16

BURSTING CELLS

Some neurons throughout the animal kingdom respond to an intracellular current injection or to an appropriate sensory stimulus with a stereotypical sequence of two to five fast spikes riding upon a slow depolarizing envelope. The entire event, termed a *burst*, is over within 10–40 msec and is usually terminated by a profound afterhyperpolarization (AHP). Such *bursting cells* are not a random feature of a certain fraction of all cells but can be identified with specific neuronal subpopulations. What are the mechanisms generating this *intrinsic firing pattern* and what is its meaning?

Bursting cells can easily be distinguished from a cell firing at a high maintained frequency by the fact that bursts will persist even at a low firing frequency. As illustrated by the thalamic relay cell of Fig. 9.4, some cells can switch between a mode in which they predominantly respond to stimuli via single, isolated spikes and one in which bursts are common. Because we believe that bursting constitutes a special manner of signaling important information, we devote a single, albeit small chapter to this topic. In the following, we describe a unique class of cells that frequently signal with bursts, and we touch upon the possible biophysical mechanisms that give rise to bursting. We finish this excursion by focussing on a functional study of bursting cells in the electric fish and speculate about the functional relevance of burst firing.

16.1 Intrinsically Bursting Cells

Neocortical cells are frequently classified according to their response to sustained current injections. While these distinctions are not all or none, there is broad agreement for three classes: *regular spiking*, *fast spiking*, and *intrinsically bursting* neurons (Connors, Gutnick, and Prince, 1982; McCormick et al., 1985; Connors and Gutnick, 1990; Agmon and Connors, 1992; Baranyi, Szente, and Woody, 1993; Nuñez, Amzica, and Steriade, 1993; Gutnick and Crill, 1995; Gray and McCormick, 1996). Additional cell classes have been identified (e.g., the *chattering cells* that fire bursts of spikes with interburst intervals ranging from 15 to 50 msec; Gray and McCormick, 1996), but whether or not they occur widely has not yet been settled. The cells of interest to us are the intrinsically bursting cells.

In response to a just-threshold current stimulus, an intrinsically bursting (IB) cell fires a single burst. If the current amplitude increases, some IB cells burst repeatedly

at a constant frequency of between 5 and 12 Hz (as in Fig. 16.1C), while others respond by repetitive single spikes. It is not uncommon for an IB cell to flip back and forth between these two firing modes. Even more complex behavior, such as the initiation of a long train of bursts in response to a brief hyperpolarizing current stimulus, has been reported (Silva, Amitai, and Connors, 1991). The spikes themselves are conventional sodium carried ones. Their amplitude during the burst frequently decreases—presumably because the sustained depolarization partially inactivates I_{Na}—while their duration increases.

Intrinsic bursting cells show a unique laminar distribution and morphology. In studies using intracellular staining, IB cells correspond to large pyramidal neurons restricted—with few exceptions—to layer 5, with stereotyped dendritic morphologies and axonal projection patterns. IB cells have an extended apical bush in layers 1 and 2, while nonbursting cells in layer 5 lack this feature (Fig. 16.1D; Larkman and Mason, 1990; Gray and McCormick, 1996; Yang, Seamans, and Gorelova, 1996).

