Neural coding with spikes and bursts: characterizing neurons and networks with noisy input

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Chapter 6

General conclusion and discussion

In this thesis, cells in two brain areas (chapters 2 and 3 are about inhibition in the CA3 of the hippocampus, and chapters 4 and 5 are about thalamocortical relay cells) were investigated to answer the question how the biophysics of spike and burst generation influences the coding properties. We chose these two types of cells, since they both show bursting behaviour, but the mechanism behind the burst generation is very different, which make them ideal candidates to answer the research question. We will argue here that biophysics does influence coding. For instance, since bursts are long-lasting events, that need a slow depolarization such as a dendritic calcium spike, they can only code for low-frequency events in the input. Moreover, the way bursts are generated influence what features in the input they respond to: the biggest difference between the inputs needed for a burst or for a spike in the hippocampus is after the first spike of a burst, whereas in thalamocortical relay cells it is in the time before the first spike. Finally, the coding scheme a cell uses could also tell us something about the biophysics, as is shown in chapter 5: a good rate coder will have another input-output curve from a good temporal coder.

6.1 Inhibition in the hippocampus

Inhibition in the hippocampus, a brain area associated with the formation of memory and with spatial navigation [73], has been investigated intensively, often in the context of oscillations such as gamma oscillations (30-80 Hz), theta (4-10 Hz) oscillations and ripples (100-200 Hz, see for instance [19], [80],[79], [138]). In chapters 2 and 3, the effects of inhibition were investigated in a model of a hippocampal CA3 cell. Inhibitory synapses have either an hyperpolarizing ($E_{\text{syn}} < E_{\text{resting membrane}}$) or a shunting ($E_{\text{resting membrane}} < E_{\text{syn}} < E_{\text{threshold}}$) [9] effect on postsynaptic neurons. Although these two mechanisms can have quite different effects on the postsynaptic cell, it is generally thought that their common feature is that they keep the postsynaptic membrane potential away from the spike-generating threshold. However, the results of hyperpolarizing input can be quite different depending on the dynamics of the postsynaptic cell [67] and in networks the effect of inhibition can be diverse, ranging from the stabilization of the activity to the separation of cell assemblies and initiators of oscillations, depending on their exact position in the network and connectivity (for an overview, see for instance [72]). The work presented in this thesis added to these conclusions about inhibition. It showed that the exact timing of inhibition is a determining factor in the effects it has on the postsynaptic cell, especially in aborting bursts. Other parameters such as the reversal potential, kinetics and location of the synapse (soma or dendrite) also contribute to this effectiveness. Finally, feed-forward inhibition enriches the response of the microcircuit much more than feedback inhibition.

6.1.1 Fast somatic and slow dendritic inhibition

In chapters 2 and 3, the effects of two types of inhibition, fast somatic inhibition and slow dendritic inhibition, were investigated. Inhibition changes the behaviour of a pyramidal CA3 cell from a slow bursting to a fast spiking regime. This regime change influences the information transfer of the microcircuit: the features in the input the cell is sensitive to

change with the regime. Fast somatic inhibition is less effective in bringing about this regime change than slow dendritic inhibition. The differentiation between fast somatic and slow dendritic inhibition was based on the following research. Pearce [109] and Banks et al. [6] showed that $GABA_A$ mediated IPSCs onto CA1 pyramidal neurons have two components that can be differentiated anatomically, pharmacologically, physiologically and functionally. The first component shows fast decay ($\sim$ 9ms) and is spatially restricted to the cell body, whereas the second shows slow decay ($\sim$ 50ms) and is restricted to the dendrites. Miles et al. [98] show that in CA3 there are two distinct groups of interneurons: those that contact pyramidal cells perisomatically and those that make contacts in dendrites. The first group can suppress sodium-dependent action potentials, whereas the second type can suppress calcium-dependent spikes. Moreover, the IPSPs from the first group have faster kinetics than those of the second group. Together these results point into the direction of the existence of two functionally different types of inhibition: inhibition with fast kinetics that projects to the soma, and inhibition with slow kinetics that projects to the dendrites. Banks et al. [7] show that in CA1 the interneurons with slow GABA-synapses ($GABA_{slow}$) do not only inhibit pyramidal cells, but also inhibit the interneurons with fast GABA-synapses ($GABA_{fast}$), thereby establishing interactions between the two groups. They claim that such an interaction can contribute both to gamma and to theta rhythms. White et al. [158] use this connection to demonstrate in a computational study that such a network including fast and slow GABA interneurons, can autonomously create a nested theta-gamma rhythm, as long as the connections within populations of the same types of interneurons are strong, the connections between the populations are weaker and the input drive is tuned. Moreover, such a network can amplify and synchronize phase-dispersed periodic input signals. Altogether, these results suggest that in the hippocampus inhibition with fast GABA kinetics and inhibition with slow GABA kinetics exists, and that these two types of inhibition can interact.

