Control of a local neural network by feedforward and feedback inhibition

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Abstract

The signal transfer of a neuronal network is shaped by the local interactions between the excitatory principal cells and the inhibitory interneurons. We investigated with a simple lumped model how feedforward and feedback inhibition influence the steady state network signal transfer. We analyze how the properties of inhibition affect the input/output space of the network and compare the results with experimental data obtained in the hippocampal CA1 circuit. The specific non-linear transfer of the cell populations determine how feedforward and feedback inhibition modulate the gain and/or shift the network signal transfer. An important biological issue is whether the two forms of inhibition can be combined in the same interneurons. Combining both functions in the same interneurons requires highly non linear addition of their inputs.

Keywords: network signal transfer; feedforward and feedback inhibition; CA1

1. Introduction

Neurons have a limited range in which they are optimally sensitive to changes in their input. Most neurons function in small networks that comprise of excitatory principal neurons and local inhibitory interneurons. The interactions between these neurons shape the signal transfer of the network. With a simple linear model, Douglas et al [2] showed the basics of how the steady state signal transfer of the principal cells in a network is influenced by excitatory recurrent connections and feedforward (FF) and feedback (FB) inhibition by the interneurons.

Recently, Wierenga & Wadman [3] described how inhibitory interneurons in the CA1 area of the hippocampus function either in a FF mode or in a FB mode in relation to Schaffer collateral inputs (fig. 1*A*) and that both have a specific relation to this input. Here, we study the functional consequences of specific non-linear input-output relations of FF and FB connected interneurons for the steady state network signal transfer and we investigate the possibility to combine both functions in the same interneurons.

2. Model

Our simple model describes the mean steady state activity of the individual cell populations. Such a lumped model assumes homogeneous cell properties within populations and uniform connectivity between the populations. The network consists of a pyramidal and an interneuron population that both receive excitatory input A_s. The pyramidal population forms recurrent connections with the interneuron population and with itself and provides the output of the network (fig. 1*B*). The steady state activity of the pyramidal population (A_p) and of the interneuron population (A_i) as a function of their weighted inputs are described by the equations:

$$A_p = G_p(w_{sp} \cdot A_s + w_{pp} \cdot A_p - w_{ip} \cdot A_i) \qquad (1)$$

and

$$A_i = G_i(w_{si} \cdot A_s + w_{pi} \cdot A_p) \qquad (2)$$

with weight constants $w_{source \rightarrow target} \geq 0$.

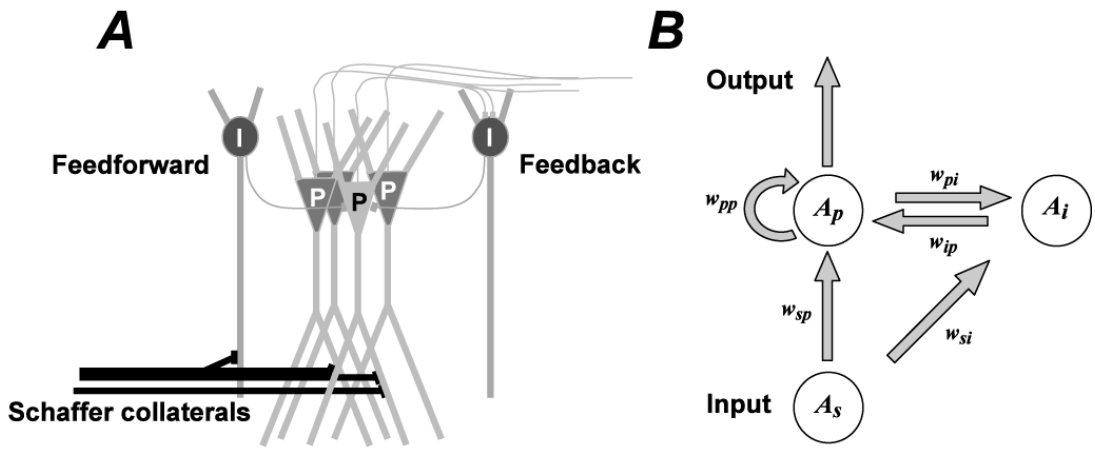

Figure 1. Connectivity of the CA1 network and the model.
A: the functional connectivity between the pyramidal cells (P) and interneurons (I) in the hippocampal CA1 area defining feedback and feedforward mode. *B*: scheme of the model with one interneuron population performing both FF and FB inhibition.