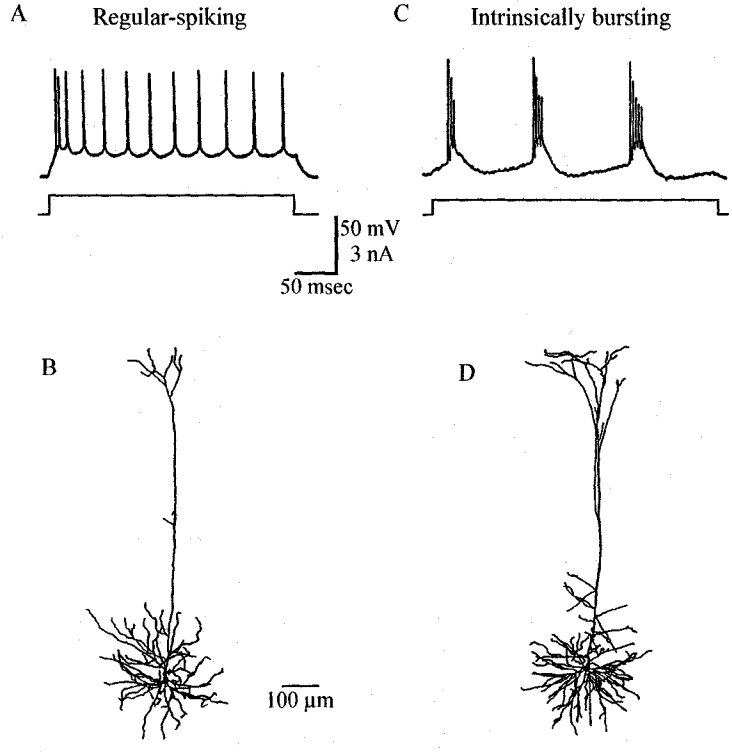

Fig. 16.1 Intrinsically Bursting and Regular Spiking Pyramidal Cells Structure-function relationship among pyramidal cells from rodent cortex. Typical firing patterns seen in response to an intracellularly injected current step in **(A)** *regular spiking*, and **(C)** *intrinsically bursting* layer 5 pyramidal cells from mouse cortex (Agmon and Connors, 1992). Drawings of biocytin-filled layer 5 **(B)** regular spiking and **(D)** intrinsically bursting (IB) pyramidal cells from the rat. IB cells tend to have an extensive apical dendrite (reaching all the way up to layer 1) while regular spiking cells show a smaller degree of dendritic arborization. The output targets of the two cell types are quite distinct, with bursting cells projecting outside the cortex proper. Unpublished data from L. J. Cauller, I. Bülthoff, and B. W. Connors, printed with permission.

Neurons whose cell bodies are located in layer 5 constitute the primary output of the neocortex. Whenever the cortex decides to do something, the message has to be sent outside the cortical system via layer 5 cells. This includes the one-million-axon (in humans) pyramidal tract that leaves the motor cortex and adjacent areas and projects into the spinal cord (Porter and Lemon, 1993).

Some evidence suggests that the cells projecting outside the cortex are of the bursting type. IB cells project to the pons and to the superior colliculus, while nonbursting layer 5 pyramidal cells project to the contralateral cortex via the corpus callosum (Wang and McCormick, 1993; Kasper et al., 1994). It is known that many of the identified layer 5 cells in the rat motor cortex that project to the spinal cord have the firing characteristics of IB cells (Tseng and Prince, 1993). It is obviously important to know whether all cells projecting to subcortical (and nonthalamic) targets are of the bursting type.

16.2 Mechanisms for Bursting

Bursting cells have been analyzed using biophysically based conductance models as pioneered by Traub and his colleagues (Traub and Llinás, 1979; Traub, 1979, 1982; Traub et al., 1991; summarized in the monograph by Traub and Miles, 1991) and from the perspective of dynamical systems theory (Chap. 7; Rinzel, 1987; Wang and Rinzel, 1996; Rinzel and Ermentrout, 1997).

There is likely to be a plurality of mechanisms that cause bursts. In Sec. 9.1.4 we discussed the critical role of a somatic low-threshold calcium current responsible for mediating bursts in thalamic cells (Fig. 9.4).

Central to the genesis of bursting in cortical cells are fast, sodium-driven action potentials at the cell body, which not only propagate forward along the axon, but also invade the dendritic tree (Rhodes and Gray, 1994). Backpropagation is aided by a low density of dendritic sodium channels that boost the signal. (For a more detailed discussion of this, see Secs. 19.1 and 19.2.) Dendritic calcium conductances build up local depolarization. In the meantime, somatic repolarization establishes a pronounced potential difference between the cell body and the dendritic tree, giving rise to ohmic currents. These will depolarize the soma and the spike initiating zone in the form of an *afterdepolarizing potential* (ADP). It is this ADP that causes the rapid sequence of fast sodium spikes. The entire chain of events is finished off by a hyperpolarization induced by a combination of voltage- and calcium-dependent potassium currents.

In this view of bursting, dendritic calcium currents are at the root of the prolonged depolarization that triggers the fast, somatic sodium spikes. However, it appears that in some systems one or more sodium currents, in combination with the "right" dendritic tree morphology, can by themselves initiate bursting (Turner et al., 1994; Franceschetti et al., 1995; Azouz, Jensen, and Yaari, 1996).