In chapters 2 and 3, it was shown that the effects of these two types of inhibition, fast somatic inhibition and slow dendritic inhibition, change the information transfer of pyramidal single spikes and bursts. Booth and Bose [14] showed, using the same pyramidal cell model of Pinsky and Rinzel [110], that the timing inhibition is crucial: feedback inhibition arriving before a burst can delay it, but if it arrives during the burst it can cause a phase advance, which can result in a switch from a slow bursting to a fast spiking regime [15]. They used hyperpolarizing dendritic synapses with fast kinetics. In chapters 2 and 3, it was found that also with noisy input, inhibition can change the firing of the pyramidal cell from a slow bursting to a fast spiking regime: every type of inhibition, slow dendritic inhibition or fast somatic, feed-forward or feedback, shunting or hyperpolarizing, always reduced the burst rate. However, what happens to the spike rate was less uniform. Whereas slow dendritic inhibition mostly increased the spike rate, fast somatic inhibition was not always capable of doing this. Moreover, slow dendritic inhibition was more effective at both reducing the burst rate and increasing the spike rate. This can be explained by the mechanism of the regime changes: well-timed inhibition can prevent the dendrite from developing the calcium-spike that causes the burst. This calcium spike would otherwise have activated the slow AHP current which makes the refractory period of the pyramidal cell longer after a burst than after a spike. However, this effect can only

occur when the inhibition reaches the dendrite within a short time-window after the first spike, when the burst can still be prevented. A somatic IPSC will have to travel to the dendrite first, which will delay and attenuate it and therefore make it less effective. So the biophysics of the inhibition determine the information transfer of spikes and bursts in the pyramidal cell.

The conclusion that inhibition can increase the activity of a pyramidal neuron seems contradictory, but has been shown before. Cossart et al. [24] showed that the loss of slow feedback O-LM interneurons in temporal lobe epilepsy results in decreased inhibition in pyramidal cell dendrites, but increased inhibition around the soma. This increased somatic inhibition is the result of hyperactivity of somatic projecting interneurons. Together these alterations could also lead to epileptiform activity. Wendling et al. [157] showed a similar result in a macroscopic model including fast somatic and slow dendritic inhibition. They report that the loss of slow inhibition results in an increase of fast IPSPs, which then leads to increased activity of the pyramidal cells.

In chapters 2 and 3, not only the change from a bursting to a spiking regime was investigated, but also how inhibition changes the filtering properties of a microcircuit, i.e. how inhibition influences the features in the input a pyramidal cell responds to. It was found that bursts and spikes are filtered separately, where bursts are sensitive to other input features than single spikes: bursts need a depolarizing input that lasts until after the first spike of a burst, whereas single spikes need hyperpolarizing input right after the spike to prevent a burst from developing. With increasing strength of the inhibitory synapse, spikes are favoured over bursts and more excitation precisely timed around the (first) spike is needed for a burst, whereas excitation before an event more easily leads to a spike. These effects are similar for fast somatic inhibition and slow dendritic inhibition, but again the effects are stronger for slow dendritic inhibition.

6.1.2 Feedback and feed-forward inhibition

In chapters 2 and 3, inhibition in both a feedback and a feed-forward construction was investigated. Feedback inhibition is more effective in decreasing the burst rate and increasing the single spike rate, i.e. in making the change from the bursting regime to the spiking regime. This makes sense intuitively, since in a feedback loop the interneuron is rather passive: it can only follow the excitatory pyramidal cell, and can therefore always give a synaptic event at exactly 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 or not, and regulate its level of activity (firing rate) independently of the pyramidal cell. This extra degree of freedom makes the behaviour of the microcircuit very versatile: regulating the burst rate and the spike rate almost independently. Feed-forward inhibition can make the timescale of interactions between output spikes and bursts much longer. This can be seen when the neuron is viewed as a filtering device: the features in the input the microcircuit responds to are extended over a longer time-span. So adding feed-forward inhibition to a pyramidal cell makes the filtering of the microcircuit more complex. This effect is stronger for feed-forward than

for feedback inhibition.

