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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 an alternative but complementary hypothesis: Bursts with certain resonant interspike frequencies are more likely to cause a postsynaptic cell to fire than bursts with higher or lower frequencies. Such a frequency preference might occur at the level of individual synapses due to 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 frequencies. This observation suggests that, in addition to increasing reliability of synaptic transmission, bursts of action potentials may provide effective mechanisms for selective communication among neurons.

Many neurons fire bursts, which are intrinsically-generated stereotypical patterns of closely-spaced action potentials (see Box 2). *What is the functional importance of generating such bursts instead of single spikes?* One prevailing answer to this question, 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] "Bursts as a unit of neural information: making unreliable synapses reliable", we argue that this classical view is only half of the story. High-frequency stimulation may not be optimal to fire a postsynaptic cell. Indeed, the postsynaptic response may depend on the frequency content of the burst because there is a **frequency preference at the**

- **synaptic level** due to the competing effects of short-term depression and facilitation, and at the
- **neuronal level** due to subthreshold membrane potential oscillations.

In both cases, depicted in 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 certain resonant interspike frequency. Since different postsynaptic cells can have different resonant frequencies, the same burst can be resonant for one cell and not resonant for another, thereby evoking 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 [2,3,5,8] and theoretically [2,4,6,7] that short-term synaptic plasticity contributes to temporal filtering of synaptic transmission (Box 1). Indeed, depression acts as a low-pass filter (see Fig. 1, top), in that it filters out (attenuates) high-frequency presynaptic firing. In 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 evoke enough facilitation and hence results in small PSPs. Similarly,

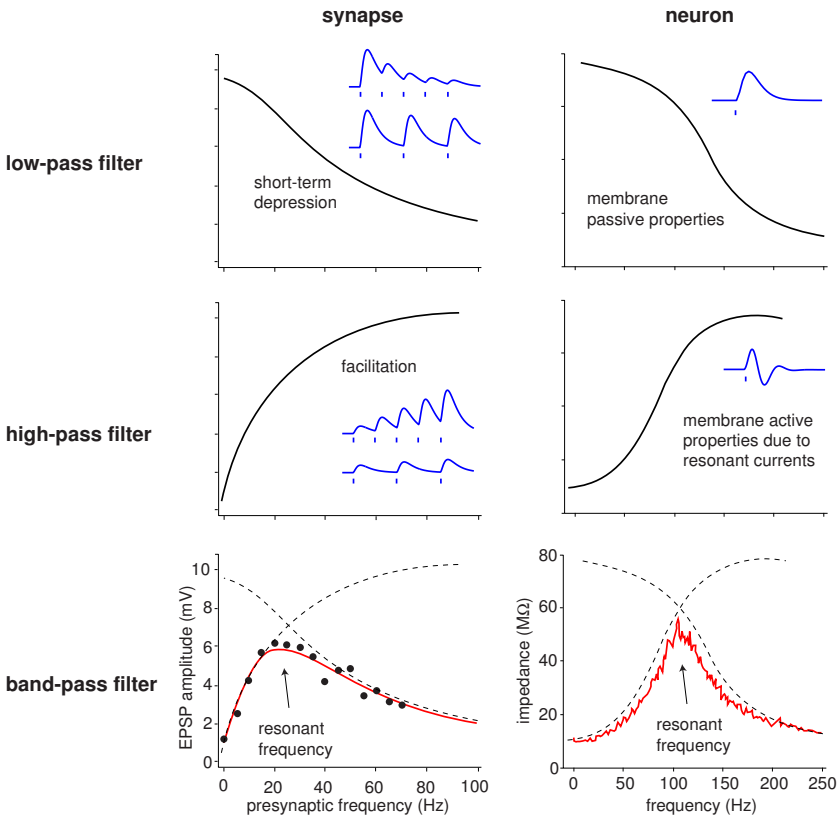


Figure 1: Low-, high-, and band-pass filtering can occur on the level of an individual synapse (neocortical pyramidal neuron, modified from [2]) due to the interplay between short-term plasticity, or on the level of an individual neuron (brainstem mes V neuron, modified from [22]) due to the membrane potential oscillations and resonance.

