photobleaching reveal that the half-life of stress-granule-associated RNA-binding proteins is very brief, on the order of seconds to minutes, despite the fact that time-lapse microscopy reveals that individual stress granules persist for hours. This rapid shuttling of protein and RNA within stress granules suggests that their mRNP contents are continually sorted via fleeting associations with the translational machinery. Unlike other types of RNA granule, such as germ cell granules or neuronal granules, stress granules are not sites of long-term mRNP storage.

What are the core components of stress granules? Stress granules are primarily composed of the stalled 48S complexes containing bound mRNAs derived from disassembling polysomes. These contain poly(A)$^+$ RNA bound to early initiation factors (such as eIF4E, eIF3, eIF4A, eIFG) and small, but not large, ribosomal subunits. In addition to these core components, stress granules contain an eclectic assembly of proteins that vary with cell type and with the nature and duration of the stress involved. RNA-binding proteins, transcription factors, RNA helicases, nucleases, kinases and signaling molecules have been reported to accumulate in stress granules. In some cases, recruitment of signaling proteins into stress granules influences cell survival. More recently, stress granules have been shown to contain the Argonaute proteins, microRNAs, a number of mRNA-editing enzymes, and proteins required for transposon activity.

What are their speculated functions? The dynamic nature of stress granules suggests that they are sites of mRNA triage, wherein individual mRNAs are dynamically sorted for storage, degradation, or translation during stress and recovery. Short-lived mRNAs bearing adenine–uridine-rich destabilizing elements in their 3' untranslated regions bind to TTP and BRF1/2, proteins that promote interactions between stress granules and processing bodies (P-bodies) and induce mRNA decay. It is therefore likely that stress granules can regulate the stability of selected mRNAs. Beyond mRNP sorting, the recruitment of other signaling molecules into stress granules suggests that they link mRNP sorting with other signaling events. Cells that express a non-phosphorylatable form of eIF2α (S51A) cannot assemble stress granules in response to arsenite-induced oxidative stress and are hypersensitive to the toxic effects of low doses of arsenite. Whether this is due to defective stress-induced translational silencing or defective stress granule assembly is not yet clear. In other cases, the sequestration of signaling molecules not directly linked to RNA metabolism (such as TRAF2, RACK1 and FAST) in stress granules has been shown to regulate the survival of stressed cells.

Any known associates…? P-bodies are related dynamic mRNP granules that often associate with stress granules. Although stress granules and P-bodies have some protein and mRNA components in common, they are structurally, compositionally, and functionally distinct (Figure 1). The core component of P-bodies is the mRNA decay machinery, which includes enzymes that remove the 7meG cap and poly(A) tail and degrade the mRNA in a 5'–3' direction; these degradative enzymes are excluded from stress granules. Conversely, many signature components of stress granules (such as eIF3 and ribosomal 40S subunits) are excluded from P-bodies. The same species of reporter mRNA can be present in stress granules and P-bodies within the same cell, suggesting that these structures house mRNPs at different stages of the mRNA life cycle, rather than different types of transcript. Interactions between stress granules and P-bodies mirror the regulation of mRNA translation and decay in stressed cells.

Where can I find out more?

Anderson, P., and Kedersha, N. (2006). RNA granules. J. Cell Biol. *172*, 803–808.

Anderson, P., and Kedersha, N. (2008). Stress granules: the Tao of RNA triage. Trends Biochem. Sci. *33*, 141–150.

Arimoto, K., Fukuda, H., Imajoh-Ohmi, S., Saito, H., and Takekawa, M. (2008). Formation of stress granules inhibits apoptosis by suppressing stress-responsive MAPK pathways. Nat. Cell Biol. *10*, 1324–1332.

Kim, W.J., Back, S.H., Kim, V., Ryu, I., and Jang, S.K. (2005). Sequestration of TRAF2 into stress granules interrupts tumor necrosis factor signaling under stress conditions. Mol. Cell. Biol. *25*, 2450–2462.

