

# Optimizing interneuron circuits for compartment-specific feedback inhibition

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## Author contribution

J.K and H.S. designed the study. J.K. performed the experiments and analyzed the data. J.K. and H.S. wrote the manuscript.

## Competing interests

The authors declare no competing interests.

## 18 **Abstract**

19 Cortical circuits process information by rich recurrent interactions between excitatory neurons and inhibitory  
20 interneurons. One of the prime functions of interneurons is to stabilize the circuit by feedback inhibition,  
21 but the level of specificity on which inhibitory feedback operates is not fully resolved. We hypothesized that  
22 inhibitory circuits could enable separate feedback control loops for different synaptic input streams, by means  
23 of specific feedback inhibition to different neuronal compartments. To investigate this hypothesis, we adopted  
24 an optimization approach. Leveraging recent advances in training spiking network models, we optimized the  
25 connectivity and short-term plasticity of interneuron circuits for compartment-specific feedback inhibition  
26 onto pyramidal neurons. Over the course of the optimization, the interneurons diversified into two classes  
27 that resembled parvalbumin (PV) and somatostatin (SST) expressing interneurons. The resulting circuit can  
28 be understood as a neural decoder that inverts the nonlinear biophysical computations performed within the  
29 pyramidal cells. Our model provides a proof of concept for studying structure-function relations in cortical  
30 circuits by a combination of gradient-based optimization and biologically plausible phenomenological models.

## 31 Introduction

32 Cortical inhibitory interneurons vary dramatically in shape, gene expression pattern, electrophysiological  
33 and synaptic properties and in their downstream targets [1]. Some cell types, e.g., somatostatin (SST)-  
34 positive interneurons [2] and some neurogliaform cells in layer 1 [3], predominantly project to pyramidal cell  
35 (PC) dendrites. Others—e.g., parvalbumin positive (PV) basket and chandelier cells—primarily inhibit the  
36 peri-somatic domain of PCs [4]. Some interneurons receive depressing synapses from PCs, others facilitating  
37 synapses [5, 6]. But what is the function of these differences?

38 One of inhibition’s core functions is to prevent run-away excitation [7] by means of feedback inhibition  
39 that tracks excitatory inputs. This has led to the concept of excitation-inhibition (E/I) balance [8], i.e., the  
40 idea that strong excitatory currents are compensated by inhibitory currents of comparable size. E/I balance  
41 is thought to shape cortical dynamics [8, 9] and computations [10, 11] and can be established by means of  
42 inhibitory forms of plasticity [12, 13, 14]. Selective disruptions of E/I balance are thought to play a key role  
43 during learning [15], while chronic disturbances have been implicated with psychiatric diseases, including  
44 autism [16, 17] and schizophrenia [18, 19].

45 Originally conceived as a balance on average [8], E/I balance turned out to be specific to sensory stimuli  
46 [20, 21], in time [22, 23], across neurons [24] and to neural activation patterns [25]. The number of excitatory  
47 and inhibitory synapses could even be balanced at the subcellular level [26], in a cell-type specific way [27]).  
48 Given this high specificity, we hypothesized that excitation and inhibition also balance individually in dif-  
49 ferent neuronal compartments, and that this could be mediated at least in part by compartment-specific  
50 feedback inhibition.

51 Different neuronal compartments often receive input from different sources [28] and integrate these inputs  
52 nonlinearly by means of complex cellular dynamics [29, 30]. For example, the apical dendrites of L5 pyramidal  
53 cells (PCs) can generate nonlinear calcium events in response to coincident somatic and dendritic inputs  
54 [31]. Hence, neuronal output spike trains can have a complex nonlinear dependence on the inputs arriving in  
55 different compartments. This poses a challenge for compartment-specific feedback inhibition, which would  
56 require interneurons to invert the nonlinear dependence by recovering local dendritic input from pyramidal  
57 output. It is therefore far from clear that a compartment-specific feedback inhibition can be achieved at all  
58 by means of biologically plausible circuits. If it can, however, it would have to rely on an interneuron circuit  
59 that is closely matched to the electrophysiological properties of the cells it inhibits. Parts of the complexity  
60 of cortical interneuron circuits could then be interpreted in light of the intrinsic properties of PCs.

61 Unfortunately, the nature of such a correspondence between the electrophysiology of inhibited cells and  
62 suitable interneuron circuits is far from obvious. We reasoned that we could gain insights by means of a

63 model-based optimization approach, in which interneuron circuits are optimized for feedback inhibition onto  
64 pyramidal cells with given biophysical properties. Here, we illustrate this ansatz by optimizing interneuron  
65 circuits for a nonlinear two-compartment model of L5 pyramidal cells [32]. We show that over the course of  
66 the optimization, an initially homogeneous interneuron population diversifies into two classes, which share  
67 many features of cortical PV and SST interneurons. One class primarily inhibits the somatic compartment  
68 of the PCs and receives depressing synaptic inputs. The other class primarily inhibits PC dendrites and  
69 received facilitating inputs. We show how this diversification can be understood from an encoding-decoding  
70 perspective, in which the biophysics of the PCs encode two different input streams in a multiplexed code  
71 [33], which is in turn decoded by the interneuron circuit. These findings support the idea that parts of the  
72 complexity of cortical interneuron circuits could be interpreted in light of the intrinsic properties of PCs and  
73 illustrate how modeling could provide a means of unravelling these interdependencies between the cellular  
74 and the circuit level.

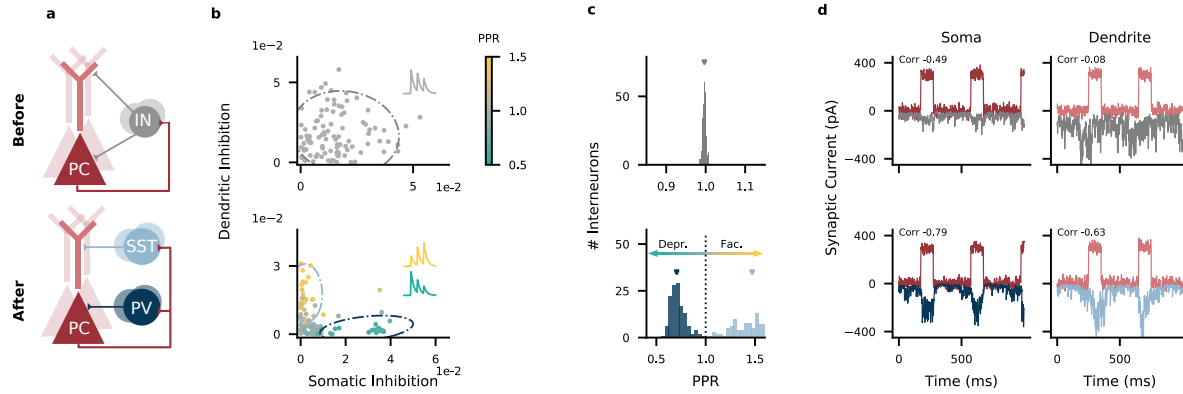
## 75 Results

76 To investigate which aspects of cortical interneuron circuits can be understood from the perspective of  
77 compartment-specific inhibition, we studied a spiking network model comprising pyramidal cells (PCs) and  
78 interneurons (INs) (see Methods). PCs were described by a two-compartment model consisting of a soma  
79 and an apical dendrite. The parameters of this model were previously fitted to capture dendrite-dependent  
80 bursting [32]. PCs received time-varying inputs in both the somatic and the dendritic compartment, and  
81 inhibitory inputs from INs. INs were described by an integrate-and-fire model. They received excitatory  
82 inputs from the PCs, and inhibitory inputs from other INs.

83 We optimized the interneuron circuit for a compartment-specific feedback inhibition. In the presence  
84 of time-varying external input, feedback inhibition tracks excitatory inputs in time [8, 23]. We therefore  
85 enforced compartment-specific feedback inhibition by minimizing the mean squared error between excitatory  
86 and inhibitory inputs in both compartments, by means of gradient descent with surrogate gradients [34].  
87 Importantly, we optimized not only the strength of all synaptic connections in the network, but also the  
88 short-term plasticity of the PC  $\rightarrow$  IN connections (see Methods).

### 89 Interneuron diversity emerges during optimization

90 Before the optimization, interneurons formed a single, homogeneous group (Fig. 1a, top). Most inhibited  
91 both somatic and dendritic compartments (Fig. 1b, top) and PC  $\rightarrow$  IN connections showed non-specific  
92 synaptic dynamics (Fig. 1c, top). Moreover, excitation and inhibition were poorly correlated, particularly

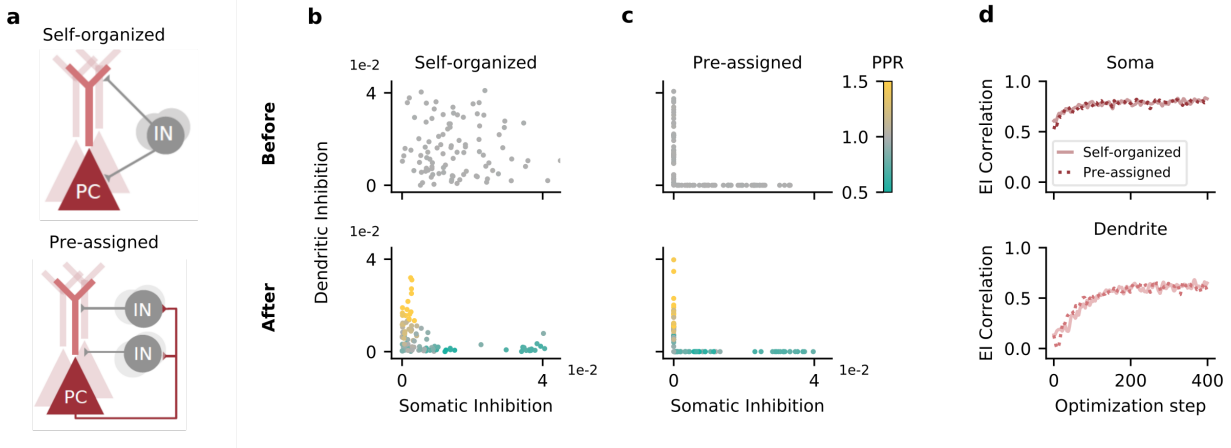


**Figure 1: Interneuron diversity emerges in networks optimized for compartment-specific inhibition**  
**(a)** Network structure before (top) and after optimization (bottom). PC, pyramidal cell; IN, interneuron; PV, parvalbumin-positive IN; SST, somatostatin-positive IN. Recurrent inhibitory connections among INs omitted for clarity. **(b)** Strength of somatic and dendritic inhibition from individual INs. Dashed lines: 95% density of a Gaussian distribution (top) and mixture of two Gaussian distributions (bottom) fitted to the connectivity and Paired Pulse Ratio (PPR) data of 5 networks (marginalized over PPR). **(c)** PPR distribution (data from 5 networks). Mean PPR before optimization: 1.00; after optimization: 0.73 (PV cluster,  $n = 133$ ) and 1.45 (SST cluster,  $n = 113$ ). **(d)** Excitatory (red) and inhibitory (top: gray, bottom: blue) currents onto PC compartments (average across  $N_E = 400$  PCs). Inset: correlation between compartment-specific excitation and inhibition.