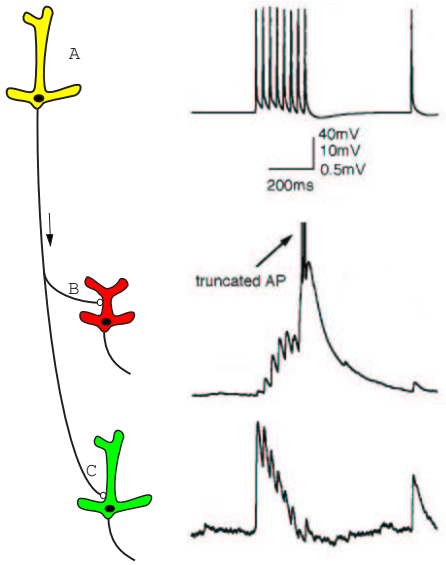


Figure 2: Selective communication via bursts (modified from [2, fig.2]). A pyramidal neuron of layer 5 somatosensory cortex (A) projects to a bipolar interneuron (B) and another pyramidal neuron (C). A burst of spikes produces different effects in neurons B and C because the synapses have different properties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

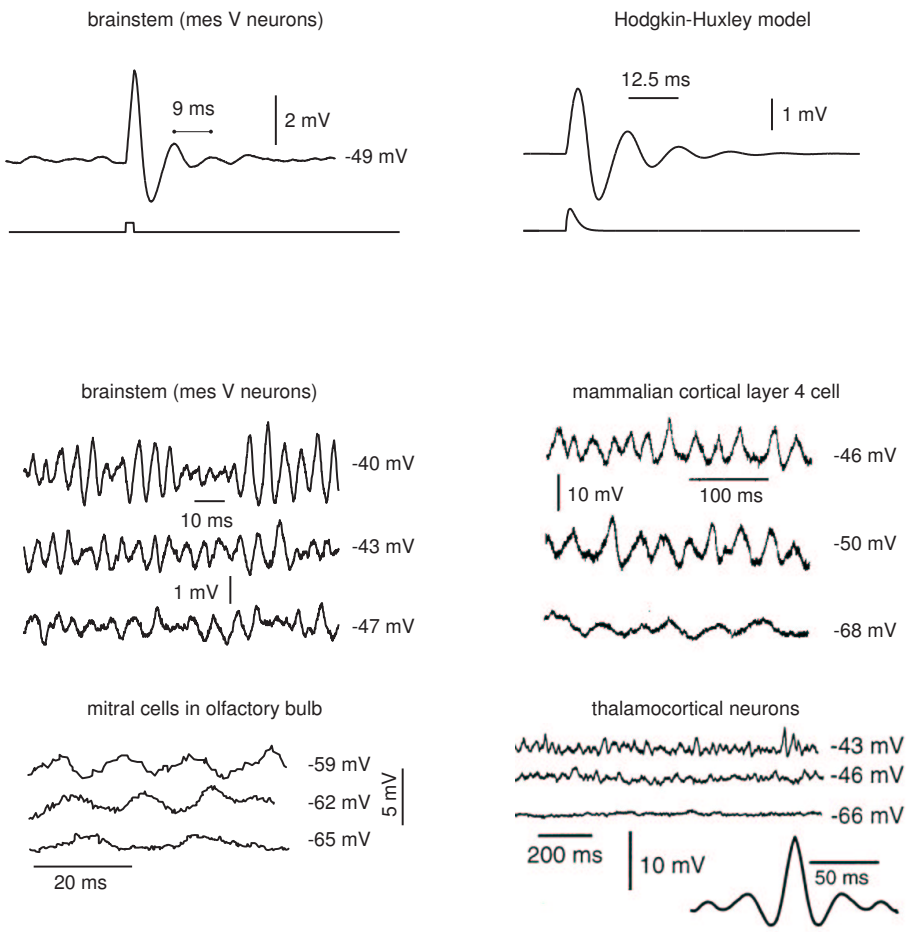


Figure 3: Examples of damped (top) or sustained (bottom) subthreshold oscillations of membrane potential in neurons and their voltage dependence. Brainstem [11]: (top) average of 10 voltage traces of rat mesencephalic V neuron, (bottom) individual voltage traces. Hodgkin-Huxley model [31]: simulations with original values of parameters and $I = 5$. Mitral cells: modified from [27]. Thalamocortical cells: modified from [18]. Mammalian neocortical layer 4 cell: modified from [14].

high-frequency presynaptic firing depresses the synapse and also results in small PSPs. There is a certain *resonant* frequency of presynaptic firing that evokes 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 [9].