As a first approximation we assume linear summation of the excitatory and inhibitory inputs to the pyramidal population in steady state, which reproduces the results of a more complex biophysical model from a recent study on inhibition by Aradi et al. [1].

In numerical calculations we define the input/output functions G_p and G_i of sigmoidal shape as a population of neurons always has a positive mean firing rate and mostly a certain firing threshold; the activity also saturates above a certain input intensity. To illustrate the effect of the inhibition on the network signal transfer analytically, we first approximate G_p and G_i by functions that consist of three linear regions: an unresponsive range below a certain input intensity, where $A = 0$, a range above high intensity where A saturates as A_{max} and in between those regions we define the dynamic range of the neurons where their activity is given by:

$$A_p = g_p \cdot (w_{sp} \cdot A_s + w_{pp} \cdot A_p - w_{ip} \cdot A_i - s_p) \tag{3}$$

and

$$A_i = g_i \cdot (w_{si} \cdot A_s + w_{pi} \cdot A_p - s_i) \tag{4}$$

using gains of g_p and g_i and thresholds of s_p and s_i. (A_p and $A_i \geq 0$).

3. Results

First the input-output relation of FF and/or FB connected interneurons is analyzed for interneuron activity in its dynamic and in its saturated range. Substituting (4) into (3) we can calculate the dependence of A_p on A_s in the dynamic range, or the network transfer gain, as:

$$\frac{dA_p}{dA_s} = \frac{w_{sp} - w_{ip} \cdot g_i \cdot w_{si}}{1/g_p - w_{pp} + w_{ip} \cdot g_i \cdot w_{pi}} \tag{5}$$

When interneuron activity is saturated to A_{i_max}, the inhibition produces a shift of the network signal transfer according to:

$$A_p = \frac{w_{sp} \cdot A_s - w_{ip} \cdot A_{i\_\max} - s_p}{1/g_p - w_{pp}} \tag{6}$$

Feedforward inhibition
When the response to the network input of the interneuron population relative to the pyramidal population is known, the effect of FF inhibition alone on the network signal transfer can be analyzed (fig. 2*A*). We use here a more realistic neuronal transfer function and define the dynamic range between 10% and 90% of the maximal activity; this allows separating the working range into two regions. For input values where the interneuron population is in its dynamic range the gain of the network is modulated similar to what was shown in *Eq. 5* with $w_{pi} = 0$. Increasing the strength of the FF inhibitory loop by increasing w_{ip} now decreases the network gain in this region. For input values where the interneuron population is saturated the signal transfer of the network is shifted as was demonstrated in *Eq. 6*. Increasing w_{ip} increases the shift in this region.

Feedback inhibition
When the interneuron transfer function is known we can analyze the effect that FB inhibition alone has on the network signal transfer (fig. 2*B*, using the same transfer functions as in 2*A*). The working space can again be separated into two regions. For the pyramidal activity levels where the interneuron population is in its dynamic range the gain is modulated similar to what was shown in *Eq. 5* with $w_{si} = 0$. Increasing the strength w_{ip} of the FB loop decreases the network gain in this region thereby preventing the network to be driven into saturation. When the interneuron activity is saturated the network signal transfer is shifted similar to what was shown by *Eq. 6*. Increasing w_{ip} increases the shift in this region.

Combination of feedforward and feedback inhibition
When the same interneuron population transmits both FF and FB inhibition, the network input A_s and the pyramidal population activity A_p provide the input to the interneuron population. When the two inputs sum linearly, two lines divide the input-output space into three regions, the first one $w_{si} \cdot A_s + w_{pi} \cdot A_p = s_i$ divides the region where interneuron activity is below threshold from the dynamic range and the second one $w_{si} \cdot A_s + w_{pi} \cdot A_p = A_{i\_\max} / g_i + s_i$, separates the dynamic range from the region where interneuron activity is saturated (fig. 2*C*). In the input-output space, where the interneurons are in their dynamic range, the gain of the network transfer is modulated similar to *Eq. 5*. Increasing the inhibition w_{ip} will decrease the gain. In the input-output space where interneuron activity is saturated the shift of the network signal transfer is similar to *Eq. 6*. Increasing w_{ip} shifts the transfer function.