93 in the dendrite (Pearson correlation coefficients 0.49 (soma) & 0.08 (dendrite)), suggesting that the network  
 94 did not generate compartment-specific feedback inhibition (Fig. 1d, top).

95 During optimization, the interneurons split into two groups (Fig. 1a, bottom) with distinct connectivity  
 96 (Fig. 1b, bottom; see also Connectivity among interneurons) and short-term plasticity (Fig. 1c, bottom). One  
 97 group received short-term depressing inputs from PCs and preferentially targeted their somatic compartment,  
 98 akin to PV interneurons. The other group received short-term facilitating inputs from PCs and targeted  
 99 their dendritic compartment, akin to SST interneurons. For simplicity, we will henceforth denote the two  
 100 interneuron groups as PV and SST interneurons. After the optimization, excitation and inhibition were  
 101 positively correlated in both compartments (Pearson correlation coefficients 0.79 (soma) & 0.63 (dendrite);  
 102 Fig. 1d, bottom). Note that the E/I balance is slightly less tight in time in the dendrites than in the somata  
 103 (Fig. 1d), because synaptic short-term facilitation causes a delay in the signal transmission between PCs  
 104 and SST interneurons [35, more details below].

105 To confirm the benefit of two non-overlapping interneuron classes, we performed control simulations in  
 106 which each interneuron was pre-assigned to target either the soma or the dendrite, while synaptic strengths  
 107 and short-term plasticity were optimized. Consistent with a benefit of a specialization, the correlation of  
 108 excitation and inhibition in the two compartments was as high as in fully self-organized networks (Fig. 2).  
 109 Optimized networks with pre-assigned interneuron classes also showed the same diversification in their short-  
 110 term plasticity, resembling that of PV and SST neurons (Figs. 2, A.1).



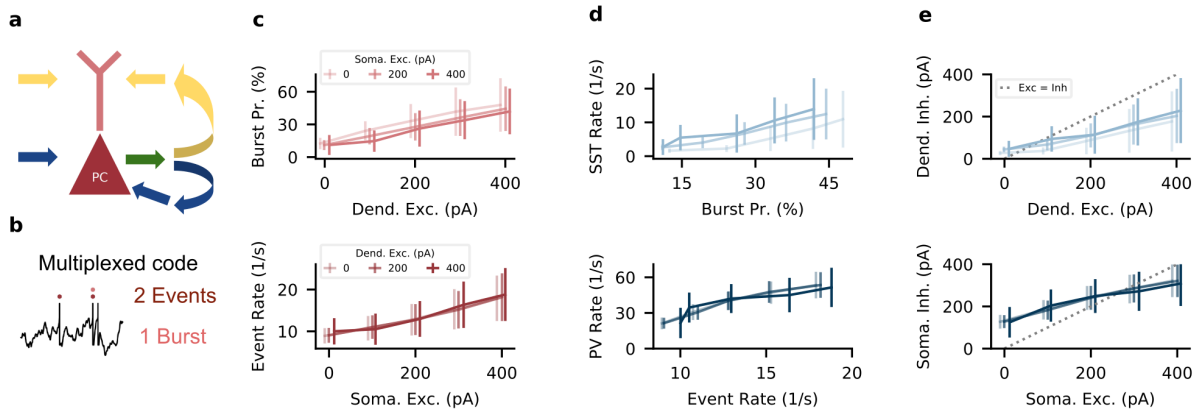
**Figure 2: Compartment-assigned interneurons develop into PV- and SST-like populations.** (a) Circuit before learning. Top, interneurons (INs) can inhibit both compartments of principal cells (PCs) and need to self-organize, as in Fig. 1. Bottom, INs are pre-assigned to inhibit a single PC compartment. (b) IN→PC weights before (top) and after (bottom) optimization. Interneurons self-organize into a population that preferentially inhibits the soma, and a population that preferentially inhibits the dendrites. Data differs from Fig. 1 due to random parameter initialization and sampling of training data. (c) As (b), but with interneurons randomly assigned to inhibit a single compartment (soma or dendrite). Mean PPR: 0.72 (soma-inhibiting population), 1.17 (dendrite-inhibiting population). (d) Correlation between compartment-specific excitation and inhibition over the course of the optimization. Solid line: INs were not assigned to a single compartment (Self-organized). Dashed line: INs were assigned to a single compartment (Pre-assigned). Data is smoothed with a Gaussian kernel (width: 2).

## 111 Feedback inhibition decodes compartment-specific inputs

112 For compartment-specific feedback inhibition, the interneuron circuit has to retrieve the somatic and dendritic  
 113 input to PCs from the spiking activity of the PCs. This amounts to inverting the nonlinear integration  
 114 performed in the PCs (Fig. 3a). How does the circuit achieve this? Recently, it was proposed that the  
 115 electrophysiological properties of PCs support a multiplexed neural code that simultaneously represents  
 116 somatic and dendritic inputs in temporal spike patterns ([33], Fig. 3b). In this code, somatic input increases  
 117 the number of events, where events can either be single spikes or bursts (see Methods). Dendritic input in turn  
 118 increases the probability that a somatic spike is converted into a burst (burst probability). Providing soma-  
 119 or dendrite-specific inhibition then amounts to decoding the event rate or burst probability, respectively.  
 120 Such a decoding can be achieved in circuits with short-term plasticity and feedforward inhibition [33], and  
 121 we expected that our network arrived at a similar decoding scheme.

122 We tested this hypothesis by injecting current pulses to PC somata and dendrites (see Methods). Stronger  
 123 dendritic input increased the burst probability, which increased the firing rate of SST interneurons via  
 124 facilitating synapses. The increased SST rate increased dendritic inhibition (Fig. 3c-e, top). Analogously,  
 125 stronger somatic input increased the event rate, which increased the firing rate of PV interneurons via  
 126 depressing synapses. The increased PV rate increased somatic inhibition (Fig. 3c-e, bottom). Importantly,  
 127 inhibition was specific to each compartment (shaded lines indicate input strength to the other compartment):

128 Because PV interneurons were selectively activated by PC events, somatic inhibition was largely unaffected  
 129 by dendritic excitation. Similarly, SST interneurons were selectively activated by PC bursts, such that  
 130 dendritic inhibition was largely unaffected by somatic excitation. In the model, interneurons therefore  
 131 provide compartment-specific inhibition by demultiplexing the neural code used by the PCs.

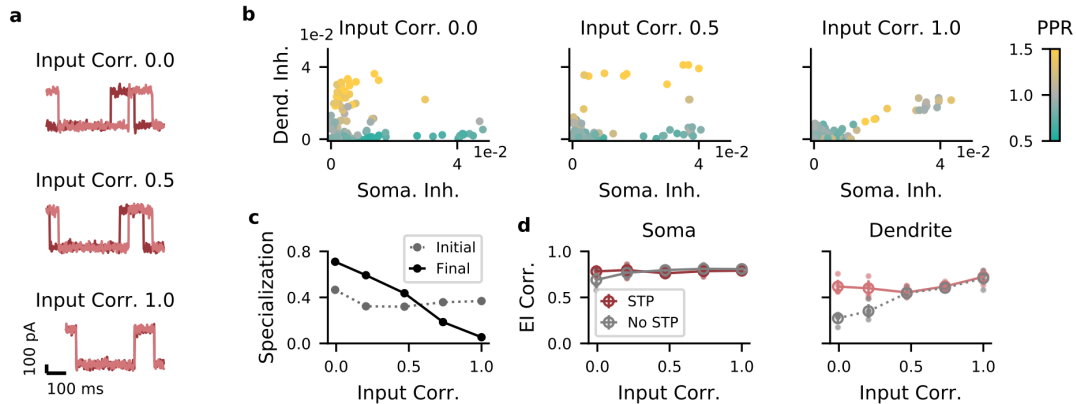


**Figure 3: The interneuron circuit decodes somatic and dendritic inputs to PCs.** (a) PC somata and dendrites receive uncorrelated input streams (yellow and blue) that, from PC output spikes (green), have to be separated into compartment-specific inhibition (yellow and blue). (b) PCs use a multiplexed neural code. Somatic input leads to events (singlets or bursts). Dendritic input converts singlets into bursts. (c) Top: Excitatory input to PC dendrites increases burst probability. In this and other top panels (d,e), the shading indicates strength of background somatic input, and error bars indicate sd over 10 stimulus repetitions. Bottom: Excitatory input to PC somata increases event rate. In this and other bottom panels (d,e), the shading indicates strength of background dendritic input. (d) Top: SST rate increases with bursts probability. Bottom: PV rate increases with PC events. (e) Top: dendritic inhibition increases with dendritic excitation, but is only weakly modulated by somatic excitation. Positions on  $x$ -axis are shifted by 10 pA for visual clarity, error bars indicate sd during 10 stimulus repetitions. Bottom: somatic inhibition increases with somatic excitation, but is invariant to dendritic excitation.

### 132 Effect of correlations between somatic and dendritic input

133 So far we assumed that PC somata and dendrites receive uncorrelated input. Recent work, however, suggests  
 134 that somatic and dendritic activity are correlated [36, 37], potentially reducing the need for compart-  
 135 ment-specific inhibition. We therefore tested how correlated inputs affect interneuron specialization by optimizing  
 136 separate networks for different input correlations. We found that increasing correlation between somatic  
 137 and dendritic inputs gradually reduced the separation between the interneuron classes (Fig. 4a,b). For high  
 138 input correlation, optimized networks contained a continuum in their connectivity and short-term plasticity  
 139 (Fig. 4a,b). However, the presence of short-term plasticity was necessary for a dendritic E/I balance for a  
 140 range of input correlations (Fig. 4c). At high correlations, somatic and dendritic inputs are sufficiently similar  
 141 to make the effect of short-term facilitation negligible. Note that although in this case, distinct interneuron  
 142 populations were not necessary, the presence of IN classes was also not harmful for E/I balance. A pre-

143 assignment of the interneurons into classes maintained the E/I correlation in both compartments and for  
 144 any correlation level (Fig. A.1). Finally, we found that interneuron specialization degraded with increasing  
 145 baseline activity of the INs (Fig. A.2), because high firing rates allow non-specialized inhibition to cancel  
 146 out (see mathematical analysis in Supplementary Materials. However, a pre-assignment of interneurons into  
 147 classes again maintained the E/I correlation for different baseline activity levels (Fig. A.1).