Uniacke, J., and Zerges, W. (2008). Stress induces the assembly of RNA granules in the chloroplast of Chlamydomonas reinhardtii. J. Cell Biol. *182*, 641–646.

Department of Medicine, Division of Rheumatology, Brigham and Women's Hospital, Smith 652, One Jimmy Fund Way, Boston, MA 02115, USA.
E-mail: panderson@rics.bwh.harvard.edu

Primer

Inhibition in cortical circuits

Rodney J. Douglas and Kevan A.C. Martin

Inhibition was introduced as a concept to physiology and psychology at the beginning of the 19th century, and by the early 20th century Sherrington had established that inhibition is an active process in spinal reflexes. Inhibition is mediated principally by the neurotransmitters γ-amino butyric acid (GABA) in the brain and glycine in the spinal cord. Knowledge of the structure and physiology of the GABA and glyine receptors has greatly aided our understanding of analgesics, anti-epileptics and especially of mood-altering drugs, such as benzodiazepine, which acts directly on the GABA receptor. Our knowledge of the neuronal types and their synaptic physiology is most advanced for the mammalian cerebral cortex, but even here the roles of inhibition in the neuronal responses evident at the circuit level are still dimly understood. Here we shall consider the varieties of inhibitor neurons and their actions in the mammalian brain.

My name is legion…

Over the past 100 years, many descriptions have accumulated of the morphological types of inhibitory neuron that inhabit the cerebral cortex, so many different descriptions in fact, that an international consortium recently convened at Ramon y Cajal's birthplace in Petilla, Spain, to find new ways of classifying and naming them. The Petilla consortium [1] concluded, ruefully, that a major overhaul of the terminology and criteria for classification was 'premature'. Nevertheless, the widespread claim is that the GABAergic interneurons of the cerebral cortex are 'exceptionally diverse' both in morphological appearance and functional properties. This view was set in cement by a recent series of nine review articles, which appeared in *Trends in Neuroscience* under the title 'Interneuron Diversity series'. The series, which concentrated on

inhibition in the hippocampus, clearly implied that the excitatory neurons, which form the majority of neurons in the CNS, are less 'diverse'.

The apparent diversity of inhibitory neurons is far from an objectively established fact, however. Because they could find no universally accepted list of features for making the classification, even the experts of the Petilla consortium [1] could not agree on a taxonomy for the GABAergic neurons. For the moment, the degree of 'diversity' of inhibitory cells, compared to that of the excitatory neurons, which form the majority in most regions, is still largely in the eye of the beholder.

There is also a natural tendency to suppose that the clear morphological similarities of the inhibitory neurons across neocortex, paleocortex and archicortex mean that there is a matching equivalence in their function. Yet data are lacking that their connectivity and functional roles in the circuits in all three cortical structures are the same. Evolution has been conservative in some respects at least: the inhibitory neurons in the primary visual cortex of the macaque and the marsupial are recognizably similar in morphology, although their ancestral lines diverged over 135 million years ago [2].

Where inhibition goes

Inhibitory neurons (Figure 1) form about 15% of all cerebral cortical neurons, and there are about a dozen morphologically distinct varieties that can be found in all species [3]. There has been a major gain in understanding recently in the embryonic origin of the GABAergic neurons. Where previously it was thought that all cortical neurons migrated radially from the underlying ventricular zone, intensive tracing over the past decade has shown that, in rodents, the embryonic GABAergic neurons in the cerebral cortex originate from the median eminence and migrate tangentially to their final sites in the telencephalon. In primates, the situation is more complex and GABAergic neurons come both from the median eminence and the ventricular zone underlying the cortex. It is also now clear that GABAergic neurons have an important role in neuronal proliferation, migration and differentiation, so the inhibitory neurons have functions that go well beyond their traditional role of curbing excitation.

