Neural coding with spikes and bursts: characterizing neurons and networks with noisy input
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Citation for published version (APA):
Zeldenrust, F. (2012). Neural coding with spikes and bursts: characterizing neurons and networks with noisy input Amsterdam: Wohrmann Print Service
Chapter 3

Feed-forward inhibition

Submitted to Neural Networks as: F. Zeldenrust and W. J. Wadman – “Timing is everything: feed-forward inhibition strongly enriches the output behaviour of a model pyramidal CA3 neuron”
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Abstract

Pyramidal cells perform computations on excitatory inputs in a local network that provides various forms of inhibition. A previous study [166] investigated two functionally separated inhibitory feedback loops: 1) one with slow synaptic kinetics (20 ms) projecting to the distal dendrite of the pyramidal cell (e.g. O-LM interneurons) 2) one with fast synaptic kinetics (9 ms, e.g. basket cells) projecting to their soma. The current computational study includes the effects of feed-forward inhibition. Gaussian noise was used as the input to both the dendrite of the pyramidal cell and the interneuron. In the pyramidal cell it evoked two types of events: spikes or bursts, in the interneuron only single spikes. The properties of the synapse between the interneuron and the pyramidal cell (reversal potential, projection site, delay, fast or slow kinetics) and the amplitude of the interneuron input were varied, and on the basis of cross-correlations and reverse correlation analysis we demonstrated that the exact timing of inhibition is a determining factor in the effects it has on the postsynaptic cell. Based on the Victor-Purpura measure of reliability we show that feed-forward inhibition makes the output more precise when all events or when only single spikes are taken into account, but not if the analysis is restricted to bursts. Feed-forward inhibition is more versatile than feedback inhibition in shaping the computation in a microcircuit.
3.1 Introduction

Pyramidal cells in the hippocampus perform computations on the input they receive under the influence of various forms of inhibition. Experimental evidence indicates at least two functionally distinct inhibitory feedback loops in the CA3 area of the hippocampus: 1) a loop in which O-LM interneurons project to the distal dendrites of pyramidal cells with synapses that have slow kinetics (‘slow dendritic inhibition’) and 2) a loop in which basket interneurons project to the somata of pyramidal cells with synapses that have fast kinetics (‘fast somatic inhibition’, [6, 98, 109, 114]). Interneurons that receive feed-forward inhibition operate differently from the ones that participate in feedback loops [40, 100], indicating a separation between feed-forward and feedback inhibitory loops. In a previous work [166] we investigated slow dendritic and fast somatic feedback inhibition, in which an excitatory neuron inhibits itself through an interneuron. The general view is that this should result mainly in regulatory effects, in which the excitatory neuron can stabilize or stop its own output activity [72, 100] or can result in oscillations between the exciting and inhibiting cell [162]. We found that feedback inhibition can also change the firing mode of the excitatory cell and its filtering properties. Whereas an IPSC generated by a feedback loop is a response to the activity of a pyramidal neuron's own activity,
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IPSCs from feed-forward inhibition can arrive even if the pyramidal cell is inactive. This increases the possibilities of the relative spike-timing of pyramidal neurons and interneurons. Therefore feed-forward inhibition could increase the versatility of the output much more than feedback inhibition.

In this work, we extended our previous research to feed-forward inhibition. The general view on feed-forward inhibition, in which an excitatory neuron and an interneuron that inhibits the excitatory neuron receive similar input, is that it dampens the output. It results in a stronger signal at the beginning than at the end of a stimulus, which increases the precision of firing by decreasing the temporal window: the pyramidal neuron can only spike at full strength before the interneuron kicks in. In this paper investigate the effects of slow dendritic and fast somatic feed-forward inhibition on the firing properties of a model pyramidal cell. To keep our analysis tractable, we needed simple models that capture most important firing characteristics of these types of cells. We used a two-compartment model of a pyramidal CA3 cell designed by Pinsky and Rinzel. Not much research has been done on the filtering properties of different types of interneurons. Therefore, we use a fairly simple interneuron model. This model is a typical ‘type 1’ neuron or ‘integrator’: it has a continuous input-output curve for constant inputs. The pyramidal cell responds to its input with either a spike or a burst. We analyzed how this coding changes under the influence of feed-forward inhibition using reverse correlation analysis. We also investigated the reliability of the output of the pyramidal cell using a measure based on the Victor and Purpura metric. Finally, we included an h-current (a non-selective cation current that activates on hyperpolarization and operates in the subthreshold voltage range) in the pyramidal neuron, since an h-current can show strong interactions with inhibitory inputs in hippocampal pyramidal cells (for a review, see).