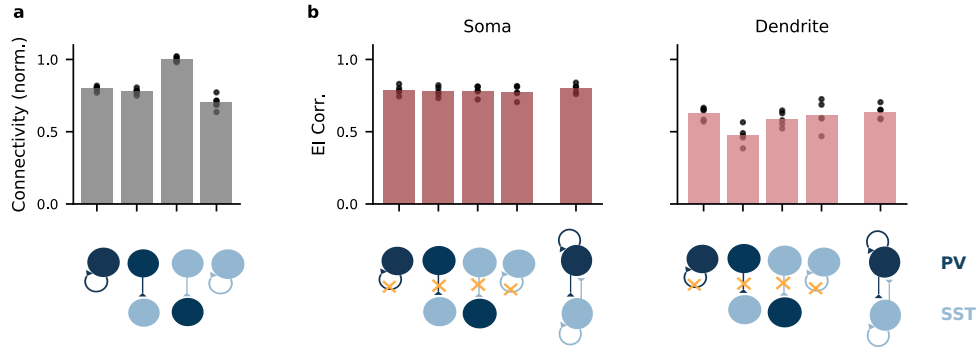
**Figure 4: Correlations between dendritic and somatic input reduce interneuron specialization.** (a) Examples for synaptic traces corresponding to different correlation levels. Dark red, somatic current; light red, dendritic input. (b) Strength of somatic vs. dendritic inhibition from all INs. Left, middle, right: input correlation coefficient 0 (low), 0.5 (medium), and 1 (high), respectively. (c) Specialization of IN  $\rightarrow$  E weights. If each IN targets either soma or dendrites, the specialization is 1 (see Methods). Gray: specialization of initial random network; black: specialization after optimization. (d) Left: In the soma, excitation and inhibition are balanced across a broad range of input correlations, with or without short-term plasticity (STP). Right: In the dendrites, excitation and inhibition are balanced only with STP when input correlations are small.

#### 148 Connectivity among interneurons

149 Because interneuron subtypes also differ in their connectivity to other interneurons [38, 39], we included IN  
 150  $\rightarrow$  IN synapses in our optimization. After classifying INs as putative PV and SST neurons using a binary  
 151 Gaussian mixture model, we found that the connections between the interneuron classes varied systematically  
 152 in strength. While PV  $\leftrightarrow$  PV connections, PV  $\rightarrow$  SST connections and SST  $\leftrightarrow$  SST connections were similar  
 153 in strength on average, SST  $\rightarrow$  PV were consistently stronger (Fig. 5a), presumably to compensate for the  
 154 relatively low SST rates (Fig. 3d).

155 To investigate which connections were necessary, we simulated knockout experiments in networks with  
 156 pre-assigned interneuron classes, in which we removed individual connections types. We found that only PV  
 157  $\rightarrow$  SST connections were necessary for a dendritic E/I balance (Fig. 5b). Note that although earlier work  
 158 did not find PV  $\rightarrow$  SST connectivity in the primary visual cortex of young mice [38], these connections seem  
 159 to be present in primary visual and somatosensory cortex of older animals [39, 40].





**Figure 5: Recurrent inhibitory connectivity after learning.** (a) Connectivity between IN populations. From left to right: PV↔PV, PV→SST, SST→PV, SST↔SST. Bars indicate mean over all networks, dots indicate individual networks. (b) Performance as measured by the correlation between excitation and inhibition to PC soma (left) and dendrites (right) of networks optimized lacking specific connections. Data at the very right: EI correlation in network with unconstrained connectivity. Only loss of PV → SST connectivity has a clear effect on dendritic EI correlations. Open circles, mean over 5 batches of 8 stimuli with random amplitudes. Small filled circles, individual batches.

160 To understand the role of the different IN→IN connections, we performed a mathematical analysis of a  
 161 simplified network model. The model also contains a population of principal cells (PC) and two populations  
 162 of interneurons corresponding to PV and SST interneurons, but in contrast to the spiking model, neural  
 163 activities are represented by continuously-varying rates. The population rates of PV and SST interneurons  
 164 are denoted by  $p$  and  $s$ , respectively. The activity of PCs is described by two rates: an event rate  $e$  that is  
 165 driven by somatic input and a burst rate  $b$  that is driven by dendritic input. The short-term plasticity of a  
 166 given synapse type is characterized by a single, static parameter, which characterizes the relative efficiency  
 167 at which events and bursts are transmitted. Synapses for which this parameter is 1 transmit events but not  
 168 bursts, i.e., they are "perfectly depressing". Synapses for which this parameter is 0 transmit bursts, i.e.,  
 169 they are "perfectly facilitating". These assumptions allowed us to mathematically analyze the interneuron  
 170 connectivity required for compartment-specific feedback inhibition. We will only summarize the results, the  
 171 full analysis is described in Supplementary Materials.

Let us first consider the case of dendritic feedback inhibition. The model states that the activity  $s$  of the  
 SST neurons is given by a linear combination of the event and burst rate:  $s = Ae + Bb$ , with factors  $A, B$   
 that depend on the connectivity and short-term plasticity in the circuit in a complicated way. If we assume  
 that SST interneurons target exclusively the PC dendrites, compartment-specific feedback inhibition requires  
 that the activity of SST interneurons depends on dendritic but not somatic input to PCs. Because those two  
 inputs drive the event rate and burst rate, respectively, this condition reduces to the mathematical condition  
 that  $A = 0$ . Using the dependence of  $A$  on the circuit parameters (see Supplementary Materials), we get the

condition

$$\beta W^{SST \leftarrow PC} - \alpha W^{SST \leftarrow PV} W^{PV \leftarrow PC} = 0, \quad (1)$$

172 where  $W^{Y \leftarrow X}$  denotes the strength of the synaptic connection between population  $X$  and  $Y$ . The two  
173 parameters  $\alpha, \beta$  are the short-term plasticity parameters and quantify how well events are transmitted via  
174 the PC→PV and PC→SST connections, respectively.

175 Condition [1] has an intuitive interpretation. The first term describes how much somatic PC input  
176 influences SST activity via the monosynaptic pathway PC → SST. The second term corresponds to the  
177 disynaptic pathway PC → PV → SST. The condition therefore states that unless PC→SST connections  
178 are "perfectly facilitating" ( $\beta = 0$ ), the disynaptic PC → PV → SST pathway is necessary (Fig. 5) to avoid  
179 that somatic input generates dendritic inhibition. The observation that a knock-out of these connections  
180 reduces the dendritic E/I correlation in the spiking network (Fig. 5b) can therefore be understood as a result  
181 of an imperfect facilitation in the PC→SST connection. Indeed, we observed that the Tsodyks-Markram  
182 model [41] we used to describe the short-term plasticity in the spiking network cannot achieve a perfectly  
183 facilitating synapse in the presence of ongoing activity, even for an initial release probability  $U = 0$ , because  
184 preceding spikes always leave behind a residual level of synaptic facilitation.

185 An analogous analysis suggests that disynaptic PC → SST→PV inhibition is necessary to prevent den-  
186 dritic inputs from generating somatic inhibition (Supplementary Materials), providing a possible function of  
187 experimentally observed SST → PV connectivity. At first sight, this appears in conflict with the observation  
188 that a knock-out of this connection did not reduce the E/I balance in the soma. However, because bursts  
189 are comparatively rare [33], event rate and overall firing (including additional spikes in bursts) are highly  
190 correlated. Therefore, the overall firing rate is a good proxy for somatic input and imperfections in synaptic  
191 depression in the PC→PV connection do not introduce a sufficiently large problem to necessitate feedforward  
192 inhibition via the PC→SST→PV pathway.

## 193 Discussion

194 Feedback inhibition ensures the stability of cortical circuits [42, 43, 11, 44]. Our model indicates that this  
195 feedback could operate on a level as fine-grained as different cellular compartments receiving different input  
196 streams, and that the required circuitry bears similarity to the one observed in cortex. In particular, we found  
197 that an optimization for feedback inhibition led to the emergence of two inhibitory cell classes that resemble  
198 PV and SST interneurons in their connectivity and short-term plasticity. This diversification was robust to

199 correlations between somatic and dendritic input, although increasing correlations prompted the SST-like  
200 model neurons to contact not only the dendritic, but also the somatic compartment. This is consistent with  
201 the extensive branching of cortical SST neurons within the layer that contains their cell body [2]. Even in  
202 cases in which the gradient-based optimization did not drive a clear division into cell classes, an artificial  
203 pre-assignment of the interneurons did not impair the feedback inhibition.

204 We would like to emphasize that while we optimized for feedback inhibition in different neuronal com-  
205 partments, the model operates on an ensemble level in the sense that all neurons in the network received  
206 the two same time-varying signals in their soma and dendrite. This allows the interneurons to use event  
207 or burst rates of the whole ensemble to infer somatic and dendritic inputs with high temporal fidelity [33].  
208 The question of the specificity of feedback inhibition on the population level is an orthogonal one and not  
209 fully resolved. The dense and seemingly unspecific connectivity of many interneurons [45, 46] suggests that  
210 feedback inhibition operates on the level of the local population, blissfully ignoring the functional identity  
211 of the neurons it targets [47]. More recent results have indicated a correlation between the sensory tuning  
212 and the synaptic efficacy of interneuron-pyramidal cell connections, however, suggesting that feedback in-  
213 hibition could operate on the level of functionally identified ensembles [48, 13]. A natural extension of this  
214 work would be to endow the pyramidal cells with a tuning to different somatic and dendritic input streams  
215 and thereby define functional ensembles. Notably, the ensemble affiliation of a given neuron may differ for  
216 soma and dendrite, e.g., two populations of neurons could receive distinct somatic, but identical dendritic  
217 inputs. How this would be reflected in the associated feedback-optimized interneuron circuit is an interesting  
218 question, but beyond the scope of the present work.

219 A natural question for optimization-based approaches is how the optimization can be performed by  
220 biologically plausible mechanisms. The gradient-based optimization we performed relies on surrogate gradi-  
221 ents [34, 49] and a highly non-local backpropagation of errors both through the network and through time  
222 [50, 51], mechanisms that are unlikely implemented verbatim in the circuit [52]. We think of the suggested  
223 optimization approach rather as a means to understanding functional relations between different features of  
224 neural circuits, i.e., the relation between the biophysics of pyramidal cells and the surrounding interneuron  
225 circuits. At this point, we prefer to remain agnostic as to the mechanisms that establish these relations.  
226 While an activity-dependent refinement of the circuit is likely, the diversification of the interneurons into PV  
227 and SST neurons is clearly not driven by activity-dependent mechanisms alone [53]. SST Martinotti cells  
228 migrate to the embryonic cortex via the marginal zone, while PV basket cells migrate via the subventricular  
229 zone [54]. Their identity is hence determined long before they are integrated into functional circuits. These  
230 developmental programs are likely old on evolutionary time scales given that interneuron diversity seems  
231 highly conserved [55, 56]. Yet, even when interpreted as an evolutionary optimization, interneuron circuits

232 probably did not evolve to perform feedback inhibition for pre-existing biophysical properties of pyramidal  
233 neurons. Such systematic relations between different circuit features are more likely a result of co-evolution,  
234 where the different features mutually enabled the successful selection of the others.