The dozen types of inhibitory neuron fall into three basic groups on the basis of whether their axonal arbours are local (neurogliaform, small basket cell, chandelier cell, common cell and small layer 1 cell), vertical (double bouquet cell, Martinotti cell, bipolar cell and cell forming axonal arcades), or horizontal (large basket cell, medium arbour cell, Cajal-Retzius cell). The axons of basket cells (small and large) and chandelier cells contain the calcium-binding protein parvalbumin and form synapses with the proximal regions of the spiny cells (soma, proximal dendrites and initial segment of the axon), which are their major targets. The neurogliaform and some small basket cells form electrically conducting gap junctions between their dendrites, a strategy that may promote synchronisation of their discharges [4], The neurons with axons that form synapses with distal portions of the dendritic tree of spiny neurons include the double bouquet cells and Martinotti cells. They frequently contain the calcium binding protein calbindin. Another calcium binding protein, calretinin, is expressed in a heterogeneous group of inhibitory neurons, which include the Cajal-Retzius cells of layer 1.

It is tempting to imagine that there exists a three-dimensional grid of inhibitory neurons embedded in a more complex lattice of excitatory neurons. In fact, the main distribution of synaptic boutons of the inhibitory neurons is dense and local, and the axon usually extends laterally not more than about 0.5 mm. By contrast, the excitatory cells form local, less dense bouton clusters and much more extensive lateral projections [5].

The observation that different inhibitory neurons form synapses with different parts of their target neurons has raised repeated speculation as to the functional consequences or such specificity. The chandelier cells, which form their synapses almost exclusively with the initial segment of the axon of pyramidal cells, were thought to act as an inhibitory 'choke' and block all output from the pyramidal cells. However, simulations using compartmental models show that there is no biophysical difference in the effect of putting inhibitory synapses on the axon initial segment, as chandelier cells do, *versus* on the cell body, as basket cells do [6]. The chandelier inhibition does not act as a switch, but is graded in its effectiveness, depending on the chandelier firing rate and the amount of excitatory current arriving at the soma of the pyramidal cell.

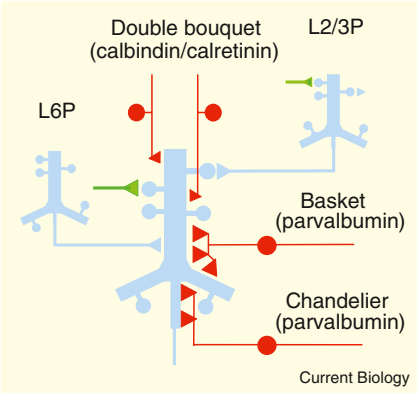

Figure 1. Simplified types of inhibitory actions (red) on cortical pyramidal neurons (blue).
Parvalbumin-positive 'horizontal' smooth cells, such as 'basket' and 'chandelier' cells, make multiple synaptic contacts on the crucial proximal dendritic output path (apical dendrite, soma, and initial segment) of superficial pyramidal neurons, where inhibition can control overall neuronal output. Calretinin/calbindin positive 'vertical' smooth cells, such as 'double bouquet' cells, make individual synaptic contacts on the more peripheral dendritic arborization, where inhibition is able to modulate or select streams of synaptic input before their final somatic integration. (Adapted with permission from [3].)

Our current view is that the parvalbumin-containing cells, like chandelier and basket cells, are concerned with controlling the output of the cell, whereas the calbindin- or calretinin-containing cells, such as the double bouquet cells, form synapses with the distal dendrites and so are more concerned with controlling the input to the neurons [6]. Interestingly, although the basket cells were so-named because they formed a pericellular nest of terminals around the cell body of pyramidal cells, they form most of their synapses with the dendrites of their target excitatory cells. Some evidence for the effectiveness of distal inhibition has come from studies of the apical dendritic tuft of large layer 5 pyramidal neurons in the somatosensory cortex of the rat. This neuron has the longest apical dendrite of any neuron in the cortex, and the apical tuft is the source of a calcium spike that can be gated by a distal inhibitory input [7].