Feedback and feed-forward inhibitory loops are the most basic building blocks of networks including interneurons. Feedback inhibition, in which an excitatory neuron inhibits itself through an interneuron, results mainly in regulatory effects, in which the excitatory neuron can stabilize or stop its own activity [72], [100] or can result in oscillations between the excitatory and inhibitory cell [162]. Feed-forward inhibition, in which an excitatory input works on both an excitatory neuron and on an interneuron that inhibits the excitatory neuron, is generally thought to dampen the output and results in a stronger signal at the beginning than at the end of a stimulus: the pyramidal neuron can only spike at full strength before the interneuron kicks in. This increases the precision of firing by decreasing the temporal window [72],[100], [113]. We explicitly tested the claim that feed-forward inhibition makes the output of a pyramidal cell more reliable in chapter 3. Feed-forward inhibition activates the pyramidal cell earlier in time; the output becomes more precise when all events or single spikes only are taken into account, but not if the analysis is restricted to bursts. Combinations of these two types of inhibition lead to more complex behaviour of the net [72]. Several experimental observations suggest that both these types of inhibition exist in the CA1 of the hippocampus. Wierenga and Wadman [160] stimulated the Shaffer-Commissural pathways in the hippocampus of rats and measured the synaptic input to different interneurons in CA1 after the local circuit was activated. They found that there where two groups of synaptic input onto the interneurons: a short-latency monosynaptic input, that occurred before the population spike, and a long-latency disynaptic input, that occurred after and only if there was a population spike. They concluded that the first group interneurons probably receives direct input, and therefore gives feed-forward inhibition, whereas the second group interneurons probably receives input form the activated pyramidal cells, and therefore gives feedback inhibition. In a different work, the same authors showed that these feed-forward and feedback loops might be sensitive to different frequencies in the input [159].

Elfant et al. [40] stimulated the hippocampal CA1 of rats by direct input from the enthorinal cortex. They found an inhibitory connection between feedback interneurons in the stratum oriens (SO, OLM-cells) and feed-forward interneurons in the stratum lacunosum moleculare (SLM, different types of cells). This implies separate feed-forward and feedback loops in the CA1 of the hippocampus, which in addition can influence each other. More precisely, if the feedback loop becomes more active, it inhibits the feed-forward loop, thereby shifting the balance between feed-forward and feedback inhibition. To investigate the effects of these two interacting loops, we incorporated both loops in a more extended network. Preliminary results (not shown in this thesis) showed that in a network with separate feedback and feed-forward inhibitory loops that inhibit each-other, the two loops can synchronize, since the interneurons will not inhibit each-other if they spike at exactly the same time (this 'window of opportunity' will of course depend on many factors such as synaptic kinetics, delays). Once the feed-forward and the feedback loops are synchronized, their effects will be indistinguishable.

We conclude that feedback inhibition is more effective in making the transition between

the bursting and the spiking regime in pyramidal cells, since it gives its input always at the right time, but feed-forward inhibition is more versatile, and can make the computation in a microcircuit much more complex.

6.1.3 Timing is everything: delays, short-term plasticity and input correlations

In the previous two paragraphs, we discussed the relevance of exact timing of inhibition. Well-timed inhibition prevents a burst by changing it into a spike or completely inhibiting any output event. Thereby it reduces the potassium currents that determine the refractory period, which enhances event-generation shortly after the inhibition. The different effects of feed-forward and feedback inhibition and of fast somatic and slow dendritic inhibition depend at least partially on timing. Delays in the system and short-term plasticity play an important role, since these can change the timing of inhibition.

In the models presented in chapters 2 and 3, the effects of timing were tested by including different mechanisms. In both the feedback and the feed-forward models, delays were included in the synapses to look at the effects of delaying the inhibitory input to the pyramidal cell. The major effect of delays in these microcircuits is that they made inhibition less effective in making the change from the bursting to the spiking regime, since the inhibition simply arrives to late to do so, both in the feedback and in the feed-forward setup, and both with slow dendritic and fast somatic inhibition. The hypothesis that the timing of inhibition is crucial was also tested in the feed-forward model, by using input to the interneuron that was anti-correlated or uncorrelated. In these cases the neuron could hardly make the change from the bursting to the spiking regime, and the change in output reliability that normally comes with the regime change was not observed.

