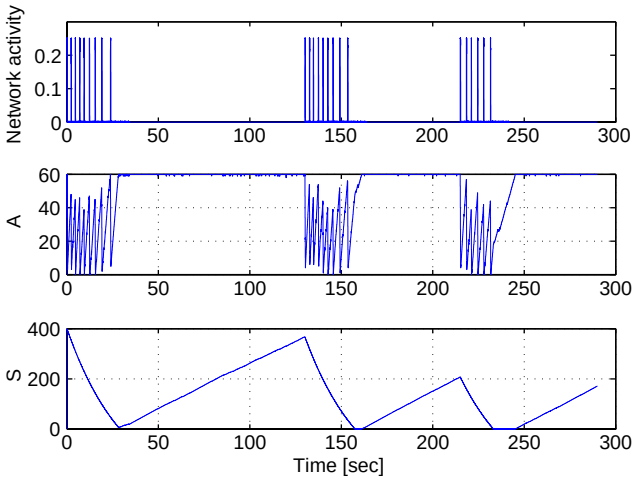

Fig. 1. Network activity and pool sizes of a sample synapse. Top panel: Network activity showing three episodes. The second episode started spontaneously, while the third one was evoked early at time 215 s, resulting in an episode of shorter length. The middle and the lower panel show time courses of pool sizes from a randomly chosen synapse. Middle panel: active pool. Lower panel: storage pool.

Generally, we found a positive correlation between length of the silent phase and length of the following episode. We also observed that shorter episodes always started with a lower cycle frequency. These correlations are qualitatively similar to experimental findings [6].

The time course of the active pool size $A(t)$ and that of the storage pool size $S(t)$ of a randomly chosen synapse are plotted in Fig. 1 in the middle and lower panel, respectively. The size of $\mathcal{A}$ fluctuates synchronously to the cycles of activity within the episodes, while $S(t)$ decreases monotonically during each episode until it reaches zero at the end of the episode. During the silent phase, $\mathcal{S}$ is refilled slowly.

4. Discussion

The nature of the correlations between episode length and length of the preceding silent phase in our model can be understood by comparing the time courses of the synaptic pool sizes with the network activity (Fig. 1). The activity cycles are reflected as an alternation between depletion and replenishment of the active pool $\mathcal{A}$. Cycles are terminated because of exhaustion of the active pool, which reduces the network activity drastically and gives $\mathcal{A}$ time to be refilled, until a new avalanche of activity initiates a new cycle that exhausts $\mathcal{A}$ once again. During the course of the episode, the storage pool $\mathcal{S}$ reduces in size, making the replenishment of $\mathcal{A}$ slower and therefore the intervals between cycles longer. At some point, the storage pool $\mathcal{S}$ is depleted and the episode terminates. The length of the silent phase determines the size of $\mathcal{S}$ at the start of the following episode, which in turn determines the episode length.

This model also attempts to address an aspect of the exceptional data that was ignored or unaccounted for in previous modeling studies. It is considered a puzzling observation that there is almost no postsynaptic depression at the end of the episode [4]. Rather, depression sets in steeply afterwards to reach its maximum 1–1.5 min later, then relaxing slowly back over the entire silent phase to reach once again the high level it had at the end of the episode (see [6], Fig. 4C). In agreement with this observation, it is not the decreased sensitivity that causes the termination of episodes in our model. Instead, it removes temporarily the hyperexcitability in the network, preventing episodes to be started spontaneously before the storage pool is sufficiently replenished. The model network displays an absolute refractory period regarding episode initiation, in which episodes cannot be triggered, even by external stimulation. The same phenomenon is observed experimentally in the developing chick spinal cord (see [6], Fig. 4B). Moreover, the slowly increasing sensitivity within the silent phase increases the amplitudes of the spontaneous synaptic events until they reach a maximum just before the initiation of a new episode, in agreement with data obtained from the developing chick spinal cord.

In our current model, we need to impose spontaneous random firing after each cycle to sustain low activity between cycles. Preliminary studies point to the possibility that self-sustained inter-cycle activity may result from bigger network sizes in combination with a distribution of pool sizes.

There has been success in modeling spontaneous activity on the network-dynamics level. This was achieved by employing both slow and fast activity-dependent *network depression* that act independently from each other [7]. However, it has proven challenging to show how such network dynamics can emerge from neuron properties. This work is an attempt to provide such an explanation, albeit with different dynamics than have been considered so far. It suggests that the limited resources of synapses and their proposed internal dynamics may lead to the typical activity patterns observed in hyperexcitable networks of diverse architectures.

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