3.2 Methods

3.2.1 Model

The basic circuits used in this study consist of a pyramidal cell and an interneuron that projects to either the soma or the dendrite of the pyramidal cell (figure 3.1). The inhibitory synapse has an exponential rise and decay, with fast kinetics if it is located on the somatic compartment of the pyramidal cell ($\tau_{\text{rise}} = 1\text{ms}$, $\tau_{\text{decay}} = 9\text{ms}$, ‘fast somatic inhibition’). When the synapse is located on the dendritic compartment is has slow kinetics ($\tau_{\text{rise}} = 5\text{ms}$, $\tau_{\text{decay}} = 20\text{ms}$, ‘slow dendritic inhibition’). Propagation delays were also included between the interneuron and the pyramidal cell: $\tau_{\text{delay}} = 2\text{ms}$.

To keep our analysis tractable, we implemented simple models that capture most important firing characteristics of these type of cells. We used a two-compartment model of a pyramidal CA3 cell designed by Pinsky and Rinzel. It shows bursting as a result of an interplay between fast somatic spikes and the slower dendritic calcium spikes (‘ping-pong’ mechanism). This model has been thoroughly validated, extensively used
Figure 3.2: Traces (left) and distribution of the somatic membrane potential (right) for the pyramidal cell model with (solid lines) and without (dotted lines) h-current. In the model with h-current the mean of the injected current was slightly lower (-0.8) than in the model without it (-0.4).
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and analyzed [77]. It is a reduction of a more extended model of a CA3 neuron originally described by [145]. The somatic compartment has ionic currents responsible for spiking (sodium current, delayed-rectifier potassium current and leak current). The dendritic compartment contains very simple calcium homeostasis and calcium-activated ionic currents (calcium current, leading to $Ca^{2+}$ increase, calcium-activated potassium current, calcium and voltage dependent afterhyperpolarization generating C type potassium current and leak current). The two compartments are equal in size and electrically connected (for details see A.1.1). For example traces, see figure 3.2.

The interneuron model is a model of a fast-spiking interneuron [156]. It consists of a single compartment with a sodium current, a potassium current and a leak current (details are given in appendix A.1.2). It was designed to model gamma oscillations, and includes a brief afterhyperpolarization and the possibility of high frequency spiking. The stable resting state loses stability through a saddle-node bifurcation off a limit cycle [166].

A fourth-order fixed time-step (0.05 ms) Runge-Kutta integration method was used.

3.2.2 Input

A slight persistent current $I_d$ was injected into the dendrite of the pyramidal cell to prevent spontaneous firing, $I_d = -0.4$ (negative current is inward). We used normalized values, as all parameters are normalized to surface area, and only have a relative meaning. When the surface to volume ratio is relevant (as in calcium accumulation), we have directly implemented the time constant in our equations. Gaussian noise ($\mu = 0, \sigma^2 = 50$) filtered with an exponential filter ($\tau = 1\text{ms}$) was continuously injected into the dendritic compartment of the pyramidal cell. In order to be able to compare experiments, in every experiment the same realization of the fluctuating input was used (‘frozen noise’). The amplitude (variance) was chosen in such a way that the pyramidal cell (without an inhibition) responded with a firing frequency of about 6Hz. This frequency was the optimal compromise that produced an interval between spikes that was large enough for most of the spikes to be considered independent. The length of the inter-spike interval for spikes to be independent was set on basis of the inter-spike interval distribution: spikes or bursts were considered to be independent if the inter-spike intervals followed an exponential distribution, as judged from the log inter-spike interval histogram (see figures 3.11 [3.13] and 3.14 [2]). This was considered separately for each simulation. A larger noise amplitude increases firing frequency of the pyramidal cell, and would result in too much event-event interference. A smaller noise amplitude would result in lower firing frequency with unacceptable long computation requirements to produce sufficient spikes for statistical analysis. To simulate feed-forward inhibition, the same frozen noise stimulus was also injected into the interneuron. The amplitude of the stimulus, denoted by its variance $\sigma^2$, was varied to make the interneuron respond with different firing frequencies. Hyperpolarization of this cell was not necessary, since it does not fire spontaneously. In the case where the reliability was calculated, trial to trial variability was simulated by adding white noise ($\sigma^2 = 1$) to the dendrite of the pyramidal cell. We used a value of $q = 1\text{ms}^{-1}$.
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3.2.3 Spike train segmentation