Mainen and Sejnowski (1996) derive what this right morphology should be. They simulate the dynamics of spiking in a number of reconstructed cortical cells with different dendritic anatomies and endowed with the same distribution and density of voltage-dependent sodium, potassium, and calcium currents (Fig. 16.2). Changing only the dendritic tree geometry, but not the mix of voltage-dependent conductances, gives rise to the entire spectrum of intrinsic responses observed in the cortex: from nonadapting and adapting cells to bursting ones. The large dendritic tree associated with layer 5 pyramidal cells prolongs the sodium spike propagating back into the dendritic arbor sufficiently for bursts to occur,

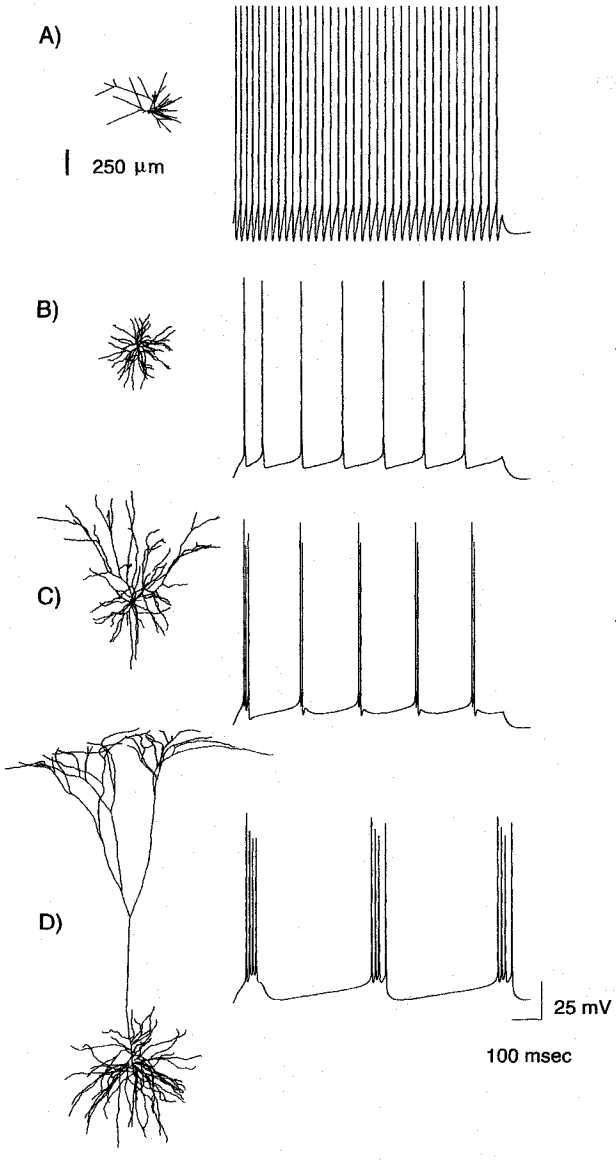

Fig. 16.2 CELLULAR MORPHOLOGY AND INTRINSIC FIRING PATTERNS Different reconstructed neurons are endowed with the same densities of voltage-dependent conductances in soma and dendritic tree in a computer model: a fast sodium current, three potassium currents, and a high-threshold calcium current (Mainen and Sejnowski, 1996). The distinct firing patterns, evoked in response to sustained current injection (of 50, 70, 100, and 200 pA for **A** to **D**, respectively), run the gamut of adapting, nonadapting, and bursting behavior seen in the cortex. The four cells are **(A)** layer 3 aspiny stellate cell from rat cortex, **(B)** layer 4 spiny stellate, **(C)** layer 3 pyramid, and **(D)** layer 5 pyramid from cat visual cortex. Reprinted by permission from Mainen and Sejnowski (1996).

while no such behavior is observed in the much more compact population of stellate or pyramidal cells in superficial layers.

These results go hand in hand with the observed correlation between cellular morphology and intrinsic firing pattern reported above and emphasizes the often subtle and complex interplay between membrane-bound conductances and cable structure.