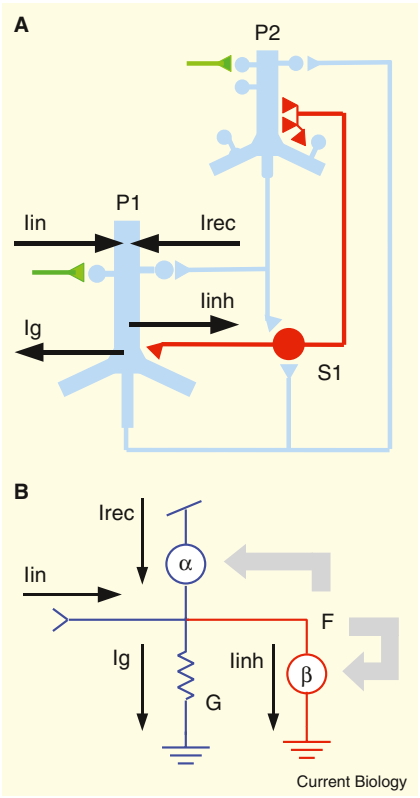

Figure 2. Simple description of the behaviour of neurons embedded in a recurrent network.

(A) Pyramidal neurons such as P1 and P2 receive inward excitatory synaptic current from two sources: feedforward input current (Iin) from other sources such as the thalamic nuclei or other cortical areas; and feedback current (Irec) from the synapses of other neurons within the recurrently connected population. Synapses from inhibitory neurons such as S1 generate an outward inhibitory synaptic current (Iinh). Action potentials generated by the neuron (frequency F) also contribute a net outward current (Ig). (B) A simple electronic circuit of the biological circuit in (A). The leak and spiking conductances of the pyramidal neuron are lumped into a single conductance, G. The various currents are labelled as in (A): α is a current source that supplies a recurrent excitatory input proportional to output discharge rate, Irec = α F; similarly, β is the current source providing the recurrent inhibitory current, Iinh = β F. Overall, this circuit amplifies its input to provide F = Iin/(1 + β – α). (Adapted with permission from [12].)

One interesting detail concerning dendritic inhibition is that inhibitory synapses are also found on the heads of dendritic spines, which are the site of most excitatory synapses. Some classes of basket cells even have spine heads as one of their major targets. Only about 7% of spines have an inhibitory input, so one attractive notion was that some critical inputs, such as the thalamic input to cortex, could be gated at the level of the spine head. Experimental testing of this hypothesis [8] proved only that spines that formed synapses with thalamic afferents received an inhibitory input with the same likelihood as the population at large (7%), so there is no evidence for selective inhibition at the level of the spine head.

Inhibition as a brake

In traditional thinking, the major function of inhibitory neurons is to curb excitation. A secondary function is to inhibit other inhibitory cells, thus releasing a circuit from inhibition. The questions remain as to why these seemingly straightforward tasks have to involve different inhibitory cell types? Why do inhibitory cells form synapses only with specific subregions of their target neurons and how do they function within the excitatory circuits? As there are few clear experimental answers to these questions, it is unsurprising that virtually all models of neural circuits use vanilla inhibitory neurons for the jobs they have to do. Only occasionally have models attempted to sketch a possible scenario in which this evident division of labour amongst the inhibitory neurons plays a real role [9].

In addition, the complex structure and biophysical properties of single neurons are so rarely taken into account in network models that there has been little incentive to explore the possible role of the differential targeting of inhibitory neurons. The major explorations of the significance of synaptic location have been in compartmental models of single neurons. In developing network models, however, we have to guess at the nature of the excitatory connections for we know rather little in detail about who excites the inhibitory neurons. The result is that in many models the inhibitory neurons are generally added 'as required' (in other words, arbitrarily) to shape spatially or temporally the desired excitatory network.