235 Given these considerations, we refrain from predictions regarding the optimization process. Still, the  
236 model can make predictions regarding the nature of the optimized state. First, it predicts that PV and  
237 SST rates correlate primarily with somatic and dendritic activity, respectively. Second, inhibiting SST  
238 neurons should increase PC bursting, as observed in hippocampus [57] and cortex [58]. The role of short-  
239 term facilitation could be tested by silencing the necessary gene *Elfn1* [59, 60]. On a higher level, the model  
240 suggests a relation between the biophysical properties of excitatory neurons and the surrounding interneuron  
241 circuit. This is consistent, e.g., with the finding that the prevalence of pyramidal cells and dendrite-targeting  
242 Martinotti cells seems to be correlated across brain regions [61].

243 While the synaptic targets and the incoming short-term plasticity of the two emerging interneuron classes  
244 are similar to those of PV and SST interneurons, the optimized inhibitory circuitry is not a perfect image of  
245 cortex. Aside from the obvious incompleteness in terms of other interneuron types, other features, such as the  
246 often observed weak connectivity from PV to SST neurons [38] did not result from the optimization (Fig. 5).  
247 However, even if our assumption that the interneuron circuit performs compartment-specific feedback in-  
248 hibition was correct, a perfect match to cortex is probably not to be expected. Firstly, the pyramidal cell  
249 model we used is clearly a very reduced depiction of a real pyramidal cell. Because the inhibitory circuitry is  
250 optimized for the nonlinear processing performed by these cells, anything that is wrong in the pyramidal cell  
251 model will also be wrong in the optimized circuit. It will be interesting to see how the suggested optimization  
252 framework generalizes to computations performed by more complex neuronal morphologies [30]. Secondly,  
253 the optimized circuitry is also sensitive to other modelling choices. For example, the circuit separates spikes  
254 and bursts by a synergy between short-term plasticity and interneuron connectivity. A wrong short-term  
255 plasticity model will therefore lead to a wrong connectivity in the circuit. Here, it will be interesting to see  
256 how a more expressive model of short-term plasticity [62] influences the optimal circuit structure. Finally, of  
257 course, our optimality assumption could be wrong to different degrees. We could be wrong in detail: Even  
258 if the idea of compartment-specific feedback inhibition was correct, our mathematical representation thereof  
259 – matching excitation and inhibition in time – could be wrong, with corresponding repercussions in the  
260 optimized circuit. Or we could be wrong altogether: PV and SST interneurons serve an altogether different  
261 function, and feedback inhibition is merely a means to a completely different end, such as behavioral circuit  
262 modulation [58, 63] or the control of plasticity [15, 64].

263 Notwithstanding the dependence of the final circuit on specific model choices, we believe that the sug-  
264 gested optimization approach provides a broadly applicable schema for analyses of structure-function rela-

265 tions of interneuron circuits. On a coarser level of biological detail, optimization approaches have recently  
266 been quite successful at linking abstract computations to the neural network level [65, 66, 67]. While similar  
267 in spirit, our approach takes this optimization ansatz from the level of dynamical systems analyses of rate-  
268 based recurrent neural networks to the detailed level of spiking circuits with multi-compartment neurons  
269 and short-term plasticity. It will be exciting to see how biological mechanisms on this level of detail support  
270 more advanced computations than the mere stabilization of the circuit considered here, but that is clearly a  
271 larger research program that extends well beyond the proof of concept presented here.

## 1 References

- 272
- 273 [1] Robin Tremblay, Soohyun Lee, and Bernardo Rudy. Gabaergic interneurons in the neocortex: from cellular properties to  
274 circuits. *Neuron*, 91(2):260–292, 2016.
- 275 [2] Joanna Urban-Ciecko and Alison L Barth. Somatostatin-expressing neurons in cortical networks. *Nature Reviews Neuro-*  
276 *science*, 17(7):401, 2016.
- 277 [3] Elisabeth Abs, Rogier B Poorthuis, Daniella Apelblat, Karzan Muhammad, M Belen Pardi, Leona Enke, Dahlia Kushinsky,  
278 De-Lin Pu, Max Ferdinand Eizinger, Karl-Klaus Conzelmann, et al. Learning-related plasticity in dendrite-targeting layer  
279 1 interneurons. *Neuron*, 100(3):684–699, 2018.
- 280 [4] Hua Hu, Jian Gan, and Peter Jonas. Fast-spiking, parvalbumin+ gabaergic interneurons: From cellular design to micro-  
281 circuit function. *Science*, 345(6196), 2014.
- 282 [5] Henry Markram, Yun Wang, and Misha Tsodyks. Differential signaling via the same axon of neocortical pyramidal neurons.  
283 *Proceedings of the National Academy of Sciences*, 95(9):5323–5328, 1998.
- 284 [6] Alex Reyes, Rafael Lujan, Andrej Rozov, Nail Burnashev, Peter Somogyi, and Bert Sakmann. Target-cell-specific facilitation  
285 and depression in neocortical circuits. *Nature neuroscience*, 1(4):279–285, 1998.
- 286 [7] Jeffrey S Isaacson and Massimo Scanziani. How inhibition shapes cortical activity. *Neuron*, 72(2):231–243, 2011.
- 287 [8] Carl Van Vreeswijk and Haim Sompolinsky. Chaos in neuronal networks with balanced excitatory and inhibitory activity.  
288 *Science*, 274(5293):1724–1726, 1996.
- 289 [9] Nicolas Brunel. Dynamics of sparsely connected networks of excitatory and inhibitory spiking neurons. *Journal of com-*  
290 *putational neuroscience*, 8(3):183–208, 2000.
- 291 [10] Guillaume Hennequin, Tim P Vogels, and Wulfram Gerstner. Optimal control of transient dynamics in balanced networks  
292 supports generation of complex movements. *Neuron*, 82(6):1394–1406, 2014.
- 293 [11] Daniel B Rubin, Stephen D Van Hooser, and Kenneth D Miller. The stabilized supralinear network: a unifying circuit  
294 motif underlying multi-input integration in sensory cortex. *Neuron*, 85(2):402–417, 2015.
- 295 [12] Tim P Vogels, Henning Sprekeler, Friedemann Zenke, Claudia Clopath, and Wulfram Gerstner. Inhibitory plasticity  
296 balances excitation and inhibition in sensory pathways and memory networks. *Science*, 334(6062):1569–1573, 2011.
- 297 [13] Owen Mackwood, Laura B Naumann, and Henning Sprekeler. Learning excitatory-inhibitory neuronal assemblies in  
298 recurrent networks. *Elife*, 10:e59715, 2021.
- 299 [14] Guillaume Hennequin, Everton J Agnes, and Tim P Vogels. Inhibitory plasticity: balance, control, and codependence.  
300 *Annual review of neuroscience*, 40:557–579, 2017.
- 301 [15] Johannes J Letzkus, Steffen BE Wolff, and Andreas Lüthi. Disinhibition, a circuit mechanism for associative learning and  
302 memory. *Neuron*, 88(2):264–276, 2015.
- 303 [16] Ofer Yizhar, Lief E Fenno, Matthias Prigge, Franziska Schneider, Thomas J Davidson, Daniel J O’shea, Vikaas S Sohal,  
304 Inbal Goshen, Joel Finkelstein, Jeanne T Paz, et al. Neocortical excitation/inhibition balance in information processing  
305 and social dysfunction. *Nature*, 477(7363):171–178, 2011.
- 306 [17] Vikaas S Sohal and John LR Rubenstein. Excitation-inhibition balance as a framework for investigating mechanisms in  
307 neuropsychiatric disorders. *Molecular psychiatry*, 24(9):1248–1257, 2019.

- 308 [18] Patricio O'Donnell. Adolescent onset of cortical disinhibition in schizophrenia: insights from animal models. *Schizophrenia*  
309 *bulletin*, 37(3):484–492, 2011.
- 310 [19] Tineke Grent, Joachim Gross, Jozien Goense, Michael Wibral, Ruchika Gajwani, Andrew I Gumley, Stephen M Lawrie,  
311 Matthias Schwannauer, Frauke Schultze-Lutter, Tobias Navarro Schröder, et al. Resting-state gamma-band power alter-  
312 ations in schizophrenia reveal e/i-balance abnormalities across illness-stages. *Elife*, 7:e37799, 2018.
- 313 [20] Michael Wehr and Anthony M Zador. Balanced inhibition underlies tuning and sharpens spike timing in auditory cortex.  
314 *Nature*, 426(6965):442–446, 2003.
- 315 [21] Peter Rupprecht and Rainer W Friedrich. Precise synaptic balance in the zebrafish homolog of olfactory cortex. *Neuron*,  
316 100(3):669–683, 2018.
- 317 [22] Michael Okun and Ilan Lampl. Instantaneous correlation of excitation and inhibition during ongoing and sensory-evoked  
318 activities. *Nature neuroscience*, 11(5):535–537, 2008.
- 319 [23] Alfonso Renart, Jaime De La Rocha, Peter Bartho, Liad Hollender, Néstor Parga, Alex Reyes, and Kenneth D Harris. The  
320 asynchronous state in cortical circuits. *science*, 327(5965):587–590, 2010.
- 321 [24] Mingshan Xue, Bassam V Atallah, and Massimo Scanziani. Equalizing excitation–inhibition ratios across visual cortical  
322 neurons. *Nature*, 511(7511):596–600, 2014.
- 323 [25] Aanchal Bhatia, Sahil Moza, and Upinder Singh Bhalla. Precise excitation-inhibition balance controls gain and timing in  
324 the hippocampus. *Elife*, 8:e43415, 2019.
- 325 [26] Daniel Maxim Iascone, Yujie Li, Uygur Sümbül, Michael Doron, Hanbo Chen, Valentine Andreu, Finola Goudy, Heike  
326 Blockus, Larry F Abbott, Idan Segev, et al. Whole-neuron synaptic mapping reveals spatially precise excitatory/inhibitory  
327 balance limiting dendritic and somatic spiking. *Neuron*, 2020.
- 328 [27] Ali Karimi, Jan Odenthal, Florian Drawitsch, Kevin M Boergens, and Moritz Helmstaedter. Cell-type specific innervation  
329 of cortical pyramidal cells at their apical dendrites. *Elife*, 9:e46876, 2020.
- 330 [28] Leopoldo Petreanu, Tianyi Mao, Scott M Sternson, and Karel Svoboda. The subcellular organization of neocortical  
331 excitatory connections. *Nature*, 457(7233):1142–1145, 2009.
- 332 [29] Michael London and Michael Häusser. Dendritic computation. *Annu. Rev. Neurosci.*, 28:503–532, 2005.
- 333 [30] Panayiota Poirazi and Athanasia Papoutsis. Illuminating dendritic function with computational models. *Nature Reviews*  
334 *Neuroscience*, pages 1–19, 2020.
- 335 [31] Matthew E Larkum, J Julius Zhu, and Bert Sakmann. A new cellular mechanism for coupling inputs arriving at different  
336 cortical layers. *Nature*, 398(6725):338–341, 1999.
- 337 [32] Richard Naud, Brice Bathellier, and Wulfram Gerstner. Spike-timing prediction in cortical neurons with active dendrites.  
338 *Frontiers in computational neuroscience*, 8:90, 2014.
- 339 [33] Richard Naud and Henning Sprekeler. Sparse bursts optimize information transmission in a multiplexed neural code.  
340 *Proceedings of the National Academy of Sciences*, 115(27):E6329–E6338, 2018.
- 341 [34] Friedemann Zenke and Surya Ganguli. Superspike: Supervised learning in multilayer spiking neural networks. *Neural*  
342 *computation*, 30(6):1514–1541, 2018.
- 343 [35] Frederic Pouille and Massimo Scanziani. Routing of spike series by dynamic circuits in the hippocampus. *Nature*,  
344 429(6993):717–723, 2004.