Since 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, as we illustrate in Fig. 2 using recordings from rat somatosensory cortex [2]. The synaptic connections from A to B and C admit different resonant frequencies so that the same burst is resonant for synapse B but non-resonant for C (notice the voltage scales). A different pattern of presynaptic firing, e.g., 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 [14–23] when stimulated by brief synaptic input or an injected pulse of current; see Fig. 3. These damped or sustained oscillations, whose frequency could be as high as 200 Hz [11], are often due to intrinsic ionic mechanisms, e.g., the alternating activation of persistent low-threshold sodium and potassium currents (Box 3), and not to periodic synaptic input. The response of such a neuron with oscillatory potentials is sensitive to the precise timing of input pulses, as we

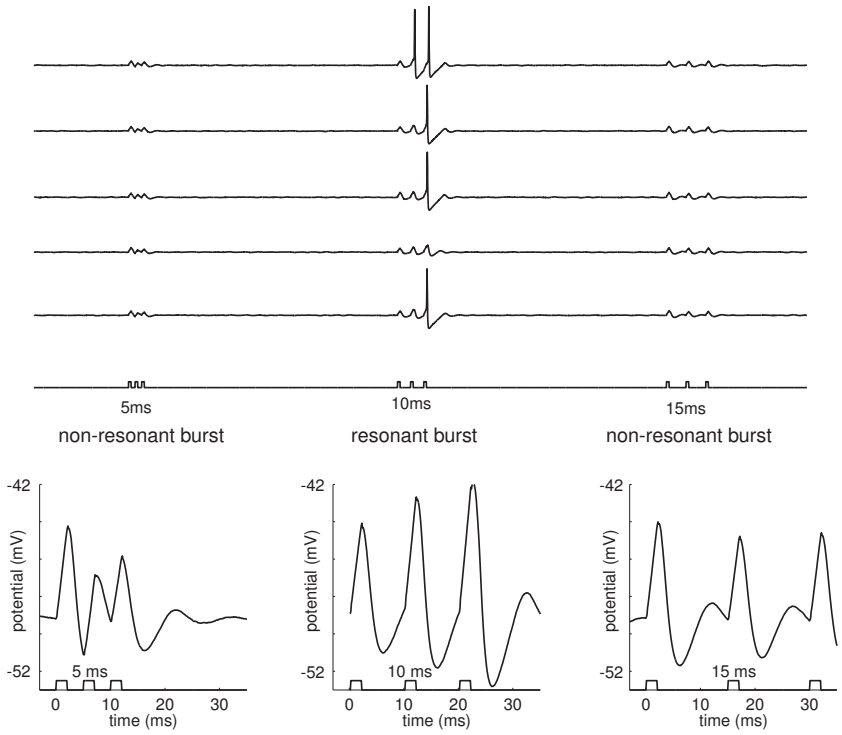


Figure 4: *Top*: Experimental observations of selective response to a resonant (10 ms interspike period) burst in mesencephalic V neurons in brainstem [11] having subthreshold membrane oscillations with natural period around 9 ms (see Fig. 3). *Bottom*: Magnified and averaged membrane voltage response to the injected pulses of current.

show in Fig. 4 using triplets with various intra-burst periods. Indeed, the first pulse in a triplet (or a short burst) evokes 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*, which is around 9 ms for the mesencephalic V neuron used 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 when the interpulse period is 15 ms (Fig. 4, right), which is 60 % greater than the natural period. The same phenomenon occurs for inhibitory synapses, as we illustrate in 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 4). 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. R. Llinas [28] 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 cell, and *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 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.