Synchrony and spatiotemporal receptive fields

Contemporary work on the hippocampus seems concerned mainly with the role of the inhibitory neurons in synchronization and generating rhythms. In the neocortex, the recurrent circuits necessarily include inhibitory neurons, which are readily able to entrain the firing of the excitatory networks to produce oscillations. However, the work in neocortex has focused more on the computational aspects of inhibition than on oscillations. One case in point is the primary visual cortex of the cat, the most salient characteristic of which is that most neurons have either 'simple' or 'complex' receptive fields, both of which have computationally interesting receptive field properties. One view is that inhibition actually shapes the structure of their receptive fields; the contrary view is that it does not, and the inhibitory neurons are merely there to make sure that the recurrent excitatory circuits do not blow up.

Concerning the spatial organization of the visual receptive fields there is more agreement. At the subcortical level of retina and visual thalamus, and at the cortical level of layer 4 simple cells, inhibition is intrinsic to the spatiotemporal structure of the receptive field. In the case of the concentric thalamic receptive fields, the inhibitory surround has a number of important roles, which include maximising the signal to noise ratio, removing redundancy, and expanding the dynamic range by transmitting only the difference between the local signal and the average. These mechanisms effectively increase the information capacity of the transmission channels.

In the simple cells of the primary visual cortex, the role of inhibition is thought to provide a seesaw-like counterbalance to excitation, to generate a so-called 'push-pull' receptive field. Experimentally, however, 'push-pull' inhibition has proved to be poorly balanced and this imbalance may be the source of significant non-linearities in the responses. Indeed, from one view, the difference between simple and complex cells is simply that inhibition masks inherently non-linear summation more strongly in the apparently 'linear' simple cells [10].

Intracellular recordings in visual cortex have emphasised that a 'diversity' of combinations of inhibition and excitation underlie the otherwise similar spiking responses of orientation and direction selective receptive fields [11]. How particular combinations arise, and how

they self-organize to produce the well-described columnar architecture of cortex, requires a much deeper understanding of the development, dynamics, and form of the neural circuits.

Roles of recurrent inhibition

The mechanism by which cortical receptive fields are formed has been the battlefield in which two quite distinct views of cortical processing, feedforward versus recurrent, have clashed. Most versions of cortical circuits are essentially feedforward in structure. Where feedback or recurrence has been used, it is generally used in the conventional control theoretic form of negative feedback, usually as a means of gain control. These model circuits reflect imperfectly the reality that cortical circuits are highly recurrent and the major connections are reciprocal connections between excitatory neurons in the same cortical area. This recurrence offers the important property of generating gain, which is crucial for any computation. Gain provides the foundation for the selective application of energy required to place systems in the improbable configurations that encode information (Figure 2) [12,13].

An enduring and elegantly simple use of recurrent inhibition is the 'normalization' model of visual cortex [14], which accounts for the experimentally observed violations of linearity seen in simple cells when their responses saturate, or adapt, or are suppressed by masking stimuli. Normalization is achieved by dividing the linear firing rate of each neuron by a number that grows with the activity of a large pool of cortical cells. The proposed mechanism of division is 'shunting inhibition', in which activity of the inhibitory synapses decreases the resistance of the target cell's membrane in proportion to the global activity of the network. Attractive as this mechanism is, it has one major flaw and that is the assumption that shunting inhibition is always divisive: it is not [15], because in most cases, the change in firing rate, even in the face of 'shunting inhibition', is subtractive.

