Bursts as a unit of neural information: selective communication via resonance☆

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What is the functional significance of generating a burst of spikes, as opposed to a single spike? A dominant point of view is that bursts are needed to increase the reliability of communication between neurons. Here, we discuss the alternative, but complementary, hypothesis: bursts with specific resonant interspike frequencies are more likely to cause a postsynaptic cell to fire than are bursts with higher or lower frequencies. Such a frequency preference might occur at the level of individual synapses because of the interplay between short-term synaptic depression and facilitation, or at the postsynaptic cell level because of subthreshold membrane potential oscillations and resonance. As a result, the same burst could resonate for some synapses or cells and not resonate for others, depending on their natural resonance frequencies. This observation suggests that, in addition to increasing reliability of synaptic transmission, bursts of action potentials might provide effective mechanisms for selective communication between neurons.

Many neurons fire bursts, which are intrinsically generated stereotypical patterns of closely spaced action potentials. What is the functional importance of generating such bursts instead of single spikes? One prevailing answer to this question, which is influenced by half a century of treating neurons as spatio–temporal integrators, is that bursts increase reliability of communication between neurons. Indeed, sending a short burst of spikes instead of a single spike increases the chances that at least one of the spikes (or exactly one [1]) avoids synaptic transmission failure. The timing of spikes within the burst does not play any role here. Moreover, it is often assumed that the shorter the interspike interval within the burst, the better: if two spikes within a burst trigger synaptic transmission, the combined postsynaptic potential (PSP) is larger when the interval between the spikes is smaller.

In this paper, which is complementary to that of Lisman [1], we argue that this classical view is only half of the story. High-frequency stimulation might not be optimal to fire a postsynaptic cell. Indeed, the postsynaptic response could depend on the frequency content of the burst because there is a frequency preference at the synaptic level (caused by the competing effects of short-term depression and facilitation) and at the neuronal level (caused by subthreshold membrane potential oscillations).

In both cases (Fig. 1), the transmission of signals from pre- to postsynaptic cell is most effective when the presynaptic cell fires a burst of action potentials with a specific resonant

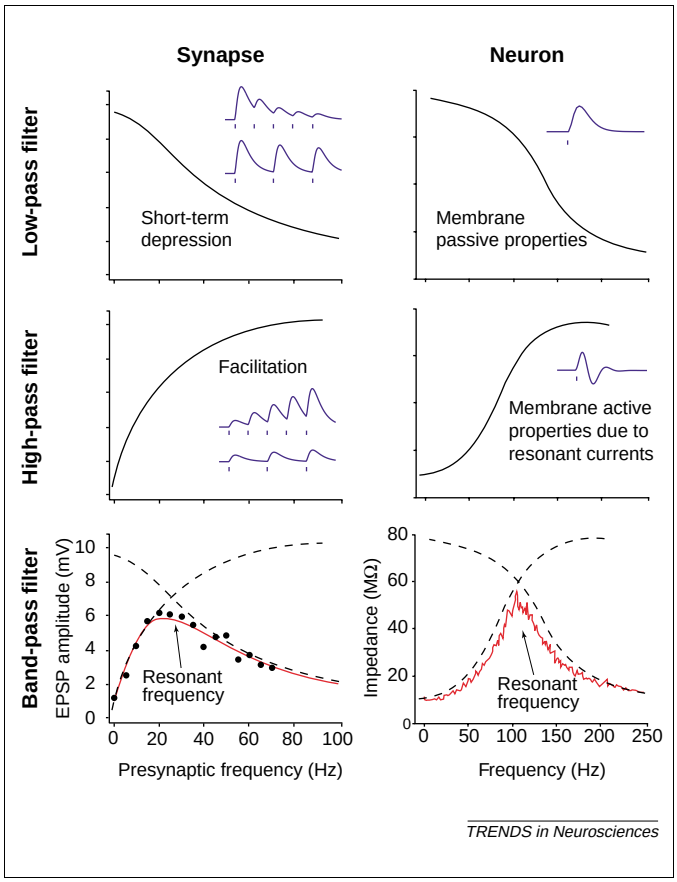

Fig. 1. Low- (top), high- (middle) and band- (bottom) pass filtering can occur at the level of an individual synapse (left; neocortical pyramidal neuron; modified from Ref. [2]), because of the interplay between short-term plasticity; or at the level of an individual neuron (right; brainstem mesencephalic V neuron; modified from Ref. [17]), because of the membrane potential oscillations and resonance. Blue traces show time course of typical postsynaptic potentials.