16.3 What Is the Significance of Bursting?

Anytime two spatially overlapping but morphologically distinct cell classes project to different locations (as the layer 5 bursting and nonbursting cells), one should assume that they encode and transmit different features (since otherwise the job could be done with the

help of a single cell class whose axons branch to innervate both areas). Viewed in this light, the existence of a cell type that responds to sustained current steps in a bursty manner and projects outside the cortical system demands an explanation in functional terms.

One broad hypothesis, first entertained by Crick (1984a), is that bursting constitutes a specialized signal, a particular code symbol, distinct from isolated spikes, conveying a particular type of information.

The relevance of bursts for conveying information reliably has been ascertained for the electrosensory system of the electric fish (Gabbiani et al., 1996). Although of a quite distinct evolutionary lineage than the cerebral cortex, it is profitable to review this study briefly. Given the conservative nature of biology, reinventing and reusing the same mechanism over and over again, it would not be surprising if its lesson also applied to the cortex (Heiligenberg, 1991).

Gabbiani et al., (1996) subject the fish *Eigenmannia* to random amplitude modulations of an electric field in the water whose carrier frequency is equal to the fish's own electrical organ discharge frequency that has been pharmacologically disabled (Fig. 16.3A), while recording from pyramidal cells in the electrosensory lateral line lobe (ELL). Signal detection theory can be used to determine which particular features of the electric field are represented by the firing of these cells. Assuming that the ELL pyramidal cells implement a linear summation and threshold operation, it can be inferred that the cells respond best to up or down strokes of the electric field.

Slightly more than half of the spikes generated by the pyramidal cells occur in short bursts (on average three spikes with a mean spike separation of 9 msec; Fig. 16.3A). The signal-to-noise ratio of this signal detection operation—based only on those spikes that make up a burst—is substantially higher than the signal-to-noise ratio of the signal based on isolated spikes (Fig. 16.3B). In other words, spikes taken from a burst signal the presence of a particular stimulus feature, here an "abrupt" change in the electric field, more reliably than isolated spikes. Intracellular evidence implicates the apical dendritic tree of the ELL pyramidal cells as the locus where the burst computation is carried out (Turner et al., 1994).

It is possible that bursty neurons communicate their messages to their target cells with the aid of two output channels multiplexed onto a single axon, one employing isolated spikes and the other bursts. Depending on the type and amount of short-term synaptic plasticity present at the output synapses of bursting cells, they could transmit one or the other channel (Sec. 13.5.4; Abbott et al., 1997; Lisman, 1997).

This would work in the following fashion. Initially the output synapses of bursting cells have a very low probability of synaptic release p_0. A single spike is unlikely to cause a release of a vesicle but will, very briefly, enhance the probability of release for the next spike. Such transient but powerful facilitation would lead to isolated spikes being effectively disregarded while bursts would cause a synaptic release with probability close to 1. The price the nervous system would pay for the usage of bursts is their limited temporal resolution as compared to individual spikes (in the Gabbiani et al., 1996, study, the interval between the first and the last spike is 18 ± 9 msec).

Conversely, a synapse with high initial probability of release and a powerful but short acting short-term depression will disregard the additional spikes contained within a burst. This hypothesis predicts that synapses made by the axon of a bursting cell have low p_0 and show a very short lasting but powerful facilitation not present at the synapses of nonbursting cells.

Koch and Crick (1994) speculate that bursting could be one of the biophysical correlates of short-term memory (via elevated, presynaptic calcium concentration during such a burst). The stimulus feature represented by a population of bursting cells would correspond to the feature "stored" in short-term memory. Because of the close association between short-