Fig. 6 illustrates the essence of the mechanism of selective communication via bursts when postsynaptic neurons are quiescent. However, theoretical studies and simulations [12, 13] have shown that the result

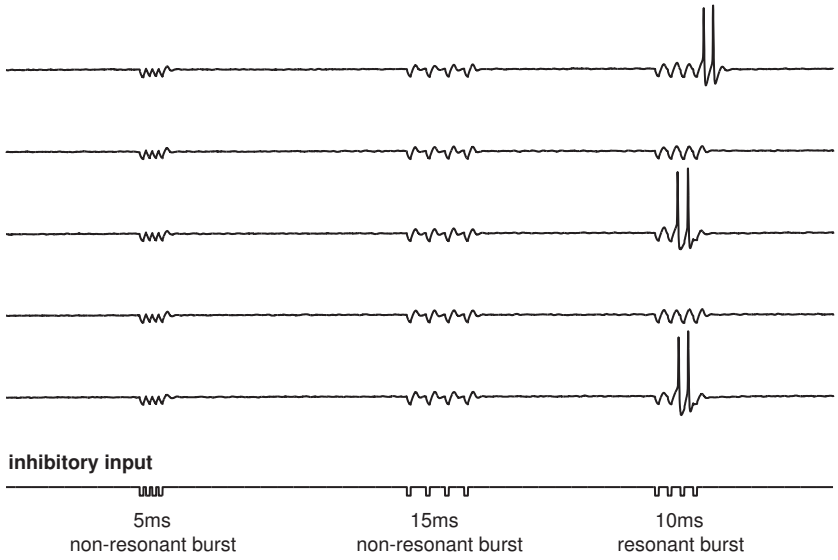


Figure 5: Experimental observations of selective response to inhibitory resonant burst in mesencephalic V neurons in brainstem [11] having oscillatory potentials with the natural period around 9 ms (see Fig. 3).

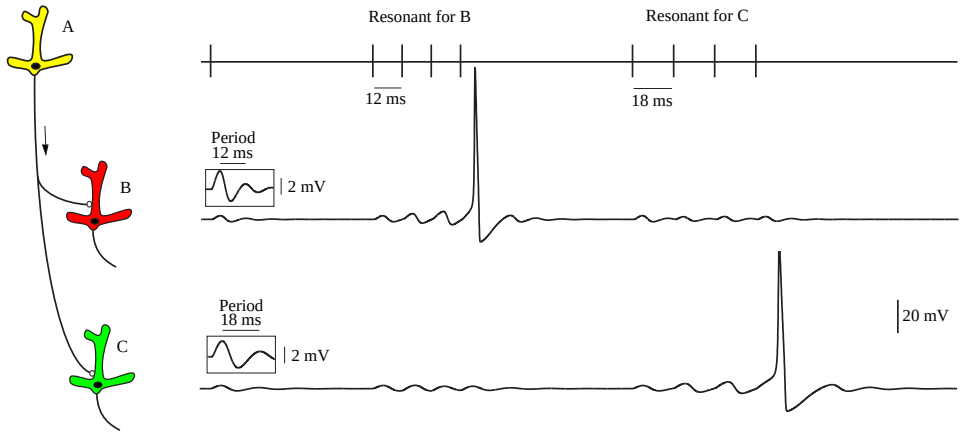


Figure 6: Selective communication via bursts: Neuron A sends bursts of spikes to neurons B and C that have different natural periods (12 ms and 18 ms, respectively. Both are simulations of the Hodgkin-Huxley model). As a result of changing the interspike frequency, neuron A can selectively affect either B or C without changing the efficacy of synapses (modified from [13]).

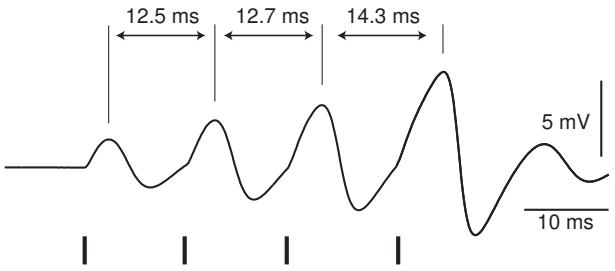


Figure 7: Instantaneous period of subthreshold oscillation in the Hodgkin-Huxley model depends on the amplitude of oscillation. The most optimal input in this case is a burst with spike frequency adaptation (bottom).