When the two inputs to the interneuron population do not sum linearly but facilitate or inhibit each other, e.g. as a consequence of the presence of voltage-dependent ion channels in the membrane, we can redefine the interneuron input-output function in the dynamic range with:

$$A_i = g_i \cdot \left(\frac{w_{si} \cdot A_s + w_{pi} \cdot A_p}{1 + k \cdot A_s \cdot A_p} - s_i\right) \qquad (7)$$

where the parameter k determines the nonlinear interaction. A supra- (k > 0) or sub-linear (k < 0) summation affects the interneuron threshold and saturation curves in the input-output space thereby decreasing or increasing the region where the interneurons are in their dynamic range (dot-dash curves in fig. 2*C*).

Next we separated the FF and the FB inhibition loop into two independent interneuron populations, which resulted in distinguished areas in the input-output space where no, one or both interneuron populations are in their unresponsive, dynamic or saturated range (fig. 2*D*). The network gain is modulated and the signal transfer shifted as shown above but now with two independent constants w_{pi} and g_i for the FF and the FB interneuron population.

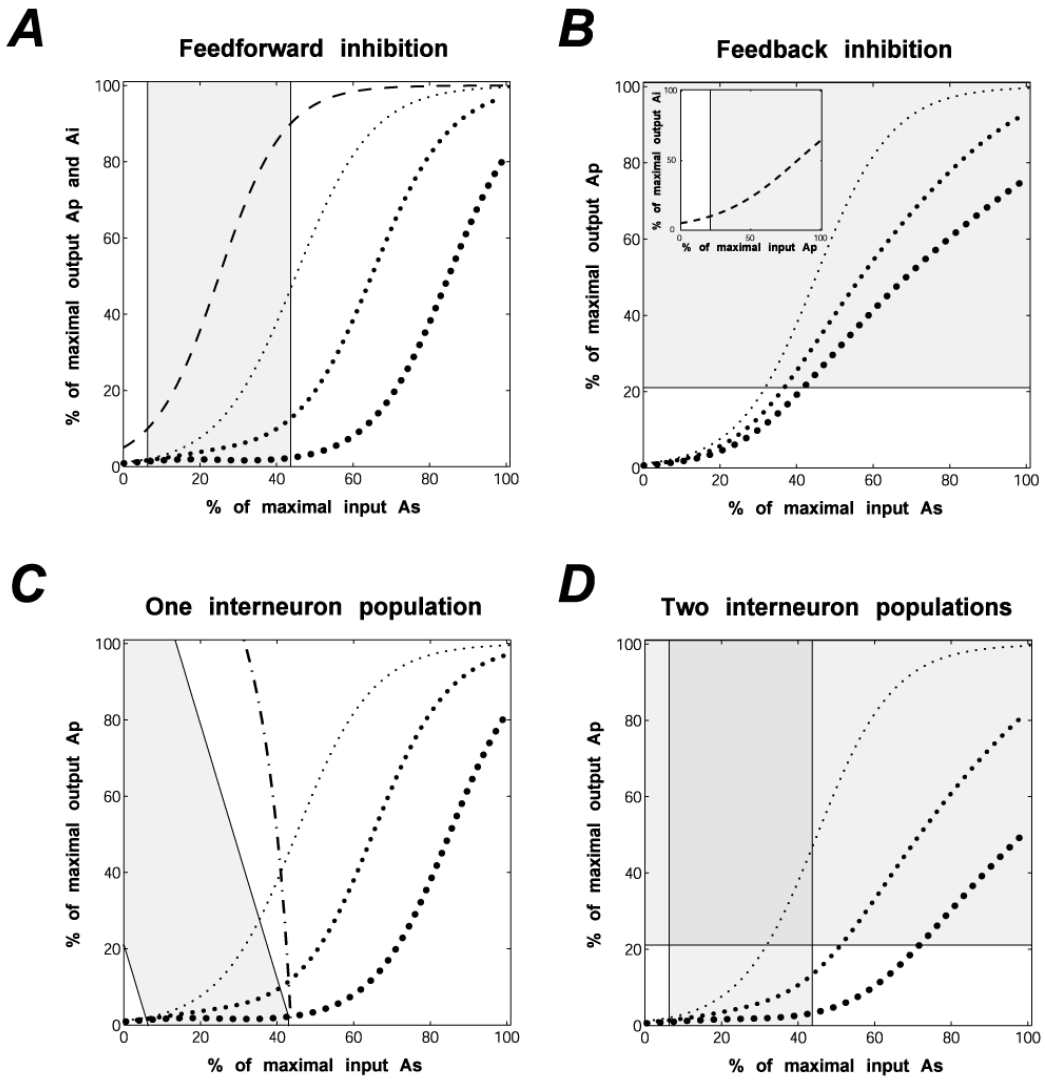

Figure 2. Inhibition shaping the steady state network signal transfer.
The graphs show how the network signal transfer is influenced by FF and/or FB inhibition. The specific transfer functions $G_p(x) = 100/(1 + \exp((45 - x)/10))$ and $G_i(y) = 100/(1 + \exp((25 - y)/8.5))$ were fitted on experimental data from the CA1 region [3] where x and y are the respective inputs, defined as a percentage of the maximum. The parameters of the model are $w_{sp} = 1$, $w_{si} = 1$, $w_{pp} = 0$ and $w_{pi} = 0.3$. The signal transfer of the network is plotted for increasing strength of the inhibition w_{ip}: 0, 0.2 and 0.4 for FF inhibition and 0, 0.5 and 1 for FB inhibition (shown by increasing thickness of the dotted lines). The relation between the interneuron output and its input is shown by dashed curve in *A* and as an inset in *B*. The grey region denotes the input-output space for which the interneurons are in their dynamic range now defined as the range between 10% and 90% of their output activity. In this region the gain of the network transfer is modulated. In the input-output space above and to the right of these areas the interneuron activity is saturated and the network signal transfer is shifted. *C* and *D* show the network signal transfer when a combination of the specific relations from *A* and *B* are performed by the same (*C*) or separate (*D*) interneuron populations. The dot-dash line in *C* shows the boundary of the input-output space where the interneuron population is in its dynamic range for a sub-linear summation of the inputs to the interneuron population as *Eq. 7* with k = 0.0001. In *D* the input-output region where both interneuron populations work in their dynamic range is shown in darker grey.

4. Discussion and conclusions