- 345 [36] Lou Beaulieu-Laroche, Enrique HS Toloza, Norma J Brown, and Mark T Harnett. Widespread and highly correlated  
346 somato-dendritic activity in cortical layer 5 neurons. *Neuron*, 103(2):235–241, 2019.
- 347 [37] Valerio Francioni, Zahid Padamsey, and Nathalie L Rochefort. High and asymmetric somato-dendritic coupling of v1 layer  
348 5 neurons independent of visual stimulation and locomotion. *Elife*, 8:e49145, 2019.
- 349 [38] Carsten K Pfeffer, Mingshan Xue, Miao He, Z Josh Huang, and Massimo Scanziani. Inhibition of inhibition in visual  
350 cortex: the logic of connections between molecularly distinct interneurons. *Nature neuroscience*, 16(8):1068–1076, 2013.
- 351 [39] Xiaolong Jiang, Shan Shen, Cathryn R Cadwell, Philipp Berens, Fabian Sinz, Alexander S Ecker, Saumil Patel, and  
352 Andreas S Tolias. Principles of connectivity among morphologically defined cell types in adult neocortex. *Science*,  
353 350(6264), 2015.
- 354 [40] Mahesh M Karnani, Jesse Jackson, Inbal Ayzenshtat, Jason Tucciarone, Kasra Manoocheri, William G Snider, and Rafael  
355 Yuste. Cooperative subnetworks of molecularly similar interneurons in mouse neocortex. *Neuron*, 90(1):86–100, 2016.
- 356 [41] Misha Tsodyks, Klaus Pawelzik, and Henry Markram. Neural networks with dynamic synapses. *Neural computation*,  
357 10(4):821–835, 1998.
- 358 [42] Misha V Tsodyks, William E Skaggs, Terrence J Sejnowski, and Bruce L McNaughton. Paradoxical effects of external  
359 modulation of inhibitory interneurons. *Journal of neuroscience*, 17(11):4382–4388, 1997.
- 360 [43] Hirofumi Ozeki, Ian M Finn, Evan S Schaffer, Kenneth D Miller, and David Ferster. Inhibitory stabilization of the cortical  
361 network underlies visual surround suppression. *Neuron*, 62(4):578–592, 2009.
- 362 [44] Alessandro Sanzeni, Bradley Akitake, Hannah C Goldbach, Caitlin E Leedy, Nicolas Brunel, and Mark H Histed. Inhibition  
363 stabilization is a widespread property of cortical networks. *Elife*, 9:e54875, 2020.
- 364 [45] Adam M Packer and Rafael Yuste. Dense, unspecific connectivity of neocortical parvalbumin-positive interneurons: a  
365 canonical microcircuit for inhibition? *Journal of Neuroscience*, 31(37):13260–13271, 2011.
- 366 [46] Elodie Fino, Adam M Packer, and Rafael Yuste. The logic of inhibitory connectivity in the neocortex. *The Neuroscientist*,  
367 19(3):228–237, 2013.
- 368 [47] Kenneth D Harris and Thomas D Mrsic-Flogel. Cortical connectivity and sensory coding. *Nature*, 503(7474):51–58, 2013.
- 369 [48] Petr Znamenskiy, Mean-Hwan Kim, Dylan R Muir, Maria Florencia Iacaruso, Sonja B Hofer, and Thomas D Mrsic-Flogel.  
370 Functional selectivity and specific connectivity of inhibitory neurons in primary visual cortex. *bioRxiv*, page 294835, 2018.
- 371 [49] Emre O Neftci, Hesham Mostafa, and Friedemann Zenke. Surrogate gradient learning in spiking neural networks: Bringing  
372 the power of gradient-based optimization to spiking neural networks. *IEEE Signal Processing Magazine*, 36(6):51–63, 2019.
- 373 [50] David E Rumelhart, Geoffrey E Hinton, and Ronald J Williams. Learning representations by back-propagating errors.  
374 *nature*, 323(6088):533–536, 1986.
- 375 [51] Paul J Werbos. Backpropagation through time: what it does and how to do it. *Proceedings of the IEEE*, 78(10):1550–1560,  
376 1990.
- 377 [52] Timothy P Lillicrap and Adam Santoro. Backpropagation through time and the brain. *Current opinion in neurobiology*,  
378 55:82–89, 2019.
- 379 [53] Simon JB Butt, Marc Fuccillo, Susana Nery, Steven Noctor, Arnold Kriegstein, Joshua G Corbin, and Gord Fishell. The  
380 temporal and spatial origins of cortical interneurons predict their physiological subtype. *Neuron*, 48(4):591–604, 2005.



- 381 [54] Lynette Lim, Janelle MP Pakan, Martijn M Selten, André Marques-Smith, Alfredo Llorca, Sung Eun Bae, Nathalie L  
382 Rochefort, and Oscar Marín. Optimization of interneuron function by direct coupling of cell migration and axonal targeting.  
383 *Nature neuroscience*, 21(7):920–931, 2018.
- 384 [55] Maria Antonietta Tosches, Tracy M Yamawaki, Robert K Naumann, Ariel A Jacobi, Georgi Tushev, and Gilles Laurent.  
385 Evolution of pallium, hippocampus, and cortical cell types revealed by single-cell transcriptomics in reptiles. *Science*,  
386 360(6391):881–888, 2018.
- 387 [56] Bradley M Colquitt, Devin P Merullo, Genevieve Konopka, Todd F Roberts, and Michael S Brainard. Cellular transcrip-  
388 tomics reveals evolutionary identities of songbird vocal circuits. *Science*, 371(6530), 2021.
- 389 [57] Sébastien Royer, Boris V Zemelman, Attila Losonczy, Jinhyun Kim, Frances Chance, Jeffrey C Magee, and György Buzsáki.  
390 Control of timing, rate and bursts of hippocampal place cells by dendritic and somatic inhibition. *Nature neuroscience*,  
391 15(5):769–775, 2012.
- 392 [58] Luc J Gentet, Yves Kremer, Hiroki Taniguchi, Z Josh Huang, Jochen F Staiger, and Carl CH Petersen. Unique functional  
393 properties of somatostatin-expressing gabaergic neurons in mouse barrel cortex. *Nature neuroscience*, 15(4):607–612, 2012.
- 394 [59] Emily L Sylwestrak and Anirvan Ghosh. Efn1 regulates target-specific release probability at ca1-interneuron synapses.  
395 *Science*, 338(6106):536–540, 2012.
- 396 [60] Tevye Jason Stachniak, Emily Lauren Sylwestrak, Peter Scheiffele, Benjamin J Hall, and Anirvan Ghosh. Efn1-induced  
397 constitutive activation of mglur7 determines frequency-dependent recruitment of somatostatin interneurons. *Journal of*  
398 *Neuroscience*, 39(23):4461–4474, 2019.
- 399 [61] Federico Scala, Dmitry Kobak, Shen Shan, Yves Bernaerts, Sophie Laturus, Cathryn Rene Cadwell, Leonard Hartmanis,  
400 Emmanouil Froudarakis, Jesus Ramon Castro, Zheng Huan Tan, et al. Layer 4 of mouse neocortex differs in cell types  
401 and circuit organization between sensory areas. *Nature communications*, 10(1):1–12, 2019.
- 402 [62] Julian Rossbroich, Daniel Trotter, John Beninger, Katalin Tóth, and Richard Naud. Linear-nonlinear cascades capture  
403 synaptic dynamics. *PLoS computational biology*, 17(3):e1008013, 2021.
- 404 [63] William Muñoz, Robin Tremblay, Daniel Levenstein, and Bernardo Rudy. Layer-specific modulation of neocortical dendritic  
405 inhibition during active wakefulness. *Science*, 355(6328):954–959, 2017.
- 406 [64] Avital Adler, Ruohe Zhao, Myung Eun Shin, Ryohei Yasuda, and Wen-Biao Gan. Somatostatin-expressing interneurons  
407 enable and maintain learning-dependent sequential activation of pyramidal neurons. *Neuron*, 102(1):202–216, 2019.
- 408 [65] Valerio Mante, David Sussillo, Krishna V Shenoy, and William T Newsome. Context-dependent computation by recurrent  
409 dynamics in prefrontal cortex. *nature*, 503(7474):78–84, 2013.
- 410 [66] Hansem Sohn, Devika Narain, Nicolas Meirhaeghe, and Mehrdad Jazayeri. Bayesian computation through cortical latent  
411 dynamics. *Neuron*, 103(5):934–947, 2019.
- 412 [67] Francesca Mastrogioseppe and Srdjan Ostojic. Linking connectivity, dynamics, and computations in low-rank recurrent  
413 neural networks. *Neuron*, 99(3):609–623, 2018.
- 414 [68] Adam Paszke, Sam Gross, Francisco Massa, Adam Lerer, James Bradbury, Gregory Chanan, Trevor Killeen, Zeming  
415 Lin, Natalia Gimelshein, Luca Antiga, Alban Desmaison, Andreas Kopf, Edward Yang, Zachary DeVito, Martin Raison,  
416 Alykhan Tejani, Sasank Chilamkurthy, Benoit Steiner, Lu Fang, Junjie Bai, and Soumith Chintala. Pytorch: An imperative  
417 style, high-performance deep learning library. In H. Wallach, H. Larochelle, A. Beygelzimer, F. d’Alché-Buc, E. Fox, and  
418 R. Garnett, editors, *Advances in Neural Information Processing Systems 32*, pages 8024–8035. Curran Associates, Inc.,  
419 2019.

- 420 [69] Diederik P Kingma and Jimmy Ba. Adam: A method for stochastic optimization. *arXiv preprint arXiv:1412.6980*, 2014.
- 421 [70] Razvan Pascanu, Tomas Mikolov, and Yoshua Bengio. On the difficulty of training recurrent neural networks. In *International conference on machine learning*, pages 1310–1318, 2013.
- 422
- 423 [71] F. Pedregosa, G. Varoquaux, A. Gramfort, V. Michel, B. Thirion, O. Grisel, M. Blondel, P. Prettenhofer, R. Weiss,
- 424 V. Dubourg, J. Vanderplas, A. Passos, D. Cournapeau, M. Brucher, M. Perrot, and E. Duchesnay. Scikit-learn: Machine
- 425 learning in Python. *Journal of Machine Learning Research*, 12:2825–2830, 2011.