The pyramidal cell responds to the dendritic noise input by generating two types of events: spikes and bursts. The events recorded in the pyramidal cell will be considered as point processes, classified as either a spike or as a burst. The classification of an event as a spike or as a burst is based on the following criteria: setting a threshold crossing in the membrane potential of the pyramidal cell soma at 0 mV is sufficient to detect all spikes (single action potentials) and the first action potential in all bursts. A burst consists of a small train of high frequency action potentials; the amplitude of the first action potential is always much larger than the amplitude of the following ones. During a burst the dendritic membrane potential is more depolarized than during a spike. If the first or second dendritic action potential, defined by a threshold crossing in the dendritic membrane potential at $-11 \text{ mV}$, falls within a time window of $2 - 9 \text{ ms}$ after the somatic action potential, the event is classified as a burst, otherwise it is a spike. The point in time where the voltage during this event reaches its maximum value defines the time of occurrence of the point process $t_n$ (spike as well as burst).

3.2.4 Analysis

Reliability

Victor and Purpura [153, 152] define the dissimilarity of two spike trains as a metric based on ‘how much it costs’ to transform one spike train into the other. They define three elementary operations with associated costs:

1. moving a spike over a distance $\Delta t$ costs $q\Delta t$
2. adding a spike costs 1
3. deleting a spike costs 1

The distance $d_{VP}$ is defined as the minimum costs to transform one spike train into the other. A metric defines a distance, that increases with the length of the spike train. We would like a similarity measure that is 1 for identical spike trains, 0 for two maximally different ones, and measures the millisecond precision rather than the number of spikes. Therefore, we normalize the metric: the metric is bound by the number of spikes in the two spike trains, since the distance between two spike trains can never be larger than the sum of the number of spikes in the two trains. By defining

$$M_{VP} = 1 - \frac{d_{VP}}{N_i + N_j} \quad (3.1)$$

The inverse of the parameter $q$ indicates the precision: it is a kernel width that denotes how far spikes can be separated in time in order to be considered part of the same event. The measure is bound between 0 and 1.
Event-triggered analysis

To analyze what features in the input trigger a spike or a burst, reverse correlation was used. We used the event-triggered average (ETA) and covariance (ETC) to analyze what characteristics the pyramidal cell extracts from the input \cite{3,16,28}. This is explained in appendix B.

3.3 Results

3.3.1 Uncoupled interneuron and pyramidal cell

First, the interneuron and the pyramidal cell were not connected, and the properties of both cells were investigated separately. The pyramidal cell model has been analyzed before \cite{166}: it responds to excitation with either a spike or a burst. Whether this response is restricted to a spike or will develop into a burst is decided right after the (first) spike: more excitation will give a burst, whereas inhibition will prevent the development of a burst, and the response stays limited to a single spike (see appendix, figure 3.15). Here we will consider the filtering properties of the interneuron. The amplitude of the input to
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The interneuron was varied, to make the interneuron spike at different frequencies (solid line, figure 3.3 left top).

The filtering of the interneuron

The reverse correlation analysis of the response of the interneuron shows that the spike-triggered average and the first filter of the spike-triggered covariance analysis have the same basic unimodal shape (figure 3.4). The filter with the second smallest eigenvalue (‘filter 2’) looks like the derivative of the first filter. For an ‘integrator’ [67] an integrating filter and its derivative are expected [3]. When the amplitude of the input is small, there are about five filters to which the interneuron is sensitive. The filter with the highest eigenvalue (figure 3.4 ‘last filter’) shows a fast fluctuation just before the spike. However, with increasing amplitude the last filter disappears and the probability distribution of the first filter shifts to the left, reflecting that it becomes ‘easier’ to make a spike (the spike frequency increases, figure 3.3). Both the STA and the first filter become more sharply timed before the spike, reflecting that the interneuron spikes with a shorter latency to its input. The biphasic second filter becomes less noisy and its probability distribution shifts towards higher projection values. It seems that the first and the second filter become interdependent: the spike-triggered manifold becomes more curved, as can be seen in figure 3.5. This could be a result of a changing threshold manifold for higher amplitude input [59], for an analysis on how some neurons behave with increasing amplitude of the input, see [41]). The other filters probably code for silence, as they show strong oscillations that do not attenuate, and stop right at the point where we put the criterium for spikes to be independent (100 ms for \( \sigma^2 = 0.5 \), and 50 ms for \( \sigma^2 = 1 \) and 2; [2]).