☆ This review is dedicated to Michael Ya. Izhikevich (1946–2002).

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 0166-2236/03/$ - see front matter doi:10.1016/S0166-2236(03)00034-1

Box 1. Kinetics of short-term synaptic plasticity

Short-term synaptic plasticity is a complex phenomenon that consists of several different mechanisms [33]. However, there is a simple phenomenological model [34] that describes thekinetics of such plasticity; it treats short-term depression and facilitation as two independent variables, R and u, respectively:

$R' = (1 - R)/D - Ru\delta(t - t_n)$ ('depression' variable)

$u' = (U - u)/F + U(1 - u)\delta(t - t_n)$ ('facilitation' variable)

(where $(1 - R)/D$ is the exponential recovery to $R = 1$ with rate D^{-1}; $Ru\delta(t - t_n)$ is the pulsed decrease due to the nth spike; $(U - u)/F$ is the exponential recovery to $u = U$ with rate F^{-1}; and $U(1 - u)\delta(t - t_n)$ is the pulsed increase due to the nth spike).

The cumulative synaptic efficacy at any moment (i.e. the amount of neurotransmitter available for release) is the product Ru. Each presynaptic spike releases all available neurotransmitter and increases the synaptic conductance by Ru (green vertical lines in Fig. Ia). It also adjusts the depression variable R by the same quantity, and the facilitation variable u by the quantity $U(1 - u)$ (Fig. I). The main advantage of this model is that it has only three parameters: synaptic efficacy U, and the time constants D and F for recovery from depression and facilitation, respectively. These parameters have been measured experimentally to fit various types of neocortical synapses [34,35].

Let us fix $u = U = 0.1$ (this value corresponds to some GABAergic synapses [35]) and consider the dynamics of a depressing synapse in response to a burst of five spikes. Such a synapse behaves as a low-pass filter, as $R \approx 1$ for low-frequency stimulation and $R \to 0$ for high-frequency stimulation (red curve in Fig. Ib). By contrast, a purely facilitating synapse (if variable $R = 1$ is fixed) behaves as a high-pass filter, as $u \approx U = 0.1$ for low-frequency stimulation and $u \approx 1$ for high-frequency stimulation (blue curve in Fig. Ib). The cumulative synaptic conductance (the area beneath the synaptic conductance curve) is proportional to the product of the curves and it behaves as a band-pass filter: it is small when the intraburst frequency is either high ($R \approx 0$, too much depression) or low ($u \approx U = 0.1$, not enough facilitation). There is a specific resonant frequency range ($\sim (UDF)^{-0.5}$ [34]) at which the product is maximal (Fig. I).

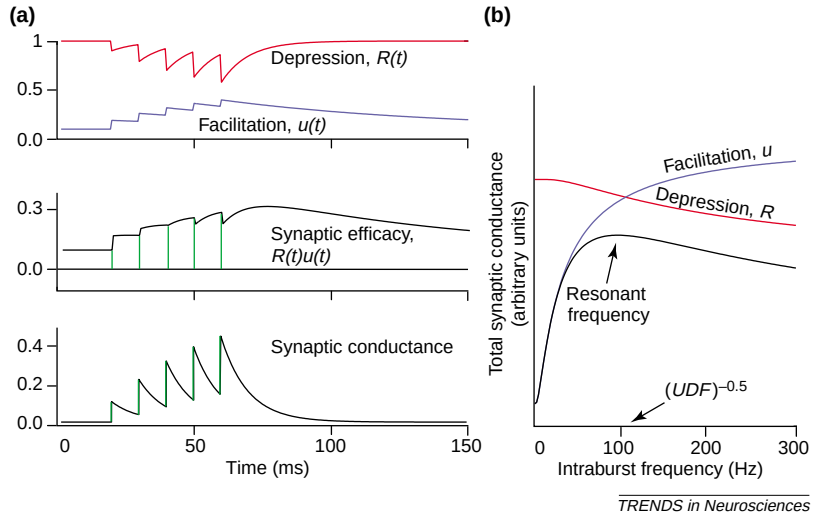

Fig. I. Kinetics of short-term synaptic plasticity. (a) Dynamics of variables in response to a burst of five spikes. Parameters: $U = 0.1$, $F = 80$ ms and $D = 10$ ms; synaptic conductance with time constant of 10 ms. (b) Integral (total area) of synaptic conductance for bursts of five spikes with various intra-burst frequencies.