## 426 Methods

### 427 Network Model

We simulated a spiking network model consisting of  $N_E$  pyramidal cells (PCs) and  $N_I$  interneurons (INs), as in earlier work [33]. PCs are described by a two-compartment model [32]. The membrane potential  $v^s$  in the somatic compartment is modeled as a leaky integrate-and-fire unit with spike-triggered adaptation:

$$\frac{dv^s}{dt} = -\frac{v^s - E_L}{\tau_s} + \frac{g_s f(v^d) + w^s + I^s}{C_s} \quad (2)$$

$$\frac{dw^s}{dt} = -\frac{w^s}{\tau_{s,w}} + b_s S(t). \quad (3)$$

Here,  $E_L$  denotes the resting potential,  $\tau_s$  the membrane time constant and  $C_s$  the capacitance of the soma.  $I^s$  is the external input, and  $w^s$  the adaptation variable, which follows leaky dynamics with time constant  $\tau_{s,w}$ , driven by the spike train  $S$  emitted by the soma.  $b_s$  controls the strength of the spike-triggered adaptation.  $v^d$  is the dendritic membrane potential, the conductance  $g_s$  controls how strongly the dendrite drives the soma, and  $f$  the nonlinear activation of the dendrite:

$$f(v) = 1/(1 + \exp(-(v - E_d)/D_d)). \quad (4)$$

The half-point  $E_d$  and slope  $D$  of the transfer function  $f$  control the excitability of the dendrite. When the membrane potential reaches the spiking threshold  $\vartheta$ , it is reset to the resting potential and the PC emits a spike. Every spike is followed by an absolute refractory period of  $\tau_r$ .

The dynamics of the dendritic compartment are given by:

$$\frac{dv^d}{dt} = -\frac{v^d - E_L}{\tau_d} + \frac{g_d f(v^d) + c_d K(t - \hat{t}) + w^d + I^d}{C_d} \quad (5)$$

$$\frac{dw^d}{dt} = -\frac{w^d}{\tau_{d,w}} + \frac{a_d(v^d - E_L)}{\tau_{d,w}}. \quad (6)$$

In addition to leaky membrane potential dynamics with time constant  $\tau_d$ , the dendrite shows a voltage-dependent nonlinear activation  $f$ , the strength of which is controlled by  $g_d$ . This nonlinearity allows the generation of dendritic plateau potentials ("calcium spikes"). Somatic spikes trigger backpropagating action potentials in the dendrite, modeled in the form of a boxcar kernel  $K$ , which starts 1ms after the spike and lasts 2ms. The amplitude of the backpropagating action potential is controlled by the parameter  $c_d$ . The dendrite is subject to a voltage-activated adaptation current  $w^d$ , which limits the duration of the plateau

potential. This adaptation follows leaky dynamics with time constant  $\tau_{d,w}$ . The strength of the adaptation is given by the parameter  $a_d$ . Note that the model excludes sub-threshold coupling from the soma to the dendrite.

The interneurons are modeled as leaky integrate-and-fire neurons:

$$\frac{dv^i}{dt} = -\frac{v^i - E_L}{\tau_i} + \frac{I^i}{C_i}, \quad (7)$$

with time constant  $\tau_i$ . Spike threshold, resting and reset potential, and refractory period are the same as for the PCs.

All neurons receive an external background current to ensure uncorrelated activity, which follows Ornstein-Uhlenbeck dynamics

$$\frac{dI^{x,bg}}{dt} = -\frac{I^{x,bg} - \mu_x}{\tau_{bg}} + \sigma_x \varepsilon. \quad (8)$$

Here,  $x \in \{s, d, i\}$  refers to the soma, dendrite, or interneuron, respectively, and  $\varepsilon$  is standard Gaussian white noise with zero mean and correlation  $\langle \varepsilon(t)\varepsilon(t') \rangle = \delta(t - t')$ .

In addition, the somatic and dendritic compartments received step currents mimicking external signals (see Optimization), as well as recurrent inhibitory inputs. The recurrent input to compartment  $x \in \{s, d\}$  of the  $i$ th principal cell was given by

$$I_i^{x,inh}(t) = -\sum_{j=1}^{N_I} |W_{ij}^{I \rightarrow x}| s^j(t). \quad (9)$$

where  $s^j$  is the synaptic trace that is increased at each presynaptic spike and decays with time constant  $\tau_{syn}$  otherwise:

$$\frac{ds}{dt} = -\frac{s}{\tau_{syn}} + S.$$

The compartment-specific inhibitory weight matrices  $W^{I \rightarrow x}$ ,  $x \in \{s, d\}$  were optimized; the absolute value in Eq. 9 ensured positive weights.

The recurrent input to the  $i$ th interneuron was given by:

$$I_i^{rec} = \sum_{j=1}^{N_E} |W_{ij}^{E \rightarrow I}| \mu_{ij}(t) s^j(t) - \sum_{k=1} |W_{ik}^{I \rightarrow I}| s^k(t). \quad (10)$$

The function  $\mu_{ij}(t)$  implements short-term plasticity according to the Tsodyks-Markram model [41].  $\mu(t)$  is the product of a utilization variable  $u$  and a recovery variable  $R$  that obey the dynamics

$$\frac{du}{dt} = -\frac{u - U}{\tau_u} + (1 - u) \cdot F \cdot S, \quad (11)$$

$$\frac{dR}{dt} = -\frac{R - 1}{\tau_R} - u \cdot R \cdot S. \quad (12)$$

428  $U$  is the initial release probability, which is optimized by gradient descent.  $F$  is the facilitation fraction, and  
 429  $\tau_R, \tau_u$  are the time constants of facilitation and depression, respectively. All parameter values are listed in  
 430 Table 1 (Supplementary Materials)

431

432 Finally, the network parameters were scaled so that the membrane voltages ranged between  $E_L = 0$   
 433 and  $\vartheta = 1$ . The scaling allowed weights of order  $1/\sqrt{N}$ , mitigating vanishing or exploding gradients during  
 434 optimization. All optimization parameters are listed in Table 2 (Supplementary Materials).

## 435 Optimization

We used gradient descent to find weights  $W$  and initial release probabilities  $U$  that minimize the difference between excitation and inhibition in both compartments:

$$\mathcal{L} = \sum_{t=1}^T \sum_{i=1}^{N_E} (E^s(t) + I_i^s(t))^2 + (E^d(t) + I_i^d(t))^2. \quad (13)$$

436  $E_i^x$  and  $I_i^x$  are the total excitatory and inhibitory input to compartment  $x \in \{s, d\}$  of PC  $i$ . To speed up the  
 437 optimization process, all output synapses from a given neuron to a given compartment type had the same  
 438 strength, i.e., the optimization of the output synapses is performed for  $N_I \times 2$  parameters. For the input  
 439 synapses onto the INs, weight and initial release probability were optimized independent for all  $N_E \times N_I$   
 440 synapses.

441

To achieve small interneuron rates necessary for interneuron specialization (Fig. A2), we subtracted the

mean background input from  $E_i^x$ :

$$I_i^x(t) = E_i^x(t) - \mu_x \quad (14)$$

To propagate gradients through the spiking non-linearity, we replaced its derivative with the derivative of a smooth approximation [34]

$$\sigma(v) = \frac{1}{(1 + \beta|v - \vartheta|)^2}. \quad (15)$$

442 We used the machine learning framework PyTorch [68] to simulate the differential equations (forward Euler  
443 with step size 1 ms), compute the gradients of the objective  $\mathcal{L}$  using automatic differentiation, and update  
444 the network parameters using Adam [69]. The optimized parameters were initialized according to the dis-  
445 tributions listed in Table 2 (Supplementary Materials). 2. We simulated the network response to batches of  
446 8 trials of 600 ms, consisting of 100 ms pulses given at 2.5 Hz. The pulse amplitudes were drawn uniformly  
447 and independently for soma and dendrites from the set  $\{100, 200, 300, 400\}$ . Training converged within 200  
448 batches (parameter updates). Before each parameter update, the gradient values were clipped between  $-1$   
449 and  $1$  to mitigate exploding gradients [70]. After each update, the initial release probability was clipped  
450 between  $0$  and  $1$  to avoid unphysiological values.

## 451 **Methods for Figures**

### 452 **Figure 1**

453 We measured the short-term plasticity of PC  $\rightarrow$  IN synapses by simulating their response to two EPSPs  
454 given 10 ms apart, a typical interspike interval within a burst. The PPR was computed as the ratio of  
455 the two EPSP amplitudes, such that a PPR  $> 1$  indicates short-term facilitation and a PPR  $< 1$  indicates  
456 short-term depression. The PPR of a single IN was defined as the mean PPR of all its excitatory afferents.  
457 Clustering of interneurons was done by fitting a single Gaussian (before optimization) or a mixture of two  
458 Gaussians (after optimization) to the three-dimensional distribution of inhibitory weights to the PC soma,  
459 to PC dendrites, and the PC $\rightarrow$ IN Paired Pulse Ratio (PPR). Both models were fitted using Scikit-learn [71]  
460 on pooled data from five networks, trained from different random initializations. The density models were  
461 fitted on 246 interneurons that were active (firing rate higher than 1 spk/s) and had a medium to strong  
462 projection to either soma or dendrites (weight bigger than 0.01). The dashed lines in Fig. 1b illustrate the  
463 two-dimensional marginal distributions of the somatic and dendritic inhibition. All PCs received the same  
464 time-varying input currents, consisting of 100 ms pulses of 300 pA, given at a rate of 2.5 Hz. Correlations

465 between compartment-specific excitation and inhibition were computed between the the currents to the PC  
466 compartments, averaged across all PCs in the network.

## 467 **Figure 2**

468 Before optimization, we assigned interneurons to inhibit either PC somata or dendrites by fixing their weights  
469 onto the other compartment to zero. Half of the interneurons was assigned to inhibit the soma, the other  
470 half was assigned to inhibit the dendrites. Otherwise, weights and initial release probabilities were optimized  
471 as before.

## 472 **Figure 3**

The definitions of burst rate, burst probability and event rate were taken from Naud & Sprekeler [33]: A burst was defined as multiple spikes occurring within 16 ms. The time of the first spike was taken as the time of the burst. An event was defined as a burst or a single spike. The instantaneous burst rate and event rate were computed by counting the number of bursts and events, respectively, in bins of 1ms and among the population of PCs, and smoothing the result with a Gaussian filter (width: 2ms). The burst probability was defined as

$$\text{Burst Probability} = \frac{\text{Burst Rate}}{\text{Event Rate}} \times 100\%. \quad (16)$$

473 We injected current pulses of 100 ms duration to either soma or dendrite while injecting a constant current to  
474 the other compartment. Currents where varied in amplitude between 100 and 400 pA; the constant current  
475 was 0 pA. The figure shows the mean and standard deviation of the total network activity during 10 current  
476 pulses. For Fig. 3e, we injected simultaneous pulses to the other compartment of amplitude 0, 200 or 400  
477 pA.