The effects of common input

In the model with feed-forward inhibition, the same frozen noise current was injected in both the interneuron and the dendrite of the pyramidal cell. With feed-forward inhibition, two aspects play an important role in the correlations between the pyramidal cell and the interneuron: the effects of the common input and the effects of the synapse between the two cells. To separate these aspects, we first looked at the correlations between the two cells without any synapse; the effects of the common input. The cross-correlations of both cells were determined (figure 3.6) for different values of the input variance to the interneuron. Since the input into the pyramidal cell is the same in all these trials, the pyramidal events are at the same time-points, so we can compare the cross-correlation figures. When the interneuron received little input, it fired at about 3.1Hz (figure 3.3) and the peak in the cross-correlogram is at negative lags (figure 3.6 left), meaning that the interneuron fired later than the pyramidal cell. More precisely, the interneuron is about 5ms later than the first spike of a pyramidal burst, and between 3ms earlier to 30ms later than a pyramidal spike. Moreover, the correlations between interneuron spikes and pyramidal bursts are much stronger than between interneuron spikes and pyramidal single spikes. Apparently, the input that triggers a pyramidal spike is not as strong a trigger for an interneuron spike as the input that triggers a pyramidal burst.

Increasing the input variance (\( \sigma^2 = 1 \)) to the interneuron increases its firing rate to
Figure 3.4: Spike-triggered average (top row) and covariance analysis (bottom three rows) for the interneuron, for different values of the amplitude (variance $\sigma^2$) of the input. Left: filters, right: probability distributions of spike triggering or random (‘prior’) stimuli onto the filters. NB We used a criterium for independence of spikes of 100 ms for $\sigma^2 = 0.5$, and 50 ms for $\sigma^2 = 1$ and 2. All the probability distributions were calculated using normalized (L2-norm) filters.
Figure 3.5: Spike-triggered inputs (grey) and random inputs (black) projected onto the first two filters of the covariance analysis for different amplitudes ($\sigma^2$) of the input injected into the interneuron.
Figure 3.6: Cross-correlations between the uncoupled pyramidal cell and interneuron due to the common input, normalized by the total number of events, for varying amplitude of the input to the interneuron ($\sigma^2$). Negative lags are where the interneuron spikes lead the pyramidal events.
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Figure 3.7: Cross-correlation changes due to slow shunting dendritic inhibition \( g_{syn,d} = 4 \) for different values of the amplitude of the input to the interneuron \( \sigma^2 \): the difference in cross-correlation with and without the synapse present. Top: bursts, bottom: spikes. Negative lags are where the interneuron spikes lead the pyramidal events.

about 6.3Hz (figure 3.3). In the cross-correlograms (figure 3.6 middle) the peaks shift to the right, indicating shorter latencies (about 1ms for both spikes and bursts), which means that the interneuron now reacts faster to its input. The input to the pyramidal cells not changed so it still spikes at exactly the same times. The interneuron now also reacts to inputs that triggered a pyramidal single spike. A similar trend can be seen when the input variance to the interneuron is increased even more: the interneuron firing rate is now about 10.1Hz (figure 3.3) and the interneuron now spikes about 1ms before a pyramidal spike or burst (figures 3.6 right). The correlations between bursts and interneuron spikes remain stronger than the correlations between spikes and interneuron spikes.

We conclude that the interneuron is an integrator. When the amplitude of the input to the interneuron is increased, it starts spiking with higher frequency and earlier in time. Its activity correlates stronger with pyramidal bursts than with pyramidal single spikes.

3.3.2 Slow dendritic feed-forward inhibition

As a next step in our analysis a synapse between the interneuron and the pyramidal cell was added: the interneuron projects to the dendrite of the pyramidal cell via a slow IPSC
Chapter 3. Feed-forward inhibition

In this model inhibitory synapses are shunting, as they have a reversal potential of $-62 \text{ mV}$, which is very close to the resting membrane potential. The effect of this synapse is that with increasing interneuron activity, the event rate of the pyramidal cell (spike rate + burst rate) increases (figure 3.3). The number of bursts is reduced; the number of spikes however, is increased. Increasing the strength of the synapse shows the same effect, but stronger (figure 3.3).