In the feedback model, short-term plasticity was included to assess the results of Pouille and Scanziani [114]. They found that interneurons which respond to spike trains of ten stimuli to the alveus can be divided into two classes: interneurons in CA1 of which the probability of spike generation is highest at the onset of the train and rapidly falls with subsequent stimuli (onset transient interneurons) and interneurons in CA1 of which the probability of spike generation after the first stimulus is low and increases to a plateau between the third and tenth stimulus (late persistent interneurons). They claim that this is the effect of four interplaying properties. Firstly, for the late-persistent neurons, the decay time of EPSCs is longer and secondly, their membrane time-constant is larger than for onset-transient neurons, resulting in stronger summation for the late-persistent neurons. Thirdly, the amplitude of the EPSCs show facilitation for late-persistent neurons, but depression for onset-transient ones. Finally, disynaptic IPSCs show depression, resulting in strong inhibition at the beginning of the spike train. This explains the transience of the onset-transient neurons, and the late response of the late-persistent neurons. The onset transient neurons project to the pyramidal cell layer (around the soma), whereas the late persistent interneurons project to more distant dendritic layers. If one assumes that the onset-transient neurons cause the fast somatic inhibition discussed before, and the late-persistent interneurons the slow dendritic inhibition, this adds an extra dimension to the

complexity of this system with respect to how these loops get activated. Moreover, the result that disynaptic IPSCs show depression, might mean that their is a 'back-synapse' from the fast to the slow feedback loop as well.

In the feedback model, short-term plasticity was included to test how the results of Pouille and Scanziani [114] influence the circuit. Short-term depression was included in the synapse between the pyramidal cell and the fast-loop interneuron, and facilitation was included in the synapse between the pyramidal cell and the slow-loop interneuron. The time constants of this short-term plasticity relative to the activity of the presynaptic neuron turned out to be crucial: for instance, if the recovery time constant of depression is much smaller than the mean inter-event interval, most synapses will recover from depression before the next event, and depression does not play a role. If the recovery time constant is much larger than the mean inter-event interval, most synapses will be depressed during baseline activity and they will no longer contribute. A similar argument holds for short-term facilitation. This means that short-term plasticity could be used to selectively turn on or off groups of (inter)neurons during different activity patterns of the network. However, without knowing the baseline activity of the network, is is hard to judge what the specific role of short-term plasticity is and vice versa. Moreover, a wide range of time constants of short-term plasticity has been found: recovery from depression time constants range from a few to hundreds of milliseconds in hippocampal pyramidal to interneuron synapses [89], [114], [159], and even hundreds of milliseconds to tens of seconds in the cortical pyramidal to interneuron synapses [43], [147], [151], and a similar range has been found for facilitation [89],[114], [151], [159]. We conclude that short-term plasticity is only functional when the recovery time constant is in the same time range as the mean inter-event interval.

6.1.4 Conclusion

We conclude that inhibition can switch the output of a pyramidal CA3 cell from a slow bursting to a fast spiking regime. With this regime change comes a change in many properties, such as the reliability of the output and the features in the input the microcircuit responds to. The timing of inhibition is crucial for this regime change: slow dendritic feedback inhibition is the most effective while any factor (e.g. the location of the projection, delays, short-term plasticity, the exact spike timing of the interneuron) that changes the timing of inhibition reduces the efficiency. Feed-forward inhibition has a richer repertoire in shaping the microcircuits output than feedback inhibition.

6.2 Bursting and spiking in thalamocortical relay cells

The thalamus is a midbrain structure that is involved in amongst others controlling the flow of sensory information to the cortex, and thereby in sensory processing, movement and attention, and in cycles of sleep and wakefulness [73], [134]. The thalamus consists amongst others of excitatory relay (TCR) cells, on which this thesis was focused, and of inhibitory reticular cells. A thalamocortical relay cell may receive excitatory input from the cortex and inhibitory input from the reticular part of the thalamus or from the

basal ganglia. The basal ganglia are another versatile brain area involved in amongst others action selection and reinforcement learning, and known for its role in Parkinson's disease [73], [120]. Like hippocampal pyramidal CA3 cells, thalamocortical relay cells show bursting behaviour. However, the bursting mechanism of thalamocortical relay cells is quite different from that of hippocampal CA3 cells. Even though both are a consequence of a slow calcium spike, the kinetics of the calcium currents underlying these spikes are very different. In the pyramidal cells the bursts are caused by a combination of a high-threshold non-inactivating calcium current and a 'ping-pong effect' between the soma and the dendrite due to back-propagating action potentials (see for instance [23] for an overview). In thalamocortical relay cells the bursts are caused by an inactivating low-threshold calcium current (T-current), that can only recover from inactivation by a period of hyperpolarization. The difference in mechanism explains why the behaviour of thalamocortical relay cells is quite different from the behaviour of pyramidal CA3 cells. In chapters 4 and 5 of this thesis, we investigate the properties of bursting thalamocortical relay cells.