## 478 **Figure 4**

We varied the correlation between the inputs to soma and dendrites by generating repeating current pulses with different temporal offsets and optimized a network for each offset. The interneuron specialization was defined as

$$\text{specialization} = 1 - \frac{x^T y}{\|x\| \|y\|}, \quad (17)$$

479 where  $x$  and  $y$  are  $N_I$ -dimensional vectors containing the inhibitory weights onto soma and dendrites and  
480  $\|\cdot\|$  the  $L_2$  norm. If each neuron inhibits either somata or dendrites, but not both, the specialization will be  
481 1. If the weights are perfectly aligned (i.e., interneurons with a strong dendritic projection also have a strong  
482 somatic projection), the specialization will be 0. Here and in all figures, the EI correlation was computed as  
483 the correlation between the time series of the compartment-specific excitation and inhibition, after averaging  
484 across all PCs. Shown is the mean over 5 batches of 600 ms, where each batch consisted of 8 trials with  
485 amplitudes from  $\{100, 200, 300, 400\}$  pA, sampled independently for soma and dendrites.

#### 486 **Figure 5**

487 Figure 5a shows the connectivity strength over five networks. We first used the Gaussian mixture models to  
488 assign INs to PV or SST clusters, and then computed the mean connectivity between and within clusters for  
489 each network. For 5b, we trained networks with predefined interneuron populations to control the interneuron  
490 connectivity. Connections between populations were knocked out by fixing them to zero during and after  
491 optimization. EI correlations are computed for 5 batches of 600 ms, where each batch consisted of 8 trials  
492 with amplitudes from  $\{100, 200, 300, 400\}$  pA, sampled independently for soma and dendrites.

#### 493 **Figure A.2**

The minimum rate of PV neurons was controlled indirectly, by varying the baseline inhibitory target current to the soma—A larger baseline requires a higher minimum PV rate. We varied the minimum inhibitory current by subtracting only a fraction  $\alpha$  of the baseline excitatory current:

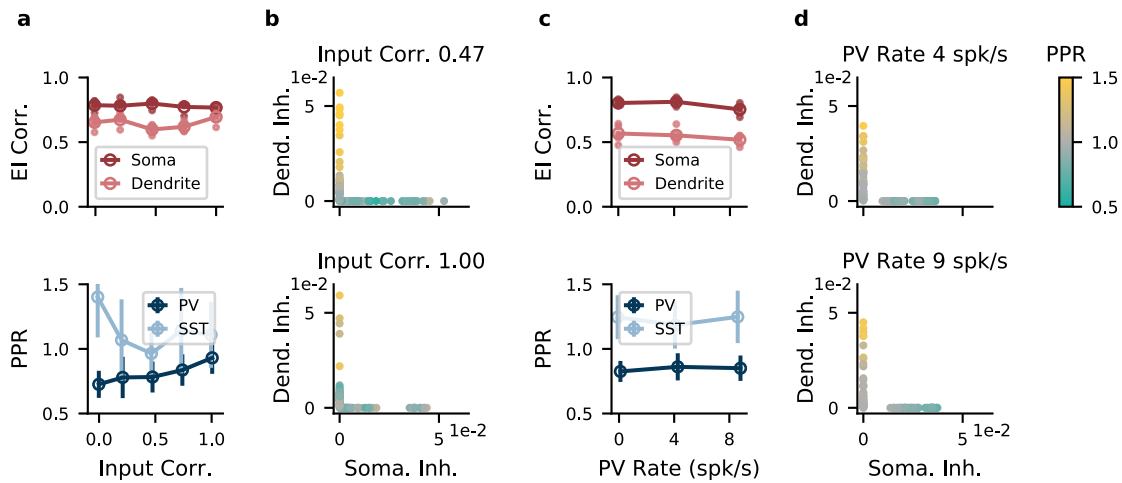
$$I^x(t) = E^x(t) - \alpha \cdot \mu_x, \quad (18)$$

494 cf. Eq. (14). In the simulations, we varied  $\alpha$  between 1 and 0.8, leading to a minimum PV rate between 1  
495 spk/s, and 9 spk/s.

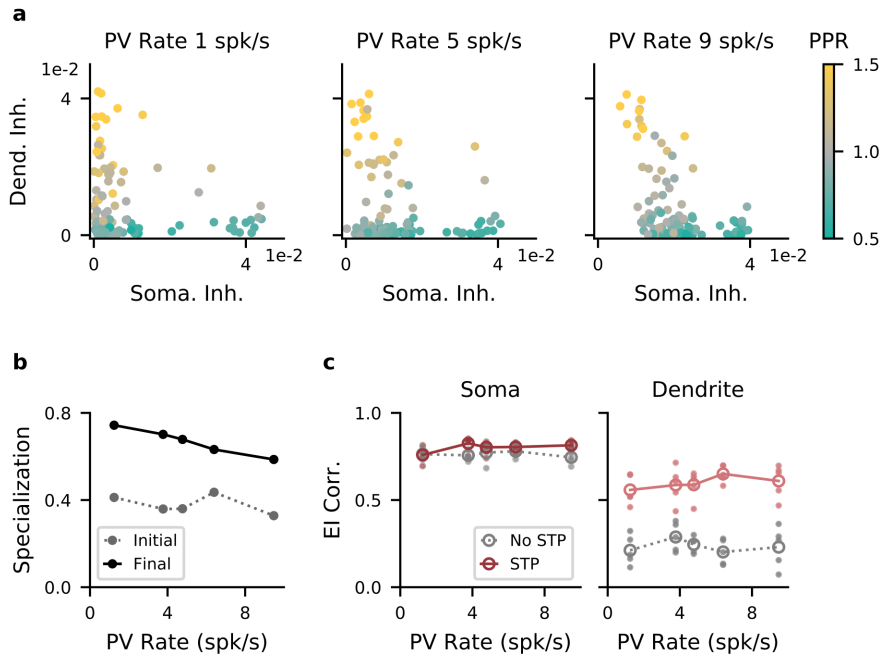


## 496 A Supplementary Materials

### 497 Supplementary Figures



**Figure A.1: Non-overlapping interneuron populations achieve compartment-specific inhibition for a range of input statistics.** (a) Top, performance as measured by compartment-specific correlation between excitation and inhibition of networks trained on different correlations between compartment-specific excitatory inputs. Open circles, mean over 5 batches of 8 stimuli with random amplitudes (see Methods). Small filled circles, individual batches. Here and in the other panels, the interneurons were assigned to inhibit only the soma or only the dendrites. Bottom, interneuron specialization as measured by Paired Pulse Ratio (PPR) decreases with input correlations. Error bars denote sd over IN populations. (b) Strength of somatic and dendritic inhibition from individual INs. Top, medium input correlation (0.47); bottom, high input correlation (1.00). Color indicates PPR. (c) Top, as a but as function of minimum PV rate. Bottom, interneuron specialization as measured by Paired Pulse Ratio (PPR) is not influenced by minimum PV rate. (d) Strength of somatic and dendritic inhibition from individual INs. Top, medium PV rate (4 spk/s); bottom, high PV rate (9 spk/s).



**Figure A.2: Higher baseline PV rates decrease the need for interneuron specialization.** (a) Strength of somatic and dendritic inhibition from individual INs. Left, middle, right: network optimized with a baseline PV rate of 1 (low), 5 (medium), and 9 spk/s (high), respectively. (b) Specialization of IN→E weights. If each IN targets either soma or dendrites, the specialization is 1 (see Methods). Gray: specialization of initial, random network; black: specialization after optimization. (c) Left, correlation between excitation and inhibition as function of minimum PV rate. Red: networks with optimized short-term plasticity. Gray: Networks without short-term plasticity. Open circles, mean over 5 batches of 8 stimuli with random amplitudes. Small filled circles, individual batches.

## 498 Mathematical Analysis of a Simplified Network Model

499 We performed a mathematical analysis of a simplified network to better understand the following results of  
500 our spiking network simulations:

- 501 1. A compartment-specific balance requires PV  $\rightarrow$  SST inhibition, but no other IN  $\rightarrow$  IN connectivity  
502 (Fig. 5).
- 503 2. Higher interneuron rates require less IN specialization, i.e., individual interneurons often inhibit both  
504 PC compartments (Fig A.2).

505 The simplified model consists of a population of principal cells (PC) and two populations of interneurons  
506 that we will refer to as parvalbumin (PV)-positive and as somatostatin (SST)-positive cells. The population  
507 activity of the PCs is represented by somatic activity  $e$  and dendritic activity  $b$ . The interneuron activities  
508 are represented by firing rates  $p$  and  $s$ . The four activity variables  $e, b, p, s$  are best thought of as deviations  
509 of the respective activity from baseline. The activity variables can hence be both positive and negative  
510 (ignoring saturation effects that arise when the baseline is very low, see below).

For our analysis, we make the following assumptions: (1) somatic input linearly increases somatic activity  $e$ , (2) dendritic input linearly increases dendritic activity  $b$ , which is in turn assumed to be independent of somatic input/activity (note that the latter assumption deviates from a BAC-firing mechanism [31], but is necessary to obtain a linear model), (3) the activities  $p, s$  of the interneuron populations increase linearly with their input, and (4) short-term plasticity is characterized by a single, static parameter (see below). Because we are interested only in qualitative statements, the analysis is done in terms of unitless variables. The model describes the dynamics of the four activity variables  $e, b, p, s$ :

$$\dot{e} = -e - w^{ep}p + E^e(t), \quad (\text{A.1})$$

$$\dot{b} = -b - w^{bs}s + E^b(t), \quad (\text{A.2})$$

$$\dot{p} = -p + \alpha w^{pe}e + (1 - \alpha)w^{pb}b - w^{ps}s, \quad (\text{A.3})$$

$$\dot{s} = -s + \beta w^{se}e + (1 - \beta)w^{sb}b - w^{sp}p. \quad (\text{A.4})$$

Here, the synaptic weight from population  $y$  to  $x$  is modeled with a non-negative weight  $w^{xy}$  ( $x, y \in \{e, p, s\}$ ;  $e$ : PCs,  $p$ : PV INs,  $s$ : SST INs). The central tenet of this simplified model is that somatic and dendritic activity both generate characteristic spike patterns in PCs—such as events and bursts—which are selectively transmitted by synapses because of short-term plasticity. The parameters  $\alpha, \beta \in [0, 1]$  describe the short-term plasticity of the PC $\rightarrow$ PV and PC $\rightarrow$ SST synapses, respectively.  $\alpha, \beta = 1$  corresponds to synapses that

only transmit somatic activity. If somatic activity generates events and dendritic activity generates bursts, this would require "perfectly depressing" synapses, i.e., synapses that transmit only the first spike of a burst.  $\alpha, \beta = 0$  corresponds to synapses that only transmit dendritic activity. For the case where dendritic activity generates bursts, this requires "perfectly facilitating" synapses that ignore individual spikes and transmit only bursts. We assumed that the projections of the interneurons are specialized, i.e., that PV interneurons inhibit the soma and SST interneurons inhibit the dendrite. We will abandon this assumption in Section A.1. We also excluded inhibitory recurrence within the two populations (PV  $\rightarrow$  PV, SST  $\rightarrow$  SST), because these connections would only change the effective time constant of the respective activation variable. The somata and dendrites of the PCs receive time-varying external inputs  $E^e(t)$  and  $E^b(t)$ , respectively. All activity variables follow leaky dynamics.