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 oscillation 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, as we illustrate 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 follow the increase of oscillation period, as in Box 2. Simulations of biophysical synaptic models [10] have shown a similar effect: adapting rather than purely periodic bursts are optimal for some synapses with short-term depression and facilitation.

Discussion

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, as we illustrate in Fig. 2.

Frequency preference and resonance can also occur at the neuronal level due to subthreshold oscillations (see review in TINS, Ref. 24). Most researchers are interested in how such oscillations can contribute to synchronization [24–27] and to neuronal processing (see review in Ref. 32). Here we propose an alternative hypothesis, namely 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, as we illustrate in Fig. 6.

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, as one can see in 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 rewire itself dynamically on a time scale of milliseconds without changing the synaptic hardware.

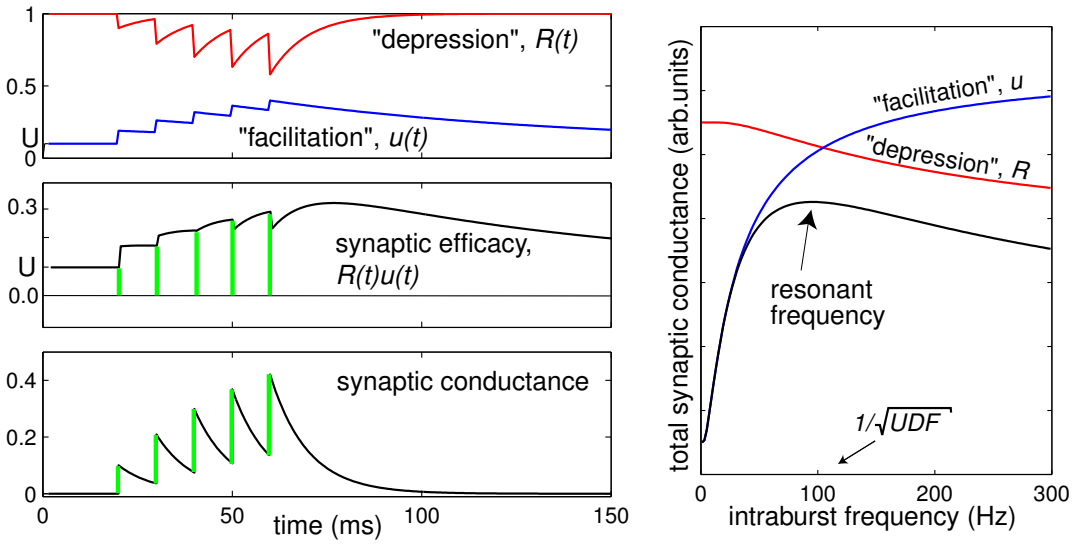
Box 1. Kinetics of Short-Term Synaptic Plasticity

Short-term synaptic plasticity is a complex phenomenon that consists of a number of different mechanisms [8]. However, there is a simple phenomenological model [2] that describes kinetics of such plasticity; It treats short-term depression and facilitation as two independent variables, R and u, respectively,

$$\dot{R} = \overbrace{(1-R)/D}^{\substack{\text{exponential recovery}\\ \text{to } R=1 \text{ with rate } D^{-1}}} - \overbrace{Ru\,\delta(t-t_n)}^{\substack{\text{pulsed decrease}\\ \text{due to } n\text{-th spike}}} \quad (\text{“depression” variable})$$

$$\dot{u} = \overbrace{(U-u)/F}^{\substack{\text{exponential recovery}\\ \text{to } u=U \text{ with rate } F^{-1}}} + \overbrace{U(1-u)\,\delta(t-t_n)}^{\substack{\text{pulsed increase}\\ \text{due to } n\text{-th spike}}} \quad (\text{“facilitation” variable})$$

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 bars in the figure, left).



Left: Dynamics of variables in response to a burst of 5 spikes. Parameters: $U = 0.1$, $F = 80$ ms, $D = 10$ ms, synaptic conductance with time constant 10 ms. Right: Integral (total area) of synaptic conductance for bursts of 5 spikes with various intra-burst frequency.