To distinguish between the correlations as a result of the common input and the correlations as a result of the synapse, we subtracted the uncoupled cross-correlogram (figure 3.6) from the cross-correlogram where the synapse was present ($g_{\text{syn},d} = 4$, figure 3.7). Since the interneuron spiking was not influenced by the synapse, this gives a measure of where pyramidal events were added or deleted due to the dendritic synapse. All correlograms in figure 3.7 are bimodal, with the positive part at the negative lags, where the interneuron spikes later than the pyramidal cell. The bimodal form of the difference diagram means that in effect the cross-correlation peak shifts to the left, indicating that activating the synapse makes the pyramidal cell active earlier relative to the unchanged interneuron spikes. The difference diagrams (figure 3.7) also show that bursts get deleted when the interneuron spike is around 4 ms later (left) to 1 ms earlier (right), whereas they have an excitatory effect when the interneuron is later. Spikes on the other hand get added when the interneuron is slightly later or coincident.

Reliability and precision

To evaluate whether the output of the pyramidal cell gets more reliable with feed-forward inhibition, we calculate the normalized Victor-Purpura distance (see section 3.2.4). As a reference we used 6 simulations that used identical frozen noise injected into the dendrite to which white noise current ($\mu = 0$, $\sigma^2 = 1$) was added. The average over the results of these 6 comparisons (with a cost-parameter of $q = 1 \text{ ms}^{-1}$) demonstrates that as inhibition becomes stronger the reliability of events and singles spikes goes up, whereas the reliability of bursts goes down (figure 3.8). This is the case for a higher output frequency of the interneuron as well as a stronger synapse. The differences are small, but systematic (the added white noise had a small variance). Apparently, there is an optimal region for bursts, where bursts are the most reliable, at a synapse strength of between 7 and 8 and the variance of the input to the interneuron at $\sigma^2 = 0.7$. In a previous paper [164] we showed that the outcomes of reliability measures depend critically on the frequency of the spike train. We also plotted the normalized Victor-Purpura distance as a function of $\Delta f / \langle f \rangle$ (figure 3.9). We conclude that the changes in reliability can hardly be attributed to the difference in frequency, and seem to be an intrinsic effect. The reliability of single spikes increases with stronger inhibition, but the reliability of bursts decreases.

Uncorrelated and anti-correlated input

The importance of the timing of the feed-forward inhibition was investigated by looking at two different scenarios: one in which the inputs to the interneuron and the pyramidal cell were anti-correlated and one in which they were uncorrelated. In both cases, the effects of inhibition are almost negligible. The effects that are visible are comparable to
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Figure 3.8: Average reliability, as measured by the normalized Victor-Purpura metric with cost parameter $q = 1$, of the output of the pyramidal cell with and without extra added noise, for different levels of feed-forward inhibition (synapse strength $g$ and amplitude of the input to the interneuron $\sigma^2$). The reliability of single spikes increases with stronger inhibition, but that of bursts decreases.
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Figure 3.9: Relation between the reliability as measured by the normalized Victor-Purpura metric and $\Delta f/\langle f \rangle$, for the amplitude of the input to the interneuron $\sigma^2 = 2$. The data was fitted using the ‘regstats’ and ‘robustfit’ functions in MATLAB. The reliability changes as in figure 3.8 cannot be merely attributed to frequency changes.
Delays and hyperpolarizing inhibition

We found that with slow dendritic shunting inhibition the total event rate and the spike rate increase, whereas the burst rate decreases. To exclude a possible excitatory effect of the shunting synapse, we investigated hyperpolarizing inhibition. When the reversal potential of the synapse on the dendrite of the pyramidal cell was hyperpolarizing ($-80mV$), the total event rate of the pyramidal cell decreased (figure 3.3, diamonds). Pyramidal events were added at the timing of the interneuron spike, but deleted when the interneuron spike occurred earlier than a pyramidal event (figure 3.10). The burst rate decreased stronger for hyperpolarizing than for shunting inhibition. The spike rate initially decreased, but increased again when the interneuron became more active (figure 3.3, diamonds). This is partly an effect of dendritic calcium spikes being stopped, so bursts are converted into spikes: when the interneuron was active at the same time as the pyramidal cell, bursts were deleted, but spikes were added (figure 3.10). More spikes were added than bursts were deleted at the interneuron spike time, which suggests other mechanisms for adding spikes. Firstly, after a burst the refractory period is longer than after a spike due to the activation of the AHP-current. Stopping a bursts would give more opportunities for an spike in this refractory period. Secondly, hyperpolarizing inhibition can de-inactivate sodium channels, causing rebound spikes.