interspike frequency. As different postsynaptic cells can have different resonant frequencies, the same burst can be resonant for one cell and not resonant for another, thereby eliciting responses selectively in one cell but not the other. By using bursts with different interspike frequencies, the presynaptic cell can selectively affect some postsynaptic targets, but not others. Such selective communication can be achieved on the time scale of tens of milliseconds without involving long-term synaptic modifications.

Resonance at the synaptic level

It has been established experimentally [2–5] and theoretically [2,6–8] that short-term synaptic plasticity contributes to temporal filtering of synaptic transmission (Box 1). Indeed, depression acts as a low-pass filter (Fig. 1, top), in that it filters out (attenuates) high-frequency presynaptic firing. By contrast, facilitation acts as a high-pass filter, in that it enhances the efficacy of high-frequency presynaptic firing. As a result, a synapse capable of exhibiting both short-term depression and facilitation acts as a band-pass filter: low-frequency presynaptic firing does not elicit enough facilitation and hence results in small PSPs. Similarly, high-frequency presynaptic firing depresses the synapse and also results in small PSPs. There is a specific resonant frequency of presynaptic firing that elicits just the right amount of facilitation but not too much depression, so that PSPs have maximal amplitudes, as in Fig. 1 (bottom). The resonant frequency can be as high as 100 Hz (A. Thompson, unpublished).

Given that the resonant frequency can be different for different synapses belonging to the same presynaptic cell [2,3], such a synaptic frequency filtering provides a potent tool for selective communication between neurons, illustrated using recordings from rat somatosensory cortex (Fig. 2) [2]. The synaptic connections from A to B and to C have different resonant frequencies so that the same burst

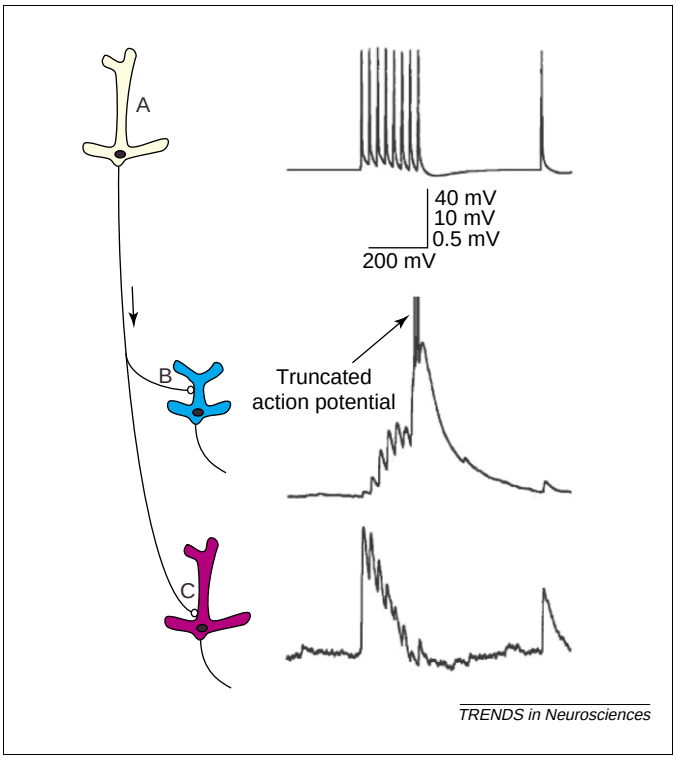

Fig. 2. Selective communication via bursts. A pyramidal neuron in layer 5 somatosensory cortex (A) projects to a bipolar interneuron (B) and another pyramidal neuron (C). A burst of spikes produces different effects in neurons B and C because the synapses have different properties of short-term plasticity. The synapse between A and B is facilitating, whereas that between A and C is depressing. Modified from Ref. [2].