The reason that inhibition is subtractive regardless of synaptic biophysics is itself interesting: the spiking mechanism clamps the membrane at a value far above the reversal potential of the inhibitory

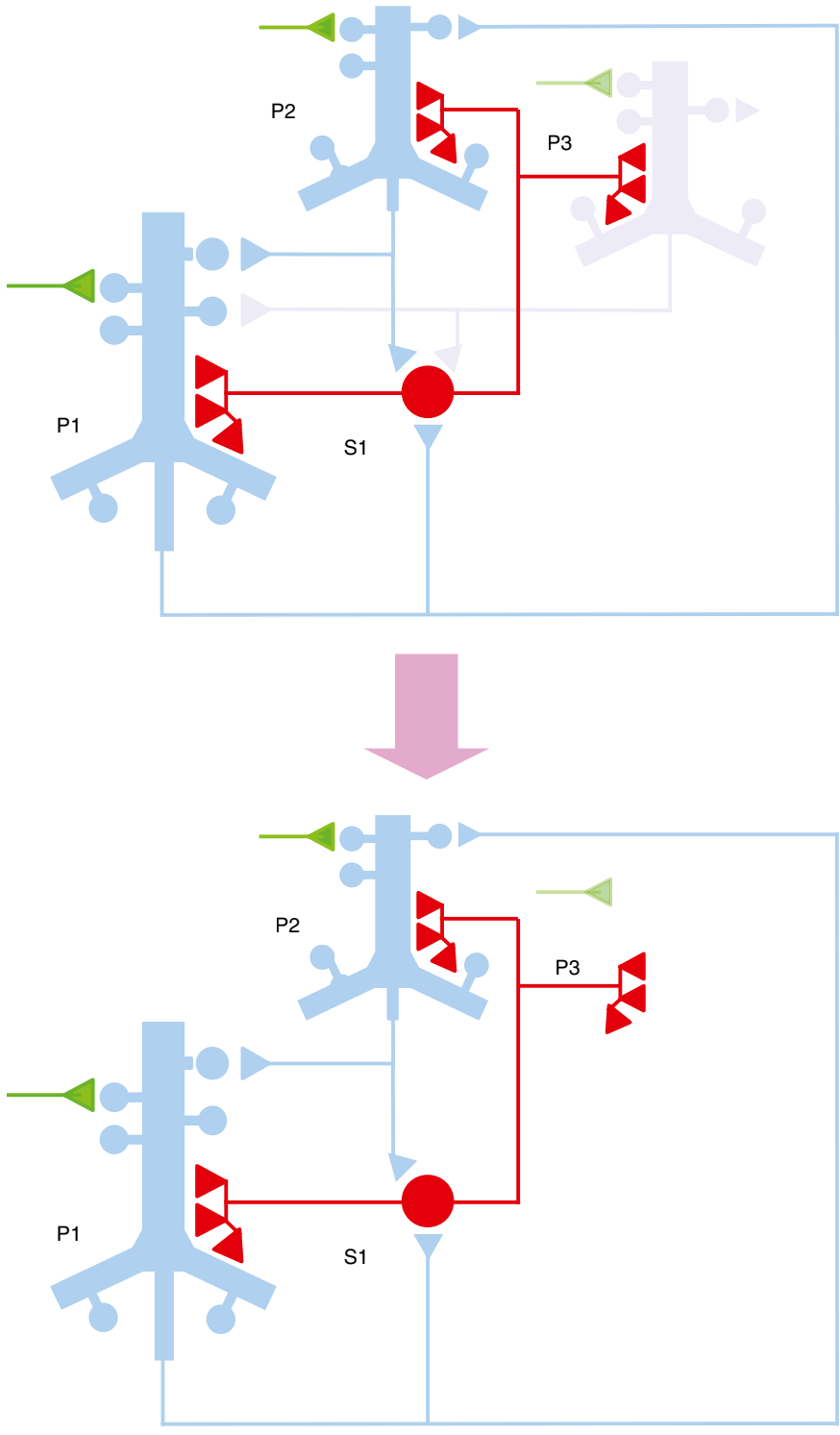

Figure 3. Schematic showing how a cortical circuit might reconfigure itself dynamically by cooperative/competitive processing.