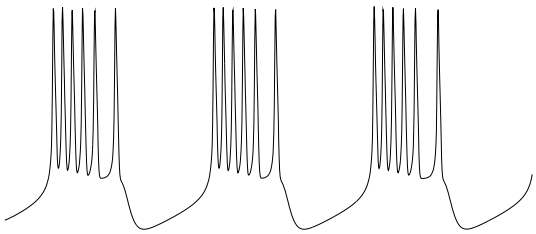
It also adjusts the depression variable R by the same quantity, and the facilitation variable u by the quantity $U(1-u)$, as we illustrate in the figure. The main advantage of this model is that it has only three parameters: utilization of synaptic efficacy U and the time constants D and F for recovery from depression and facilitation, respectively. These parameters have been measured experimentally to fit various types of neocortical synapses [2,3].

Let us fix $u = U = 0.1$ (this value corresponds to some GABAergic synapses [3]) and consider the dynamics of a depressing synapse in response to a burst of 5 spikes. Such a synapse behaves as a low-pass filter, since $R \approx 1$ for low-frequency and $R \to 0$ for high-frequency stimulation (red curve in the right of the figure). In contrast, a purely facilitating synapse (if variable $R = 1$ is fixed) behaves as a high-pass filter, since $u \approx U = 0.1$ for low-frequency, and $u \approx 1$ for high-frequency stimulation (blue curve in the right of the figure). 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 certain resonant frequency range (approximately at $1/\sqrt{UDF}$ [2]), where the product is maximal, as one can see in the figure above.

Box 2. Bursting

A burst is a train of closely-spaced action potentials. It is convenient to treat doublets (two spikes) and triplets (three spikes) as short bursts. Bursting can be generated by a strong synaptic input, which drives the neuron over the threshold and makes it fire repetitive action potentials. Alternatively, bursting can be generated by an intrinsic voltage- or Ca^{2+}-gated ionic mechanism, which may be triggered by a brief synaptic input. In this case the bursting pattern is stereotypical, usually with a constant or slowly decreasing interspike (intraburst) frequency [a, b].

Looking at a spike train of a neuron recorded *in vivo*, it might be difficult to discern whether the neuron is an intrinsic burster or not, that is, whether the closely spaced spikes are due to the strong synaptic input or to the intrinsic ionic mechanisms. The propensity to generate bursts can be revealed in a simple current-clamp experiment. When the amplitude of an injected dc-current is small, the neuron remains quiescent (provided that the synaptic input is absent or blocked); when the amplitude is sufficiently large (greater than the cell's rheobase), the neuron fires action potentials, which could be grouped into bursts, as in the figure.



From a theoretical point of view there could be many different scenarios for why the action potentials are not tonic, but grouped into bursts. All of the scenarios are based on the existence of a resonant gating variable (see Box 3) that slowly builds up and terminates the repetitive spiking state. During the quiescence, the variable relaxes and the spiking state resumes. The following are five of the most plausible scenarios:

- Slow voltage-gated activation of an outward current, such as a delayed rectifier I_{K}.
- Slow voltage-gated inactivation of an inward current that is partially activated during the repetitive spiking.
- Slow deactivation of hyperpolarization-activated inward current, such as the h-current I_{h}. This is related to the previous scenario if we treat the h-current as a normal current that is always activated, but can be inactivated (turned off) by depolarization and de-inactivated (turned on) by hyperpolarization (see Box 3).
- Slow Ca^{2+}-gated activation of an outward current, such as the AHP-current $I_{\mathrm{K(AHP)}}$.
- Slow Ca^{2+}-gated inactivation of an inward current, such as the L- or N-currents, $I_{\mathrm{Ca(L)}}$ and $I_{\mathrm{Ca(N)}}$.