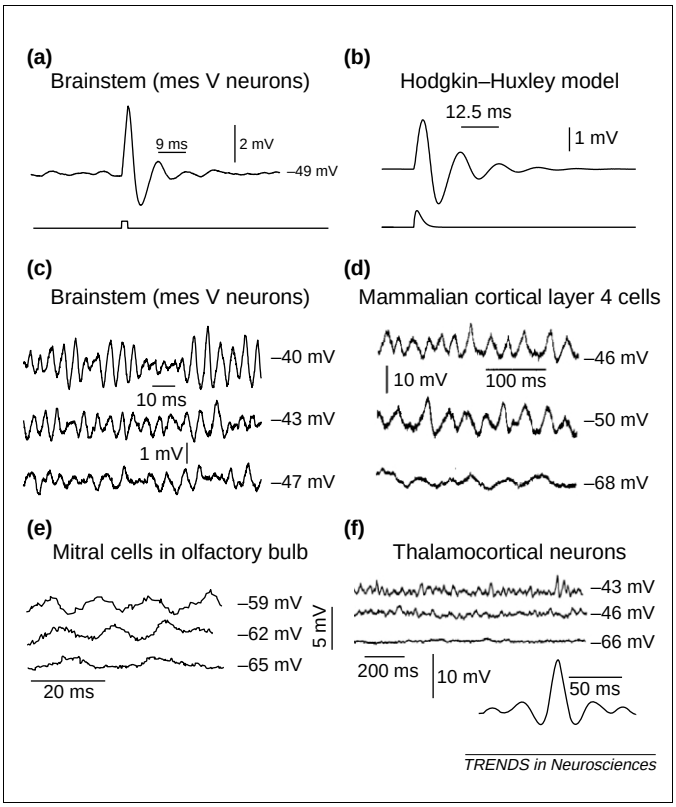

Fig. 3. Examples of damped (a,b) or sustained (c–f) subthreshold oscillations of the membrane potential in neurons, and their voltage dependence. Average of ten voltage traces (a) and individual voltage traces (c) from rat mesencephalic V (mesV) neurons of the brainstem (E.M. Izhikevich *et al.*, unpublished). (b) Hodgkin–Huxley model [28]: simulations with original values of parameters and $I = 5$. Subthreshold oscillations of the membrane potential in mammalian neocortical layer 4 cells (d), olfactory bulb mitral cells (e) and thalamocortical neurons (f) are modified from Refs [9], [26] and [13], respectively.

is resonant for synapse B but non-resonant for C (notice the voltage scales). A different pattern of presynaptic firing, such as a burst with different interspike frequency, can become resonant for C or non-resonant for both of the synapses in Fig. 2, but resonant for some other synapse. Thus, by changing the intraburst frequency, a presynaptic cell can selectively affect some postsynaptic cells but not others.

Resonance at the cellular level

Some neurons exhibit subthreshold membrane potential oscillations [9–18] when stimulated by brief synaptic input or an injected pulse of current (Fig. 3). These damped or sustained oscillations, whose frequency could be as high as 200 Hz (E.M. Izhikevich *et al.*, unpublished), are often caused by intrinsic ionic mechanisms, such as the alternating activation of persistent low-threshold Na^+ and K^+ currents, and not because of periodic synaptic input. The response of such a neuron with oscillatory potentials is sensitive to the precise timing of input pulses, as we show in Fig. 4 using triplets with various intra-burst periods. Indeed, the first pulse in a triplet (or a short burst) elicits a damped oscillation in the membrane potential, which results in an oscillation of distance to the threshold, and hence an oscillation of the firing probability. All of these oscillations have the same period – the natural period – that is, around 9 ms for the mesencephalic V neuron illustrated in Fig. 4. The effect of the second spike depends on its timing relative to the first spike: if the interval between the spikes is near the natural period (e.g. 10 ms in Fig. 4, middle), the second spike arrives during the rising phase of oscillation, and it increases the amplitude of oscillation even further. In this case, the effects of the spikes add up. The third spike increases the amplitude of oscillation even further, thereby increasing the probability of an action potential.