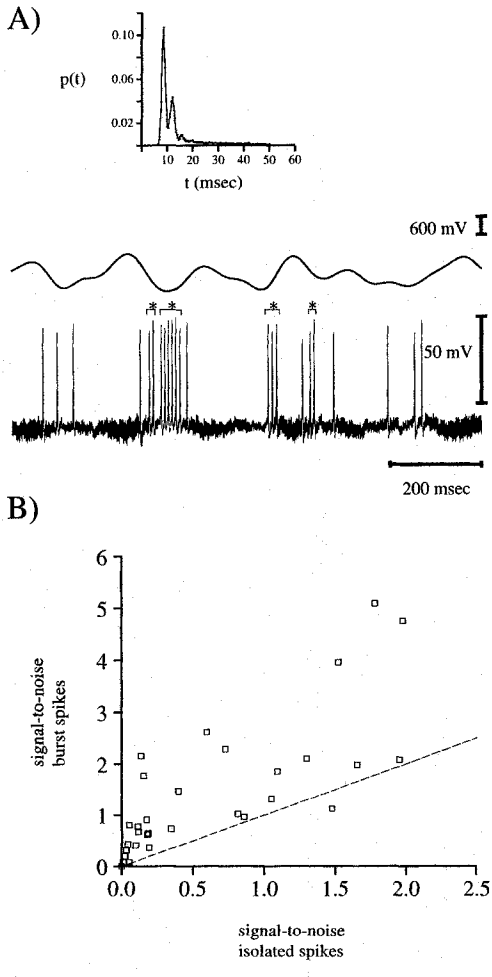

Fig. 16.3 Reliable Encoding of Sensory Information in Bursts **(A)** In experiments carried out in the electric fish *Eigenmannia*, Gabbiani and colleagues (1996) stimulate its electrosensory system using zero-mean random amplitude modulations (thick smooth line) superimposed onto a fixed carrier frequency of an electric field while recording from pyramidal cells in the electrosensory lateral line lobe (ELL). A large fraction of all spikes belongs to bursts (*) that show up as a prominent peak in the interspike intervals (here bursts are defined as spikes separated by <14 msec; see the inset). **(B)** On the basis of signal detection theory individual pyramidal cells can be shown to detect either up or down strokes of the electric field amplitude with up to 85% accuracy. The signal-to-noise ratio of this pattern discrimination operation, which assumes that ELL pyramidal cells perform a linear threshold computation, is enhanced (by more than a factor of 2) when considering only spikes from bursts compared to isolated spikes. In other words, burst spikes encode information in a more reliable manner than isolated action potentials. Reprinted by permission from Gabbiani et al., (1996).

term memory and awareness, it is possible that bursting cells are preferentially involved in mediating the neuronal correlate of awareness, in particular considering their strategic location in the cortical layer projecting to the tectum, pulvinar, and other extracortical targets (Crick and Koch, 1995).

Quite a different explanation for the utility of a particular subclass of spike patterns has been advanced in Traub et al., (1996). In some cells, *spike doublets*, consisting of two fast spikes separated by a stereotyped 4–5 msec interspike interval, are frequently observed. Spike doublets are characteristic of GABAergic, axo-axonic cortical interneurons (Buhl et al., 1994). Computer modeling of the underlying cortical networks show that such doublets mediate the frequently observed temporal synchronization of distant neuronal populations. Their oscillatory activities are synchronized with a near-zero phase lag, even though they are separated by propagation delays of 5 msec or more.

16.4 Recapitulation

Bursts, that is, two to five closely spaced, sodium-dependent fast action potentials riding on top of a much slower depolarization, are a dominant feature of a number of cell classes,

not only in the cortex but also among thalamic relay neurons and elsewhere. In the cortex, intrinsically bursting cells have a unique morphology and are confined to layer 5, where they constitute the dominant output cell class.

The biophysical mechanisms underlying bursting are diverse. A low-threshold calcium current at the soma is the principal agent for bursting in thalamic cells (Sec. 9.1.4). Bursts in pyramidal cells can originate when sodium spikes propagate back into the dendritic tree, causing parts of the arbor to be depolarized. Under the right circumstances, for instance, when amplified by dendritic sodium and/or calcium currents, this signals returns to the soma in the form of an afterdepolarization that triggers several fast sodium spikes.

It has been argued that bursting represents a special code, quite distinct from the firing of an isolated action potential. This hypothesis has some experimental support from the electrosensory system of the electric fish. Spikes taken from bursts signal the presence of particular features in the input in a much more reliable manner than isolated spikes.

This implies that spiking cells are not restricted to using an asynchronous binary code but might employ a two-channel multiplexing strategy, with the decoding being carried out by rapidly adapting synapses.

A non-exclusive alternative is that bursts serve to synchronize distant neuronal populations.