When a delay of 2ms was included in the shunting synapse, the spike rate in the slow loop still increases, but not as strongly (figure 3.3). The burst rate still decreases, but also not as strongly. When the interneuron receives stronger input, it spikes not only
faster burst also earlier, partly overcoming the delay in the synapse. The delayed synapse shows that indeed, when less bursts are stopped, less extra spikes are added.

When a delay of 2ms \[113\] was included in the hyperpolarizing synapse (figure 3.3, stars), the inhibition is less effective in decreasing the burst rate than without the delay. The spike rate however, does not increase. Apparently a delayed synapse can not increase the spike rate by any of the mechanisms discussed before.

We conclude that slow dendritic shunting feed-forward inhibition decreases the burst rate and increases the single spike rate. This is a combined effect of the excitatory part of shunting inhibition, the conversion of bursts into spikes, a reduction of the activation of the AHP-current and a rebound effect.

Filtering

Until now, we used event rates to detect changes in activity for the different combinations of parameters we have investigated. Even if firing rates do not change, the information processing as reflected in the detection filters could still be altered (figure 3.11, ETA and ETC). Compared to the coding of the pyramidal cell without inhibition (figure 3.15), the filters have changed. When inhibition is present, they are more spread out in time, and they show oscillations. Especially for bursts, a set of filters arises that show long-lasting interactions. A similar conclusion follows from the ISI distributions and autocorrelograms: there are long interactions when the synapse is present. Without inhibition, single spikes show a strong autocorrelation, suggesting that they often occurred in doublets with a 6 ms time interval. Events become independent at about 50 ms (exponential tail of the ISI distribution). The inhibitory synapse almost completely annihilates the autocorrelation-peaks of the single spikes, preventing doublets, and it increases the interaction time to about 125 ms, as can be seen in the ISI distribution and the filters (figure 3.11, bottom left).

3.3.3 Fast somatic inhibition

With fast somatic inhibition the event rate does not increase as a function of the interneuron activity (figure 3.3, second and fourth column). The burst rate decreases and the spike rate is more or less constant. Also, making the synapse hyperpolarizing and/or introducing a propagation delay does not have a strong effect on the spike rate. To understand the differences between slow dendritic inhibition and fast somatic inhibition, we looked both at the cross-correlation difference and at what this microcircuit filters out of its input. The event-triggered analysis for spikes in fast somatic shunting inhibition with synaptic strength \( g_{\text{syn}} = 8 \) and the variance of the input to the interneuron \( \sigma^2 = 2 \) was calculated, since this case differed the most from slow dendritic inhibition (figure 3.3, triangles). The cross-correlation difference (figure 3.12) shows that pyramidal spikes get added when coincident with the interneuron spike, but deleted when the interneuron is faster. Moreover, with slow dendritic inhibition (left) hardly any spikes get deleted, whereas with fast somatic inhibition (right) about the same number of spikes were added.
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![Graphs showing ETA, ETC Bursts, and ETC Spikes](image)

Figure 3.11: Event-triggered average (left) and event-triggered analysis of the pyramidal cell for bursts (middle) and spikes (right), with a slow hyperpolarizing synapse with strength $g = 4$ and the variance of the input to the interneuron $\sigma^2 = 2$. 

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Figure 3.12: Cross-correlation changes in single spikes due to slow dendritic (left) and fast somatic (right) shunting inhibition: the difference in cross-correlation with and without the synapse present, with a synaptic strength of $g_{\text{syn}} = 8$ and input variance to the interneuron $\sigma^2 = 2$. Negative lags are where the interneuron spikes lead the pyramidal events.

Figure 3.13: ISI distribution (left) and event-triggered average (middle and right) for single spikes (grey) and bursts (black) for slow dendritic (solid lines) and fast somatic (dotted lines) feed-forward inhibition, with the strength of the synapse $g = 8$ and the variance of the input to the interneuron $\sigma^2 = 2$. 