If the interval between pulses is near half the natural period (e.g. 5 ms in Fig. 4 (left), the second pulse arrives during the falling phase of oscillation, and it leads to a decrease in oscillation amplitude. The spikes effectively cancel each other out in this case. Similarly, the spikes cancel each other out when the inter-pulse period is 15 ms (Fig. 4, right), which is 60% greater than the natural period. The same phenomenon occurs for inhibitory synapses (Fig. 5). Here, the second spike increases (decreases) the amplitude of oscillation if it arrives during the falling (rising) phase.

This mechanism of frequency preference is related to the well-known phenomenon of subthreshold membrane resonance (Box 2). The response of a neuron having subthreshold oscillatory potentials depends on the frequency content of the input doublet, triplet or a short burst of spikes. Llinás [19] refers to such a neuron as being a resonator.

We say that the input burst to such a cell is resonant if the intra-burst interval is near the natural period of the

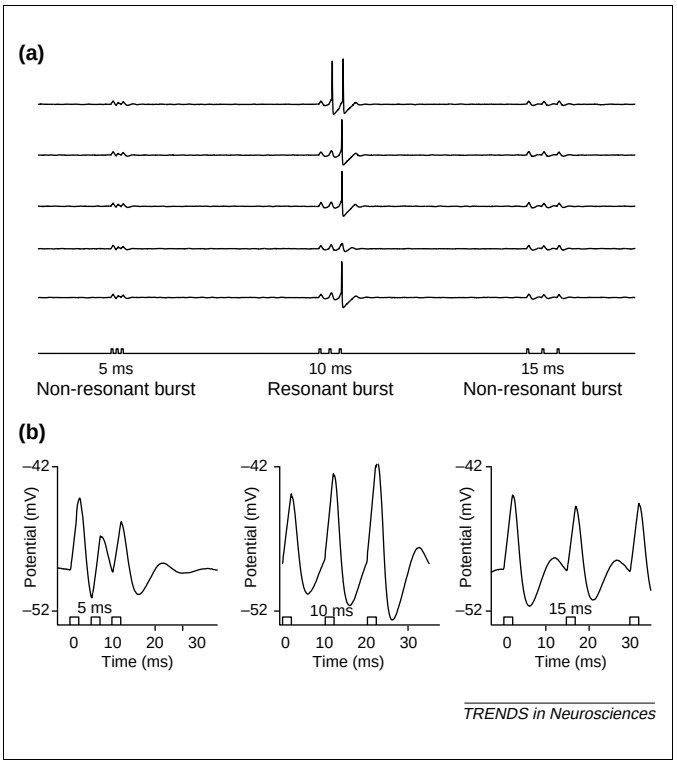

Fig. 4. Selective response to resonant bursts. (a) Six experimental observations of selective responses to a resonant (10 ms interspike period) bursts in brainstem mesencephalic V neurons that have subthreshold membrane oscillations with natural period of ~9 ms (the same neuron as in Fig. 3a,c). (b) Magnified and averaged membrane voltage response to the injected pulses of current.

cell, but non-resonant otherwise. A key observation is that the same burst can be resonant for one neuron and non-resonant for another, depending on their natural periods. For example, in Fig. 6, neurons B and C have different periods of subthreshold oscillations: 12 and 18 ms, respectively. By sending a burst of spikes with interspike interval of 12 ms, neuron A can elicit a response in neuron