Our simple model investigates the steady state network signal transfer for a network that consists of excitatory principal cells and local inhibitory interneurons that are either connected in a feedback mode or in a feedforward mode. Analytically we approximated the input-output functions of the cell populations by piece-wise linear functions; numerically, we could use more realistic sigmoid functions that were fitted to experimental data [3]. Our study only analyzed steady state conditions and did not incorporate the specific dynamics of the individual synapses present in the network [4], which would have enormously expanded the response possibilities.

The study was inspired by experimental data from the CA1 area by Wierenga & Wadman [3] that suggested that basket cell interneurons were either functionally participating in a feedback loop or in a feedforward configuration but very rarely in both. This suggested that the feedback wired interneurons modulate the steady state gain of the network output, while FF inhibition primarily shifts the network signal transfer. There is no anatomical evidence that these functions are attributed to distinct interneurons, but our model study suggests that combining the two forms of inhibition is only feasible if the inputs that the interneurons receive from Schaffer collaterals and pyramidal cells are summated in a highly non-linear way. Alternatively competitive learning schemes could result in specialized functions in distinct but otherwise non-distinguishable interneurons.

Our model demonstrates that FF and FB inhibition both shift and/or modulate the gain of the network signal transfer depending on whether the interneurons are in their dynamic range (gain modulation) or in the saturated range (modulation by shift). For FF inhibition the effect depends on the specific relation between the pyramidal and the interneuron input-output function relative to the Schaffer collateral input. For FB inhibition this depends in particularly on the transfer function of the interneurons.

When both FF and FB inhibition are present and combined in one interneuron population the loops interfere because both pathways activate the interneurons. This leads to a limited input-output space where both FF and FB inhibition modulate the network gain. A non-linear summation of the inputs to the interneuron population could expand the size of this input-output space. Separating FF and FB inhibition over two interneuron populations allows an independent scaling of the inhibition by the network input (by the FF loop) and by the output range (by the FB loop).

References

[1] I. Aradi, I. Soltesz, Modulation of network behaviour by changes in variance in interneuronal properties, J. Physiol. 538 (2002) 227-251.

[2] R.J. Douglas, C. Koch, M. Mahowald, K.A.C. Martin, H.H. Suarez, Recurrent excitation in neocortical circuits, Science 269 (1995) 981-985.

[3] C.J. Wierenga, W.J. Wadman, Functional relation between interneuron input and population activity in the rat hippocampal cornu ammonis 1 area, Neuroscience 118 (2003) 1129-1139.

[4] C.J. Wierenga, W.J. Wadman, Excitatory inputs to CA1 interneurons show selective synaptic dynamics, J Neurophysiol 90 (2003) 811-821.

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