Control of a small neuronal network by feedforward and feedback inhibitory interneurons

Electrophysiological measurements in the CA1 area of the rat demonstrated two functional classes of interneurons that differed in the way they were related to the main, Schaffer collateral, input. Feedforward interneurons are directly activated by the input and project to the pyramidal output cells (PCs), while feedback interneurons transfer PC activity back to PC input.
In a model we investigated how the steady state activity in the network is determined by the properties of the three classes of neurons and their connectivity.

First we use a lumped mathematical model, which describes the steady state input/output relations of the populations and the transfer of synaptic connections. In this part of the study we assume uniform connectivity that describes the coupling between populations. In the second phase of the study we have used explicit descriptions of populations of individual neurons and their connections.

The model implemented a network with a connectivity based on the CA1 area of the hippocampus. The Schaffer collaterals provided the input to the pyramidal cells and also to one class of the interneurons (FF, the feed forward coupled interneurons). The pyramidal cells provided the output of the network and they also activated the second class of interneurons (FB, the feed back coupled interneurons) which formed the recurrent connections.

Linear gain functions were used to analyze the fundamental differences between FF and FB inhibition. The feedforward inhibition controls the gain of the network in cooperation with the Schaffer collateral mediated excitation. The feedback inhibition is driven by the pyramidal cell activity and scales the gain of the network transfer.
Because neurons can only have positive firing rates which start at a certain baseline firing frequency and saturate for high values, the gain functions need to be non linear.

In the non-linear case we used the experimental work published by Wierenga & Wadman to restrict the relations between and the shape of the different gain functions thereby reducing the parameter space considerably.
The experimental work showed that feedforward interneuron input showed large sensitivity to input changes at stimulus intensities that evoked little activity in the pyramidal cell population and they saturated at lower stimulus intensities than the pyramidal neurons. One of the surprising experimental findings was that the input to each feedback interneuron closely reflected the population activity in the pyramidal cells and that it gradually increased with enhanced principal cell activity.

Feedforward inhibition
The non-linear gain functions in the model were defined in accordance with the experimental data. The direct consequence of these functions was that feedforward inhibition could not inhibit the pyramidal cells at high activity levels. The interneurons were already saturated and could not provide more inhibitory input, but they could reduce the firing rate to below baseline level. The feedforward interneurons therefore have a subtractive effect on the network signal transfer at higher input rates and shift the pyramidal gain function depending on the strength of the inhibition.

We conclude that feedforward inhibition expands the output range of the pyramidal cells, while the dynamic range of the input is extended. This means that the network is able to differentiate over a wider range of inputs.

Feedback inhibition
The gain functions for feedback inhibition were also constructed from the experimental data; the properties of the inhibitory connections were taken from the literature and assumed to be similar in all populations.
As long as pyramidal cell activity saturates before interneuron activity, the feedback inhibition is able to control pyramidal activity over the full activity range. This condition was also observed in the experiments.
Our model showed that feedback inhibition is able to scale the pyramidal cell activity and therefore confirms the hypothesis that Wierenga & Wadman formulated to explain their data. In the optimal working range, that is the range above threshold and below saturation, feedback interneurons have a divisive effect on the signal transfer and they linearize the signal transfer of the network.
The total gain in the feedback loop is determined by a combination of several non-linear gain functions, which result in a complex function. In our model we analyzed the consequences that result from these experimentally determined gain functions for network transfer.

We concentrate here on the steady state transfer of the network, but we realize that since the dynamic properties of cell firing and synaptic transfer are different for the various elements in our models the total transient behavior of the network will be far more complex.

In real biological networks a complicating factor is the existence of patterned connectivity, which leads to specific spatial behavior. In our system there seems to be a large convergence in connections from pyramidal cells to feedback interneurons, which is the only way to explain the close correlation between population activity and the input of the feedback interneurons. Such a constellation would provide global activity scaling and normalization in a network where large changes in local activity may occur.

A second question that is not yet resolved is whether it is necessary to have two distinct population of interneurons that perform the two kinds of inhibition that we describe here or whether these function can be combined in the same neurons. Opposing requirements for the gain function in these neurons could exclude such a combination.

Wierenga C. J. and Wadman W. J. Functional relation between interneuron input and population activity in the rat hippocampal CA1 area, Neuroscience (in press).