Bursts come in different shapes and sizes. For example, some exhibit spike frequency adaptation, as in the figure, others have a relatively constant or increasing interspike frequency; some exhibit spike overshoot, others exhibit undershoot; some have a coexistence of resting and spiking state so that they can be switched from one to the other by a brief pulse of injected current, others do not have this property. Theoretical studies of topological types of bursters [c,d,12] revealed that different types of bursters can have different neuro-computational properties; that is, they can synchronize, interact, and process information differently [12].

a Connors B.W., and Gutnick M.J. (1990), Intrinsic firing patterns of diverse neocortical neurons, TINS, 13:99–104

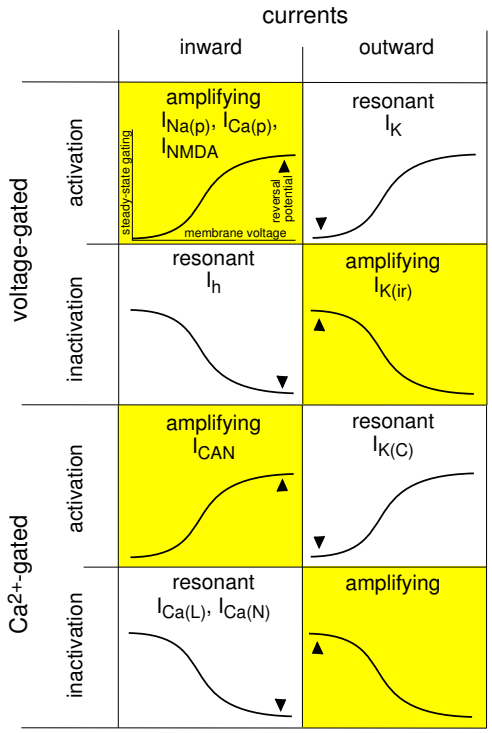
b Timofeev I., Grenier F., Bazhenov M., Sejnowski T.J., and Steriade M. (2000) Origin of Slow Cortical Oscillations in Deafferented Cortical Slabs. Cerebral Cortex, 10:1185–1199

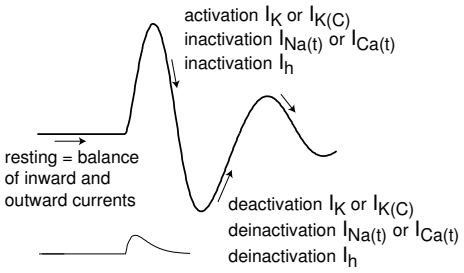
c Rinzel J. (1987) A formal classification of bursting mechanisms in excitable systems. In: E. Teramoto, M. Yamaguti, eds. *Mathematical Topics in Population Biology, Morphogenesis, and Neurosciences*, vol. 71 of Lecture Notes in Biomathematics, Springer-Verlag, Berlin.

d Bertram R., Butte M.J., Kiemel T., and Sherman A. (1995) Topological and phenomenological classification of bursting oscillations. Bulletin of Mathematical Biology 57:413–439.

Box 3. Ionic Mechanisms of Subthreshold Oscillations

Damped or sustained subthreshold oscillations of membrane potential are ubiquitous in neurons, and they can be found in many brain regions, including cortex [14,15,16,17], thalamus [18,19,20], hippocampus [21], brainstem [22] and olfactory bulb [23], see Fig. 3. Since the phase of oscillation can be reset by a brief pulse of injected current, these oscillations are generated by voltage-gated membrane currents, and not by an oscillatory synaptic input. Though based on different ionic mechanisms, such oscillations arise because of the interplay between resonant and amplifying currents, as we describe here.





Dynamics of most currents can be completely described by the Hodgkin-Huxley gating variable formalism. For example, the transient Na^+ current $I_{Na(t)}$ is described by activation and inactivation gating variables, m and h, respectively. All gating variables can be divided into eight categories depending on whether they describe voltage/Ca^{2+}-sensitive activation/inactivation of an inward/outward current, as we summarize in the table. (From the theoretical point of view [a] it is convenient to treat the hyperpolarization activated h-current I_h and K^+ inwardly rectifying current $I_{K(ir)}$ as "normal" currents having only inactivation variables; Obviously, depolarization inactivates (closes) the currents, and hyperpolarization deinactivates (opens) the currents). The eight types of gating variables can be further divided into two categories depending on how they affect membrane potential:

- **(amplifying)** If the reversal potential of the current gated by the variable is at the top of the gating curve (yellow boxes in the table), then there is a positive feedback loop that amplifies membrane potential changes.
- **(resonant)** If the reverse potential of the current is at the bottom of the gating curve (white boxes in the table), then there is a negative feedback loop that resists membrane potential changes.