6.2.1 Regime changes

The burst mode of firing in thalamocortical relay cells is associated with slow-wave sleep and occurs during pathological conditions [140]. The original hypothesis was that the burst mode prevents the correct relay function. Later research indicated that burst firing in these cells does not exclude effective relay properties in awake animals ([121], for a review see [133]). Theories about the function of bursts in this system were summarized in chapter 1. In chapter 4, we investigated what bursts and single spikes can tell us about the input to the TCR neuron. We looked at how this code depends on the background or regime the neuron is in.

In chapters 4 and 5, we show that depolarization moves the neuron from a bursting to a spiking regime. In between the neuron is in a mixed regime, in which it responds to input with both single spikes and bursts. This mixing of the two regimes was demonstrated before [163]. In chapter 4, it is shown that in a mixed regime, spikes transfer different information than bursts: they phase-lock to and transfer information at higher frequency and they are more selective for fluctuations than bursts. In addition, a single spike contains less information than a burst, but especially in the spiking regime there are many more of them, so they do carry the bulk of the information in the spike train. Bursts on the other hand are highly informative but rare, especially in the spiking regime. They can only phase-lock to and transmit information at low frequency, and are especially in the bursting regime more a response to integration than to fluctuations.

The neural code changes with the mean of the input. On depolarization, the neuron shifts from a bursting to a spiking regime, in which it responds earlier in time and more reliable. The features in the input it is sensitive to show that it responds more to fluctuations and less to integration. Because of the transfer from bursting to spiking, it is capable of responding to higher frequencies and shows a more broadband phase-locking and information transfer, and the impedance of the subthreshold membrane potential is

higher at higher frequencies at a more depolarized membrane potential.

Even in the spiking regime the information transfer of these neurons depends mainly on the power of the input signal in a frequency band up to about 50 Hz. TCR neurons are not capable of transferring information at frequencies higher than $50 - 100$ Hz. This explains the result that when the high frequencies in the input are not filtered out, we need a higher total power to let the neuron respond at all. Bursts transmit information in a lower frequency band than spikes. In agreement with this, Lesica and Stanley [86] claim that white noise causes less bursts than pink noise, in which frequencies decay according to a power-law. So it seems that TCR neurons can only respond if there is enough power in the low frequency band of the input, and that more power in the lowest bands promotes bursting.

The finding that bursts are rare but highly informative is in agreement with a 'feature detection' [22], [86], [104]) or 'wake-up call' role [133] for bursts. Reinagel et al. [121] found that bursts and spikes code for similar information. However, since they used visual stimuli with a cutoff frequency of about 16 Hz, they could never see the difference of high-frequency phase-locking and information transfer we did, a limitation they mention in their discussion. In vivo, cortical neurons are assumed to be in a high-conductance state: a state in which they receive a bombardment of synaptic input, which strongly increases the membrane conductance (and therefore reduces the membrane integration time-constant), and causes membrane potential fluctuations of about $2 - 6$ mV [35]. Our model neuron hardly bursts in a simulated high-conductance state, which is in agreement with the findings of Swadlow and Gusev [141]. They measured the response of the neocortex to thalamic bursts in awake rabbits, and found that the neocortex is powerfully activated by bursts. However, the burst rate of the thalamus never exceeded 0.5 Hz. This suggests a 'rare but highly informative' role of bursts in the high-conductance state. We hypothesize that the T-current is overpowered by synaptic inputs.

6.2.2 Conclusion

Like in the case of the hippocampus, we found a regime change in these thalamocortical relay cells, in which cells go from a slow bursting to a fast spiking regime. Like in the hippocampal case this regime switch changes the information transfer of these cells. However, this regime change is caused by a different aspect of the input: where in the hippocampus the regime change is triggered by well-timed dendritic inhibition, the regime change in TCR cells is very sensitive to the mean membrane potential, since thalamocortical relay cells need to be hyperpolarized to make a burst, which is not the case for hippocampal pyramidal cells. We did not test what inhibition timed exactly around the initiation of a burst would do in thalamocortical relay cells, whether this could have a similar effect as in the hippocampal case. This could be an interesting question for future research. Secondly, the analysis of the TCR cells has shown us what the neuron responds to in different regimes. In future research one could make 'optimal stimuli' to make the neuron respond in specific ways, for instance to make the neuron burst only or spike only.