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and deleted. The event-triggered average (ETA) shows that the 20 ms leading to an event are about the same for any type of event (figure 3.13, middle panel). The difference between types of events is made in the 150 – 20 ms before the event, and a short period after. To generate a single spike, the dendritic calcium spike that induces a burst has to be repressed, which is easier for slow dendritic than fast somatic inhibition. In the later case, hyperpolarizing input is needed to prevent the burst (dashed line). With fast somatic inhibition the burst rate is less reduced than in the case of slow dendritic inhibition (figure 3.3). Apparently, it is more difficult to convert bursts into spikes.

when strong inhibition is present, long interactions before the event play a role in the filtering, independent of location. The ISI histogram (figure 3.13, left) shows that for fast somatic inhibition there are interactions until at least about 130 ms. The ETA figure 3.13 (middle) shows slow oscillations leading up to bursts, which differed between fast somatic inhibition than for slow dendritic inhibition. The oscillations were not due to the period of silence before each spike that was a demand for spikes to be independent (analysis not shown). The addition of a single neuron and synapse, change the interactions between events; they become longer and more complicated. The location and kinetics of the inhibition strongly determine to which filter the microcircuit is sensitive: a quite different input signal is needed to generate a burst in a circuit with slow dendritic inhibition than to generate one in a circuit with fast somatic inhibition.

3.3.4 Effects of h-current

To investigate the effect of the h-current on spiking and bursting, we added it to the dendrite of the pyramidal cell model; as this is a single compartment, the amplitude of the h-current will be uniformly distributed over the dendrite. The parameters came closest to [92] in the model of [67]:

\[
I_h = g_h h(V - E_h)
\]

\[
\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h}
\]

\[
h_\infty(V) = \frac{1}{1 + \exp((V_1 - V)/k)}
\]

\[
\tau_h(V) = C_{\text{base}} + C_{\text{amp}} \exp\left(\frac{-(V_{\text{max}} - V)^2}{\sigma^2}\right)
\]

The parameters are given in table 3.1. The inclusion of the h-current resulted in the well-

<table>
<thead>
<tr>
<th>$V_{\text{max}}$</th>
<th>$-75$ mV</th>
<th>$V_1$</th>
<th>$-90$</th>
</tr>
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<tbody>
<tr>
<td>$\sigma$</td>
<td>20</td>
<td>$k$</td>
<td>$-8.5$</td>
</tr>
<tr>
<td>$C_{\text{base}}$</td>
<td>10</td>
<td>$C_{\text{amp}}$</td>
<td>40</td>
</tr>
<tr>
<td>$E_h$</td>
<td>$-30$ mV</td>
<td>$g_{h,d}$</td>
<td>1</td>
</tr>
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Table 3.1: Parameters of the h-current (equation (3.2)).
known transient ‘sag’-response on hyperpolarization (not shown). It did not have a strong effect on the firing rates that are induced by frozen noise (see figure 3.2). The bifurcation diagram (not shown) was very similar to the one with h-current. It shows that the stable resting state loses stability at a slightly lower current value \( I_d = -0.75 \mu A/cm^2 \) instead of \( I_d = -0.32 \mu A/cm^2 \) and the membrane potential is slightly higher at that point. This was expected, since the h-channels only open at hyperpolarized values and are mostly closed for higher input currents. For rapidly varying input, the h-current can contribute a dynamic component. Superposition of frozen noise to a hyperpolarizing current \( I_d = -0.8 \mu A/cm^2 \) injected into the dendritic compartment of the pyramidal cell enhanced the spike- and burst-rate (figure 3.3). This is also reflected in the ISI distribution (figure 3.14), which is more skewed towards shorter time intervals. The h-current introduced interactions between events in the 40 – 140 ms range and made the event-triggered averages sharper, probably reflecting a smaller membrane time-constant (figure 3.14 top panels). Introducing the h-current reduced the effect of hyperpolarizing inhibition (longer time-scale interactions, reducing short (< 100 ms) ISI intervals and reducing the burst rate); the burst rate (figure 3.3), the short time intervals in the ISI distribution and the negative part of the ETA for spikes are reduced less (figure 3.14).

3.4 Discussion

Feed-forward inhibition dampens the output and results in a suppresses the signal at the end of a stimulus. It increases the precision of firing by decreasing the temporal window \[72, 100, 113\]. Our analysis confirmed that feed-forward inhibition activates the pyramidal cell earlier in time. The output becomes more reliable if all events or single spikes only are taken into account, but it reduces the reliability of bursts. The effect of feedforward inhibition on the level of output activity is less straightforward. The burst rate decreases with interneuron activity and with the strength of the feed-forward connection. Depending on factors, such as the timing and activity of the interneuron, the target location and kinetics of the synapse, the reversal potential, the strength and propagation delays in the circuit, the single spike rate can either go up, go down or stay relatively constant. Controlling these parameters, will modulate the burst-to-spike ratio and the total output frequency almost independently, which could play a major role in the coding of the module in which this circuit is embedded. There is evidence that bursts and spikes are processed differentially postsynaptically in the brain \[26, 69, 88\]. They also play a different role in the coding of information in several systems such as weakly electric fish \[104\] and in cat lateral geniculate nucleus cells \[87\].