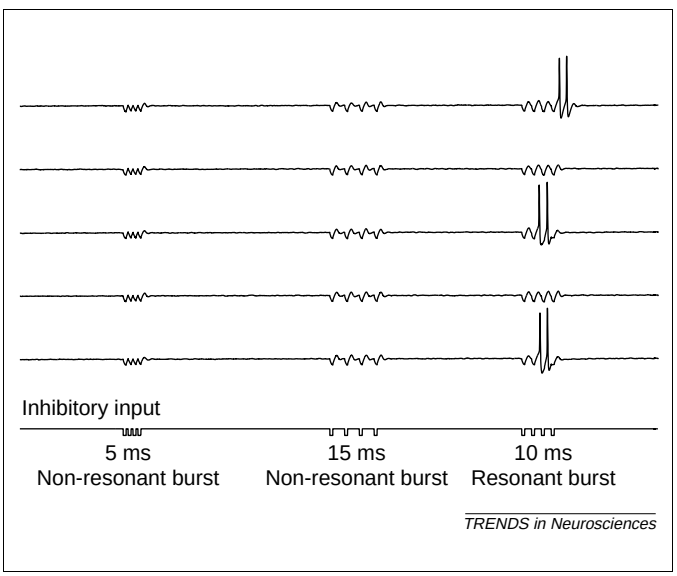

Fig. 5. Experimental observations of selective responses to inhibitory resonant bursts in brainstem mesencephalic V neurons that have oscillatory potentials with the natural period of ~9 ms (the same neuron as in Fig. 3a,c).

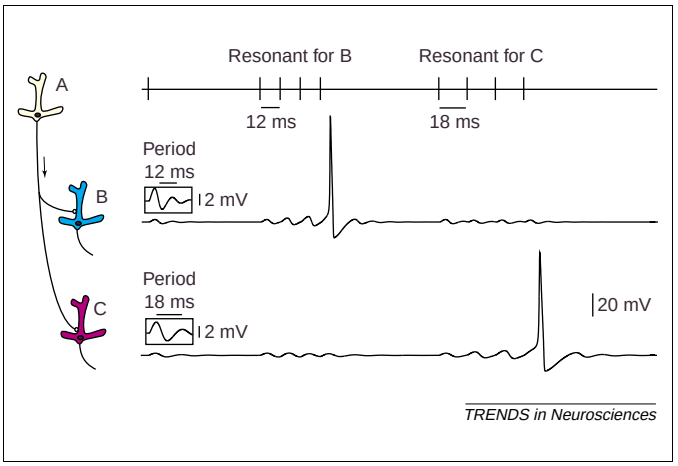

Fig. 6. Selective communication via bursts: neuron A sends bursts of spikes to neurons B and C, which have different natural periods (12 ms and 18 ms, respectively. Both are simulations of the Hodgkin–Huxley model). As a result of changing the interspike frequency, neuron A can selectively affect either B or C without changing the efficacy of synapses. Modified, with permission, from Ref. [21].

B, but not in C. Similarly, the burst with interspike interval of 18 ms elicits a response in neuron C, but not in B. Thus, neuron A can selectively affect either neuron B or C by merely changing the intra-burst frequency without changing the efficacy of synaptic connections.

Figure 6 illustrates the essence of the mechanism of selective communication via bursts when postsynaptic neurons are quiescent. However, theoretical [20,21] and experimental (E.M. Izhikevich *et al.*, unpublished) studies have shown that the result persists even when neurons B and C are part of a large network, and they receive hundreds of other inputs at the same time.

The frequency of subthreshold oscillations is often voltage dependent, as one can clearly see in Fig. 3. It depends on the background synaptic input and action of neuromodulators. In addition, the instantaneous frequency can also depend on the amplitude of oscillation, illustrated in Fig. 7 using the Hodgkin–Huxley model. The greater the amplitude, the greater the interval between two successful maxima of oscillation. This phenomenon is ubiquitous in conductance-based neuronal models. Interestingly, the optimal input to such a neuron is a burst of spikes with adapting frequency, i.e. when the instantaneous interspike period increases with each spike to

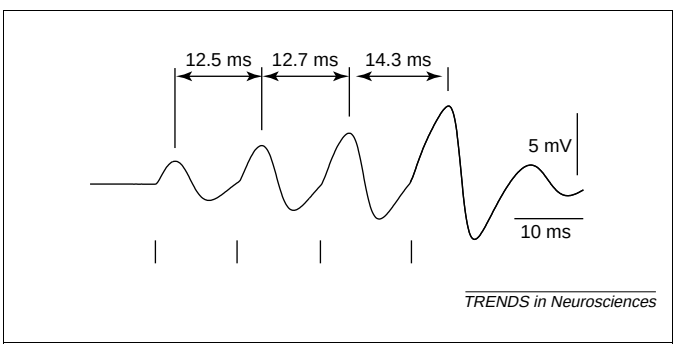

Fig. 7. Instantaneous period of subthreshold oscillation in the Hodgkin–Huxley model depends on the amplitude of oscillation. The most optimal input in this case is a burst with spike frequency adaptation.