The dynamical system can be written as  $\dot{r} = Wr + I$ , where the vector  $r$  contains the activation variables  $r = (e, b, p, s)^T$ ,  $I$  contains the external inputs  $I = (E^e, E^b, 0, 0)^T$ , and  $W$  is the matrix of effective connectivity strengths

$$W = \begin{pmatrix} -1 & 0 & -w^{ep} & 0 \\ 0 & -1 & 0 & -w^{bs} \\ \alpha w^{pe} & (1 - \alpha)w^{pe} & -1 & -w^{ps} \\ \beta w^{se} & (1 - \beta)w^{se} & -w^{sp} & -1 \end{pmatrix}. \quad (\text{A.5})$$

Assuming that the time constant of the network is sufficiently short to adiabatically follow the input currents, we can consider the steady state by setting  $\dot{r} = 0$  and solving for  $r$ :

$$Wr + I = 0 \implies r = -W^{-1}I. \quad (\text{A.6})$$

## 511 Influence of IN $\rightarrow$ IN connections on compartment-specific E/I balance

In the steady state Eq. (A.6), the IN rates are equal to

$$p = -[W^{-1}]_{31}E^e - [W^{-1}]_{32}E^b, \quad (\text{A.7})$$

$$s = -[W^{-1}]_{41}E^e - [W^{-1}]_{42}E^b. \quad (\text{A.8})$$

Here,  $[W^{-1}]_{ij}$  refers to the element in row  $i$  and column  $j$  of the matrix  $W^{-1}$ . Assuming that the interneurons specialize by inhibiting a single compartment, a necessary (and, up to scaling, sufficient) condition for

compartment-specific balance is that the PV rate  $p$  is proportional to the external input targeting the soma and independent of the input targeting the dendrite. Similarly, the SST rate should be proportional to the external input targeting the dendrite and independent of the input targeting the soma. By Eq. (A.7), a compartment-specific balance hence requires  $[W^{-1}]_{32} = 0$  and  $[W^{-1}]_{41} = 0$ . Computing these matrix entries yields:

$$[W^{-1}]_{32} \propto w^{pe}(1 - \alpha) - w^{ps}w^{se}(1 - \beta) = 0 \quad (\text{A.9})$$

$$[W^{-1}]_{41} \propto -w^{pe}w^{sp}\alpha + w^{se}\beta = 0. \quad (\text{A.10})$$

512 These equations have a simple interpretation. Each of the two terms in  $[W^{-1}]_{32}$  represents a pathway by  
 513 which dendritic activity reaches the PV interneurons. The first term quantifies how much dendritic activity  
 514 reaches PV interneurons via the direct excitatory PC→PV projection, the second represents corresponding  
 515 feedforward inhibition via the PC→SST→PV pathway. If these two pathways cancel, PV activity is inde-  
 516 pendent of dendritic activity. Similarly, the two pathways in  $[W^{-1}]_{41}$  that transmit somatic activity to the  
 517 SST need to cancel.

What is the role of short-term plasticity? For illustration, let us first consider the limiting case of  
 ”perfect” synaptic depression ( $\alpha = 1$ ). Perfectly depressing PC → PV synapses would imply that the PV  
 interneurons only receive somatic activity from the PCs via the direct PC→PV pathway. The condition  
 (A.9) then reduces to

$$[W^{-1}]_{32} \propto -w^{ps}w^{se}(1 - \beta) = 0, \quad (\text{A.11})$$

518 i.e., dendritic activity should not reach PV interneurons via the indirect PC→SST→PV pathway, because this  
 519 would render PV activity dependent on dendritic activity. Because dendritic activity need to be transmitted  
 520 to the SST interneurons to reach an E/I balance in the dendrite, this implies that the SST→PV connection  
 521 should be absent.

522 ”Perfect” synaptic depression ( $\alpha, \beta = 1$ ) or facilitation ( $\alpha, \beta = 0$ ) are hard to implement, certainly by a  
 523 Markram-Tsodyks model in the presence of background activity. However, the effect of imperfect depression  
 524 in the PC→PV connection ( $\alpha < 1$ ) can be compensated by feedforward inhibition along the PC→SST→PV  
 525 pathway. Similarly, imperfect PC→SST facilitation picks up somatic activity, which can then be canceled  
 526 by feedforward inhibition via the PC→PV→SST pathway. The role of IN→IN synapses is therefore to  
 527 complement ”imperfect” short-term plasticity in decoding compartment-specific inputs.

528 The observation that PV→SST connections are the most important IN→IN connections in our model

529 results from "imperfect" facilitation in the excitatory synapses onto SST interneurons. Because events occur  
 530 more frequently than bursts, the excess excitation they trigger in SST interneurons needs to be actively  
 531 cancelled via the PV→SST pathway. The converse SST→PV connection is less critical, because bursts are  
 532 comparatively rare, such that their transmission via PC→PV synapses causes only minor disturbances of  
 533 the compartment-specific E/I balance.

## 534 A.1 Influence of IN baseline firing rates on interneuron specialization

The previous analysis assumed that interneurons were specialized to inhibit a single compartment. When should we expect specialization in the first place? We can investigate this question by extending the simplified model by inhibition from all INs onto all PC compartments:

$$W = \begin{pmatrix} -1 & 0 & -w^{ep} & -w^{es} \\ 0 & -1 & -w^{bp} & -w^{bs} \\ \alpha w^{pe} & (1 - \alpha)w^{pe} & -1 & -w^{ps} \\ \beta w^{se} & (1 - \beta)w^{se} & -w^{sp} & -1 \end{pmatrix}. \quad (\text{A.12})$$

A compartment-specific balance now requires external input to be canceled by the inhibition from both interneurons:

$$E^e = w^{ep}p + w^{es}s, \quad (\text{A.13})$$

$$E^b = w^{bp}p + w^{bs}s. \quad (\text{A.14})$$

535 Without additional constraints, this system has an infinite number of solutions, i.e., weight configurations  
 536 that achieve a compartment-specific balance. However, the simple constraint of low baseline firing rates of  
 537 the interneurons collapses the solution space to the specialized one ( $w^{es} = w^{dp} = 0$ ), for the following reason.

538 The activity variables  $p, s$  represent deviations of the interneurons firing rates from baseline. If the  
 539 baseline is sufficiently high, these deviations can be both positive and negative. In that case, inhibition  
 540 from one interneuron class can be cancelled by disinhibition from the other interneuron class. PV and SST  
 541 interneurons are then both free to respond to both somatic and dendritic activity, as long as the weighted  
 542 sums of the inhibition and disinhibition they provide to PC somata and dendrites mirrors the excitatory  
 543 input to those compartments. There are many ways of doing so.

544 For low baseline firing rates, disinhibition is no longer available, because negative deviations from baseline  
 545 are limited by the fact that activities cannot be negative. For illustration, let us consider the case where

**Table 1:** Parameter values related to network simulation

Symbol	Value	Unit	Description
$N_E$	400	-	Number of exc. neurons
$N_I$	100	-	Number of inh. neurons
$E_L$	-70	mV	reversal and reset potential
$\vartheta$	-50	mV	spiking threshold
$\tau_{s/d/i}$	16 / 7 / 10	ms	time const. soma/ dend./inh. membrane
$\tau_r$	3	ms	refractory time soma and inh.
$g_{s/d}$	1300 / 1200	pA	Coupling from dend to soma
$C_{s/d/i}$	370 / 170 / 100	pF	Conductance of soma/dend./inh.
$\tau_{s/d,w}$	100 / 30	ms	Time const. adaptation soma/dend.
$b_s$	-200	pA	Spike-triggered adaptation (soma)
$a_d$	-13	nS	Voltage-driven adaptation (dend)
$c_d$	2600	pA	Coupling soma to dend.
$E_d$	-38	mV	position dend. nonlinearity
$D_d$	6	mV	steepness of dend. nonlinearity
$\mu_{s/d/i}$	400 / -300 / -100	pA	mean background input soma/dend./inh.
$\sigma_{s/d/i}$	450 / 450 / 400	pA	sd background input
$\tau_{bg}$	2	ms	time const. background input
$\tau_{syn}$	5	ms	time const. synapses
$\tau_u$	100	ms	time const. facilitation
$\tau_R$	100	ms	time const. depression
$F$	0.1	-	facilitation jump

546 both PV and SST neurons have zero baseline activity. By definition, the excitatory signals  $E^{e/b}$  are zero  
547 for baseline activity, because they represent deviations from baseline. Therefore, we can assume that there  
548 exists a moment where the input to one PC compartment is zero, while the input to the other compartment  
549 is positive (e.g.,  $E^e = 0$ ,  $E^b > 0$ ). By Eq. (A.13) and because all weights and rates must be positive,  
550  $w^{ep}p + w^{es}s = 0$  implies that  $w^{ep} = 0$  or  $p = 0$  and  $w^{es} = 0$  or  $s = 0$ . At least one weight has to be non-zero  
551 (otherwise balancing the soma is impossible), and at least one rate has to be non-zero (otherwise balancing  
552 the dendrite is impossible). Without loss of generality we can conclude that  $w^{ep} > 0$ ,  $p = 0$ ,  $w^{es} = 0$ , and  
553  $s > 0$ : The PC soma is only inhibited by the PV neuron. Analogously, the existence of a moment when  
554  $E^b = 0$  but  $E^e > 0$  implies that  $w^{ds} > 0$ ,  $w^{dp} = 0$ , meaning that the PC dendrite is only inhibited by the  
555 SST neuron. If the baseline activity is low, but not strictly zero, this saturation arguments still hold, if  
556 the variations in the firing rates that are required to balance the external input are larger than the baseline  
557 activity. Low baseline firing rates therefore imply interneuron specialization, because they prevent inhibition  
558 and disinhibition from non-specialized neurons to cancel.

**Table 2:** Parameter values related to optimization

Symbol	Value / Init. Distribution	Dimensions	Description
$U$	$\mathcal{U}(0.1, .25)$	$N_E \times N_I$	Initial release prob.
$W^{E \rightarrow I}$	$\mathcal{N}(0, 1/N_E)$	$N_E \times N_I$	Exc. to Inh. weight
$W^{I \rightarrow I}$	$\mathcal{N}(0, 1/N_I)$	$N_I \times N_I$	Inh. to Inh. weight
$W^{I \rightarrow D}$	$\mathcal{N}(0, 0.2/N_I)$	$N_I \times 1$	Inh. to Exc. Dend. weight
$W^{I \rightarrow S}$	$\mathcal{N}(0, 0.2/N_I)$	$N_I \times 1$	Inh. to Exc. Soma weight
-	1e-3	-	learning rate for weights
-	4e-3	-	learning rate for $U$
$\beta$	10	-	Slope spiking derivative
-	1.0	-	Gradient (absolute value) clipping