P1–3, pyramidal neurons, and S1, smooth neuron, are part of a recurrently connected network (not all their connections are shown). Top, initial state; bottom, final state, later in time. Inputs (green) drive all the pyramidal neurons. The inputs to P1 and P2 are more similar than those to P3, and so P1 and P2 excite one another more strongly by their recurrence than they do P3. The overall network activity is normalized by S1, which samples the output from all excitatory neurons in its network. Finally, the activity of P3 falls below the increasing inhibitory normalization threshold and so it no longer participates in the circuit computation (bottom).

synapses, which means that the magnitude of the excitatory current leaked through the inhibitory synapses is largely independent of the firing rate. The normalization model, by contrast, requires strict proportionality between activity and the size of the shunt. In recurrent circuit models, this multiplicative change is the result of a change in the open-loop gain caused by the action of inhibitory synapses. If the inhibition is fed back then even if it is mediated by 'linear' synapses, the change in the gain gives a multiplicative change in output. If the inhibition is mediated by feedforward synapses, then it acts more like an offset and reduces the input current by a given amount (Figure 2) [16]. Obviously, any mechanism that can change the probability of a spike being produced, such as background noise, or changes in the probability of neurotransmitter release, will have a divisive or normalizing effect on the firing rate.

Topography of inhibition

The spatial arrangement of the inhibition used in recurrent models ignores the reality that the axons of excitatory neurons generally extend much further laterally than those of inhibitory neurons, and that their major targets are other excitatory neurons. Most models reverse this spatial arrangement and arrange for a ring-fence of inhibition to surround the excitatory core. This 'Mexican Hat' configuration is used for good reasons: it ensures the stability of the recurrent network models. *In vivo*, the cortical networks are stable, which presumably means that for a given neuron at 'rest' the net excitatory current is less than the total negative currents dissipated through its membrane leak, through its action potential conductances, and the synaptic inhibition applied to it. On the other hand, during the transient behaviour of these networks, the positive feedback is such that the network can be unstable [17]. It is in the potential to modulate the strength of positive feedback that the computationally interesting properties of recurrent cortical circuits rest, and where inhibition can have its most sensitive effects.

One important consequence of inhibition is that it can change dynamically the configuration of the circuit itself (Figure 3). This is because neurons that are below threshold and not firing are effectively disconnected from the circuit, even if temporarily. This changes dramatically the interactions of the remaining neurons that remain above threshold. Since all these neurons are connected recurrently, there can be transient changes in gain, even instabilities, which are computationally important.

Final thought

It is worth noting that while early anatomists like Ramon y Cajal, and later Lorente de No, described many of the cell types of the cerebral cortex, and they knew of Sherrington's evidence for active inhibition, they made no attempt to differentiate inhibitory from excitatory cells. That step only came much later when the fundamental details of the underlying biophysics and ionic basis of inhibitory synapses were worked out by Eccles and his colleagues and their functional data were correlated with the morphology and ultrastructure of the synapses of the neurons.

For Sherrington, excitatory and inhibitory neurons were always hand-in-glove and together they provided the algebra of the nervous system: "The net change which results there when the two areas are stimulated concurrently is an algebraic sum of the plus and minus effects producible separately by stimulating singly the two antagonistic nerves" [18]. In recurrent circuits, there is an inherent balance between excitation and inhibition and because these recurrent excitatory circuits offer the means of amplification, small changes in the timing or strength of inhibition can effectively change the response of the entire network.

We have emphasised the importance of the spike threshold, because neurons that are below threshold no longer contribute to the network activity. By keeping the membrane potential below threshold, inhibitory neurons can control dynamically the configuration of the circuit. While past research has focused almost exclusively on the output of the inhibitory neurons, one crucial aspect of future circuit analysis is to determine the source of the inputs to the inhibitory neurons and to then combine this with knowledge of the dynamics of spiking patterns and synaptic plasticity.