Box 2. Subthreshold oscillations and resonance

Many electrical, mechanical and biological systems exhibit free vibrations or damped oscillations when stimulated by a brief strong pulse. The frequency of such oscillations is known as the natural frequency or 'eigenfrequency' of the system, and the period is known as the natural period. For example, the Hodgkin–Huxley model [36] exhibits oscillatory potentials with natural period 12.5 ms when a single brief pulse of current is injected (Fig. I). If the injected current is sinusoidal, sweeping through many frequencies (a so-called ZAP current), then the elicited oscillations of membrane potential have largest amplitudes (possibly resulting in action potentials) when the frequency of the input is near the natural frequency of the system, which is 80 Hz (1/0.0125 s) in the Hodgkin–Huxley model. (This frequency might be slightly different when an oscillating synaptic conductance rather than a current is injected.)

When such an amplified response of the system is subjected to a periodic stimulation with frequency at or near its natural frequency, the response is known as resonance. Resonances can be destructive for mechanical or electrical systems. Many neurons exhibit oscillatory potentials and, hence, resonance. In an excellent review [37], Hutcheon and Yarom use a band-pass filter formalism similar to the one in Fig. 1 of the main text to describe resonances in neurons. We present an alternative geometrical illustration for why subthreshold oscillations lead to resonance and frequency preference. In the top part of Fig. Ib, we stimulate the Hodgkin–Huxley model with doublets that have various inter-pulse periods. The response is augmented when the inter-pulse period is near the natural period of oscillation (i.e. resonant doublet), and the response is attenuated when there is a mismatch (non-resonant doublets). The same idea is illustrated in the bottom of Fig. Ib using phase-plane analysis of the 'resonate-and-fire' model [38]. Its dynamics can be depicted as trajectories on the (I,V) phase plane. Similar to the well-known 'integrate-and-fire' model, the resonate-and-fire model is said to fire an action potential when the trajectory crosses the threshold (blue). An incoming pulse displaces the trajectory from the stable equilibrium (central black circle), and the model exhibits spiral damped oscillations towards the stable resting state (black trajectory) with the natural period of 12.5 ms. The effect of the second pulse (red trajectory) depends on the timing of its arrival. If the inter-pulse interval is 6 ms, the trajectory is still in the left semi-plane and the second pulse pushes it closer to the equilibrium, thereby cancelling the effect of the first pulse. If the inter-pulse interval is 12 ms, the trajectory has already made one full rotation, it is in the right semi-plane, and it is pushed away from the equilibrium, thereby increasing the amplitude of oscillation with a possibility of crossing the firing threshold. If the inter-pulse interval is 18 ms, the trajectory is again in the left semi-plane, so the effect of the second pulse is small.