What explains the difference between slow dendritic inhibition, and fast somatic inhibition on the spike rate? A possible answer is in the research of Gulledge and Stuart \[50\]. They showed that in cortical pyramidal neurons shunting inhibition at the dendrite is excitatory regardless of timing, whereas somatic shunting inhibition is inhibitory when it is coincident with excitatory input, but excitatory at earlier times. Similarly, Jonas \[72\] states that the excitatory part of shunting inhibition can have an effect over a large distance within a neuron, whereas the inhibitory part is more local. This is caused by
3.4. Discussion

Figure 3.14: The effect of adding an h-current to the dendritic compartment on the ISI distribution (top) and ETA (bottom) for single spikes (right) and bursts (left) for a pyramidal cell without (black) and with (grey) an extra dendritic h-current, and without (solid lines) and with (dotted lines) slow hyperpolarizing feed-forward inhibition ($g = 4$, $\sigma^2 = 1$).
the fact that an IPSP has a longer time course than the underlying conductance change. If the reversal potential of the inhibitory synapse is higher than the average membrane potential, the depolarizing part of the IPSP outlasts the conductance change, resulting in an excitatory effect.

Shunting feedback inhibition increases the single spike rate and decreases the burst rate both with slow dendritic and with fast somatic projections [166]. In contrast, the present study shows that fast somatic feed-forward inhibition does not increase the single spike rate. In a feedback loop the interneuron is passive: it can only follow the excitatory pyramidal cell, and will therefore always give a synaptic event at the right time to prevent a burst. With feed-forward inhibition the interneuron plays a more independent role, filtering the input and ‘deciding’ whether to inhibit the pyramidal cell. It can regulate its firing rate independently from the pyramidal cell. Since not much is known about the filtering properties of interneurons, we used a very simple model here, but even then this extra degree of freedom makes the behaviour of the circuit quite versatile. Feed-forward inhibition results in interactions in the response filters that are longer (figure 3.11 and 3.13), which suggests the features to which a small network is sensitive can be longer and more complicated than those of a single cell. So the addition of one cell and one synapse expands the possibilities of what the network can code for considerably.

The h-current is assumed to reduce the excitability of a neuron due to an increased membrane conductance. However, it also causes the membrane to depolarize, which results in an increase in excitability [39, 45, 92]. We also looked at the effects of the h-current. Introducing an h-current into the dendrite of the pyramidal cell depolarized the membrane and reduced its time constant, all well known effects of the h-current [13, 103]. We did not find a reduction of dendritic calcium spikes causing bursts [146]. In our model, the dendritic h-current increased the output frequency, it introduced spike-spike interactions over a longer time scale and it made inhibition less effective. This last effect was also described earlier [161, 53]. However, one cannot simply conclude that the introduction of an h-current works purely excitatory, as we have not investigated the effect on excitatory synapses.

Expanding the principal excitatory information processing pyramidal cell with just a feed-forward connected interneuron already enhances the information processing considerably. We investigated two different connectivities: fast somatic and slow dendritic inhibition. We also investigated the difference between shunting and hyperpolarizing inhibition as well as the influence of including an h-current in the dendritic compartment. Inhibition causes the pyramidal cells to go from a slow bursting to a fast spiking regime, in which the spike rate is increased due to bursts that are converted into spikes, the excitatory effects of shunting inhibition, the reduction of the AHP-current-caused refractory period and rebound effects. This regime change influences the information transfer in these cells. The timing of inhibition is crucial for the regime change.
3.5 Supplementary material
Figure 3.15: Event-triggered analysis of the pyramidal cell, without any inhibition. Note that bursts have a strong positive part after the first spike \( t = 0 \) in the ETA and select strongly for the first and second filter, whereas spikes have a strong negative part after the spike and select for the first, third and fourth filter (figure modified from [166]. Whether a spike or a burst is fired is decided right after the (first) spike: more excitation will give a burst, whereas inhibition will prevent the development of a burst, and the response stays limited to a single spike.