6.3 Final remarks

In this thesis, we investigated how biophysical properties of neurons determine the code the neuron uses. We showed that the biophysical properties influence the coding of a cell: the biophysical mechanism underlying bursts influences what these bursts code for. Firstly, bursts are relatively slow events compared to single spikes. They span more time, and are associated with a longer refractory period in both systems we investigated. This limits the frequency band in the input they can code for. Another correspondence between the two systems is that when a cell can make bursts, this seems to influence the 'meaning' of a single spike too: the occurrence of a single spike is also the absence of a burst. Therefore, the occurrence of a single spikes gives information about the stimulus around this spike: not only about the input leading up to it, but also about the input in a short period after a the single spike. The fact that a single spike was fired and not a burst means that also just after the spike the input was unfitting for a burst to develop. Finally, in both cases bursts and single spikes give similar, but not the same information about the stimulus within a single spike train. So the 'burst code' and the 'spike code' can be seen as a parallel code.

The different biophysical mechanisms that are responsible for burst initiation in the two systems investigated, influence the input features that a burst or single spike are sensitive to. Firstly, both pyramidal cells and TCR cells can show a regime change between a slow bursting and a fast spiking regime. But these regime changes are brought about by different mechanisms: in a TCR neuron, a change in the mean of the input triggers the regime change, whereas it does not in the pyramidal cells, that need well-timed inhibition. Secondly, the differentiation between a spike and a burst in a hippocampal pyramidal cell seems not to be in the input leading up to the spike or burst, but in the input after the (first) spike, where further depolarization results in the development of a burst, but hyperpolarization results in the abortion of a burst, so a single spike. Inhibition can take over this role of hyperpolarization, which in the case of feed-forward inhibition means that the input leading up to the spike has to be just right to activate the pyramidal cell and the interneuron, so that the interneuron sends its synaptic input at the right time to prevent a spike. Similarly, the input leading up to a burst has to activate the pyramidal cell, but not the interneuron (or at least make the interneuron spike too late or too early). In a TCR cell, the decision between a burst or a spike is made before the event, where stronger hyperpolarizing input will result in a burst, since this activates the T-current, and less hyperpolarizing input results in a single spike. But also here the input after the (first) spike does have an influence, as can be seen in the STA for bursts: it shows a longer depolarizing input than for spikes.

An reverse deduction in relation to biophysics and coding can also be made: if we assume a neuron uses a certain code, this would mean that it also should have certain biophysical properties. In chapter 5, we showed that the reliability of the output of a neuron decreases with a steeper input-output curve. This shows that there is a tradeoff between reliability and sensitivity: the steeper the input-output curve of a neuron, the lower in general its reliability will be, but the more sensitive it is to changes in the mean input. So a neuron

with a steep input-output curve can be a good 'rate coder'. A more or less constant input-output curve can have a high reliability. It will not be able to signal any change in the mean of the input in its output frequency, but it can signal other characteristics of the input in the timing of the output spikes. So this might be an ideal situation for a neuron that shows 'temporal coding'. Therefore, the steepness of the input-output curve might be a telltale of the type of coding a neuron is doing.

The conclusions discussed here are conclusions for single cells and small microcircuits. The influence of network activity was incorporated in a simplified way in all the models and experiments discussed here. This makes it necessary for the conclusions to be extended to models or experiments where these microcircuits are embedded in larger, more elaborate networks. However, since timing is so important, but many time-constants, delays and other important parameters about for instance the heterogeneity of cells in the network are not known, it is almost impossible to construct these networks in a non-trivial way. Therefore, it is hard to make predictions, as was concluded from both a more extended feedback model in chapter 2 and a more extended model including both feedback and feed-forward inhibition as discussed in section 6.1.2. The results we found in the microcircuits are valid, but it remains to be seen what emergent properties could arise in larger networks. It is important that experimental values are obtained and included in models like this for all aspects influencing timing, such as delays and short-term plasticity, but also the filtering properties (and therefore their spiketimes and the correlation of these spiketimes with the neurons they project to) of different types of neurons in the network considered.