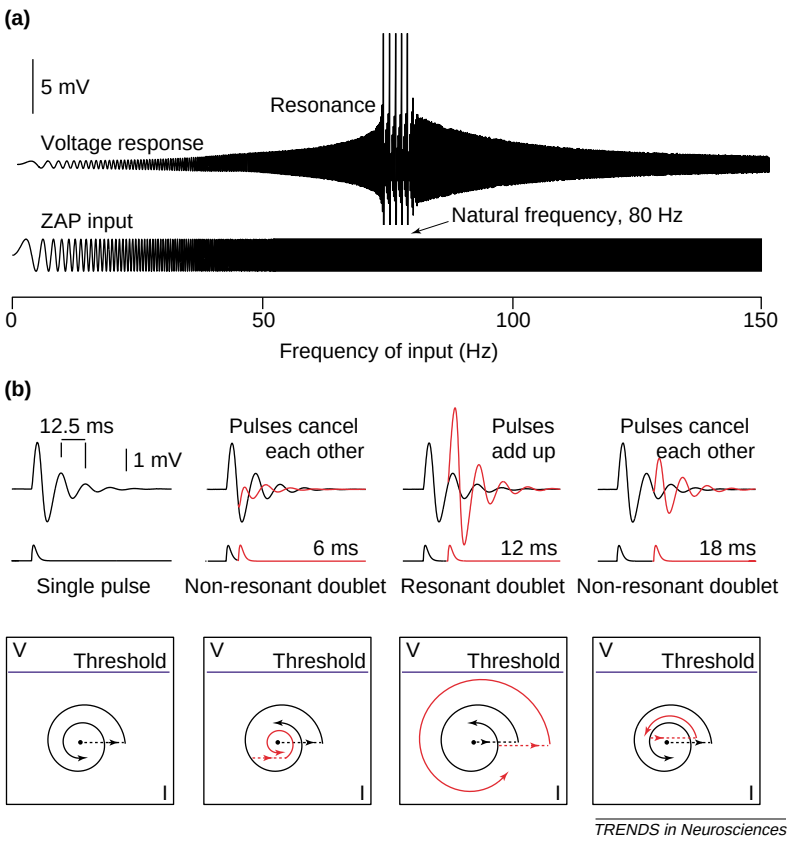

Fig. I. Mechanism of subthreshold potential resonance. (a) Resonant response of the Hodgkin–Huxley model to the sinusoidal input with slowly increasing frequency (ZAP input). (b) Phase portrait of resonate-and-fire model.

follow the increase of oscillation period. Simulations of biophysical synaptic models [22] have shown a similar effect: adapting, rather than purely periodic, bursts are optimal for some synapses with short-term depression and facilitation.

Summary

Temporal filtering of rhythmic signals is a nonlinear phenomenon related to resonance, and it occurs at various levels of the nervous system, including the synaptic and cellular levels discussed above. Such filtering determines

how the postsynaptic response depends on the frequency content of the presynaptic burst of spikes.

An interplay between short-term depression and facilitation results in a synaptic transfer function that rejects presynaptic bursts with high (too much depression) or low (not enough facilitation) interspike frequencies. Even though there is no oscillation at the synapse, there is still an optimal resonant interspike frequency that maximizes the synaptic throughput, and it differs for different synapses. This gives the presynaptic neuron a mechanism to affect some postsynaptic neurons selectively (Fig. 2). Such a selective communication can be achieved via firing bursts with a constant number of spikes (e.g. exactly five spikes) (Box 1). Increasing the number of spikes increases the total synaptic conductance and hence causes more cells to fire even when the burst is non-resonant.

Frequency preference and resonance can also occur at the neuronal level because of subthreshold oscillations [23]. Most researchers are interested in how such oscillations can contribute to synchronization [23–26] and to neuronal processing [27]. We propose an alternative hypothesis: that subthreshold oscillations are important for selective communication via resonant bursts. The same burst of action potentials can be resonant for some neurons and non-resonant for others, depending on their natural frequencies. Therefore, by generating such a burst, a presynaptic neuron selects a subset of postsynaptic targets to affect (Fig. 6). Such frequency-modulated (FM) interactions are well understood in the context of weakly coupled periodic oscillators [29,30], quasi-periodic (multi-frequency) oscillators [31] or bursting neurons [32]. The number of spikes within the burst does not play a significant role here because adding more spikes to a non-resonant burst does not increase the voltage response in postsynaptic cells.

Although bursts are usually stereotypical trains of action potentials, the exact interspike frequency can vary. It depends on the state of the presynaptic neuron, which in turn depends on the background synaptic input converging on the presynaptic neuron and on the action of neuromodulators.

The same factors affect the natural frequency of subthreshold oscillations of the postsynaptic neuron (Fig. 3). Thus, neither presynaptic nor postsynaptic neurons 'choose' their frequencies 'at will'. Instead, the frequencies are determined by the intrinsic properties of the neurons and the overall activity of the brain. Therefore, by changing the frequency content of bursts and subthreshold oscillations, the brain determines who talks to whom at any particular moment. In this sense, the brain can reorganize itself dynamically within a few milliseconds, without changing the synaptic hardware.

Acknowledgements

We thank Joseph Gally, Jeffrey Krichmar, Douglas Nitz, Alex Thomson, John Lisman, Rodolfo Llinás, Yosi Yarom and Bruce Hutcheon for reading the first draft of the manuscript and making several useful suggestions. This research was supported by the Neurosciences Research Foundation and a grant from the Alafi Family Foundation, and by the NSF grant DMS-0109001 (F.C.H.).

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