References

1. Petilla Interneuron Nomenclature Group, Ascoli, G.A., Alonso-Nanclares, L., Anderson, S.A., Barrionuevo, G., Benavides-Piccione, R., Burkhalter, A., Buzsáki, G., Cauli, B., Defelipe, J., Fairén, A. et al. (2008). Petilla terminology: nomenclature of features of GABAergic interneurons of the cerebral cortex. Nat. Rev. Neurosci. *9*, 557–568.
2. Tyler, C.J., Dunlop, S.A., Lund, R.D., Harman, A.M., and Dann, J.F. (1998). Anatomical comparison of the macaque and marsupial visual cortex: common features that may reflect retention of essential cortical elements. J. Comp. Neurol. *400*, 449–468.
3. Douglas, R.J., and Martin, K.A.C. (2004). Neuronal circuits of the neocortex. Annu. Rev. Neurosci. *27*, 419–451.
4. Galarreta, M., and Hestrin, S. (1999). A network of fast-spiking cells in the neocortex connected by electrical synapses. Nature *402*, 72–75
5. Binzegger, T., Douglas, R.J., and Martin, K.A.C. (2007). Stereotypical bouton clustering of individual neurons in cat primary visual cortex. J. Neurosci. *27*, 12242–12254.
6. Douglas, R.J., and Martin, K.A.C. (1991). Control of neuronal output by inhibition at the axon initial segment. Neural Comput. *2*, 283–292.
7. Pérez-Garci, E., Gassmann, M., Bettler, B., and Larkum, M.E. (2006). The GABAB1b isoform mediates long-lasting inhibition of dendritic Ca^{2+} spikes in layer 5 somatosensory pyramidal neurons. Neuron *50*, 603–616.
8. Dehay, C., Douglas, R., Martin, K., and Nelson, C. (1991). Excitation by geniculocortical synapses is not 'vetoed' at the level of dendritic spines in cat visual cortex. J. Physiol. *440*, 723–734.
9. Wang, X.-J., Tegnier, J., Constantinidis, C., and Goldman-Rakic, P.S. (2004). Division of labor among distinct subtypes of inhibitory neurons in a cortical microcircuit of working memory. Proc. Natl. Acad. Sci. USA *101*, 1368–1373.
10. Wielaard, D.J., Shelley, M., McLaughlin, D., and Shapley, R. (2001). How simple cells are made in a nonlinear network model of the visual cortex. J. Neurosci. *21*, 5203–5211.
11. Monier, C., Chavanne, F., Boudot. P., Graham, L., and Frégnac, Y. (2003). Orientation and direction selectivity of synaptic inputs in visual cortical neurons: a diversity of combinations produces spike tuning. Neuron *37*, 663–680.
12. Douglas, R.J., Mahowald, M., Martin, K.A., and Stratford, K.J. (1996). The role of synapses in cortical computation. J. Neurocytol. *25*, 893–911.
13. van Vreeswijk, C., and Sompolinsky, H. (1996). Chaos in neuronal networks with balanced excitatory and inhibitory activity. Science *274*, 1724–1726.
14. Carandini, M., Heeger, D.J., and Movshon, J.A. (1997). Linearity and normalization in simple cells of the macaque primary visual cortex. J. Neurosci. *17*, 8621–8644.
15. Holt, G.R., and Koch, C. (1977). Shunting inhibition does not have a divisive effect on firing rates. Neural Comput. *9*, 1001–1013.
16. Douglas, R.J., Koch, C., Mahowald, M., Martin, K.A.C., and Suarez, H.H. (1995). Recurrent excitation in neocortical circuits. Science *269*, 981–985.
17. Hahnloser, R., Sarpeshkar, R., Mahowald, M., Douglas, R., and Seung, S. (2000). Digital selection and analogue amplification coexist in a cortex-inspired silicon circuit. Nature *405*, 947–951.
18. Sherrington, C. (1908). On the reciprocal innervation of antagonistic muscles. Thirteenth note. On the antagonism between reflex inhibition and reflex excitation. Proc. R. Soc. Lond. B *80*, 565–578.

Institute of Neuroinformatics, UZH/ETH, Winterthurerstrasse 190, 8057 Zurich, Switzerland.
E-mail: kevan@ini.phys.ethz.ch