Any neuronal model capable of generating an action potential consists of at least one amplifying and at least one resonant gating variable. As a rule of thumb, the amplifying gating variable must be faster than the resonant one.

If one or more resonant gating variables are active (partially open) at rest, then the membrane potential may exhibit subthreshold damped oscillations. Such oscillations can be amplified and become sustained or supra-threshold by amplifying gating variables. Below are some examples of minimal conductance-based models [a] having subthreshold oscillations via a mechanism depicted in the figure.

- $I_{Na(p)}$+I_K**-model**. Resonant current I_K must be partially activated at rest. In this case the resting state is a balance of leak current, partially activated $I_{Na(p)}$ and I_K. A brief depolarization activates more I_K and produces a net outward current that repolarizes and then hyperpolarizes the membrane potential. During the hyperpolarized state, I_K deactivates below its resting value, shifts the balance toward inward currents, and produces rebound depolarization, which in turn produces hyperpolarization, and so on. This is believed to be the mechanism of subthreshold oscillations of some mammalian cortical layer 4 neurons [14], mitral cells in olfactory bulb [23] and the mesencephalic V neurons in the brainstem [22].

Box 3. (continuation)

- $I_{\mathrm{Na(p)}}$+I_{h}**-model**. Resonant current I_{h} is partially opened at resting state, which is a balance of inward currents $I_{\mathrm{Na(p)}}$ and I_{h} and an outward leak current. A brief hyperpolarization opens (de-inactivates) more I_{h}, creates an excess of inward current, and results in rebound depolarization. During the depolarized state, I_{h} decreases significantly below its resting value, and shifts the balance toward outward leak current, which repolarizes and then hyperpolarizes the membrane potential, and so on. This mechanism is believed to be responsible for subthreshold oscillations in some cortical neuron [16,29].

- $I_{\mathrm{Na(t)}}$**- or** $I_{\mathrm{Ca(T)}}$**-model**. In both models, the transient inward current must be a window current so that it is only partially inactivated at resting state. A brief depolarization slightly inactivates the inward current and leak outward current hyperpolarizes the cell. This hyperpolarization de-inactivates the inward current and produces rebound depolarization. Such a mechanism is believed to contribute to fast subthreshold oscillations in the brainstem mesencephalic V neurons [22].

- $I_{\mathrm{Ca(p)}}$+$I_{\mathrm{K(C)}}$**-model**. If $I_{\mathrm{Ca(p)}}$ is partially activated at rest, there is a constant inflow of Ca^{2+} ions resulting in partial activation of $I_{\mathrm{K(C)}}$. A brief depolarization activates more of $I_{\mathrm{Ca(p)}}$ resulting in increased Ca^{2+} inflow. This activates more Ca^{2+}-sensitive outward current $I_{\mathrm{K(C)}}$ and hyperpolarizes the cell. During the hyperpolarization, the Ca^{2+} current deactivates, internal Ca^{2+} ions are removed or buffered, and $I_{\mathrm{K(C)}}$ deactivates below its resting value. This shifts the balance toward the inward current $I_{\mathrm{Ca(p)}}$ resulting in rebound depolarization. Similar effect is achieved in the $I_{\mathrm{Ca(N)}}$-model having Ca^{2+}-sensitive inactivation of inward current instead of Ca^{2+}-sensitive activation of an outward current $I_{\mathrm{K(C)}}$.

Despite diversity of ionic mechanisms, there is only one mathematical mechanism for subthreshold oscillations: The neuron as a dynamical system has a stable equilibrium (resting state) with a pair of complex-conjugate eigenvalues [a]. The imaginary part of the eigenvalues is the natural frequency of oscillations. (Typically, such an equilibrium is near Andronov-Hopf bifurcation [a,b,12], and dynamics of the model can be described by two variables). This explains many aspects of oscillatory potentials, such as

- Oscillations become sustained when noise is present in the system [30].

- Typically, a neuron could fire a post-inhibitory spike in response to a brief inhibitory stimulation, as in Fig. 5 [12].

- Neuron is Class 2 excitable [c], that is, when the amplitude of the injected dc-current increases, the neuron starts to fire action potentials in a narrow frequency range.

From the neuro-computational point of view, such a neuron is a resonator [12], as we discuss in Box 4.

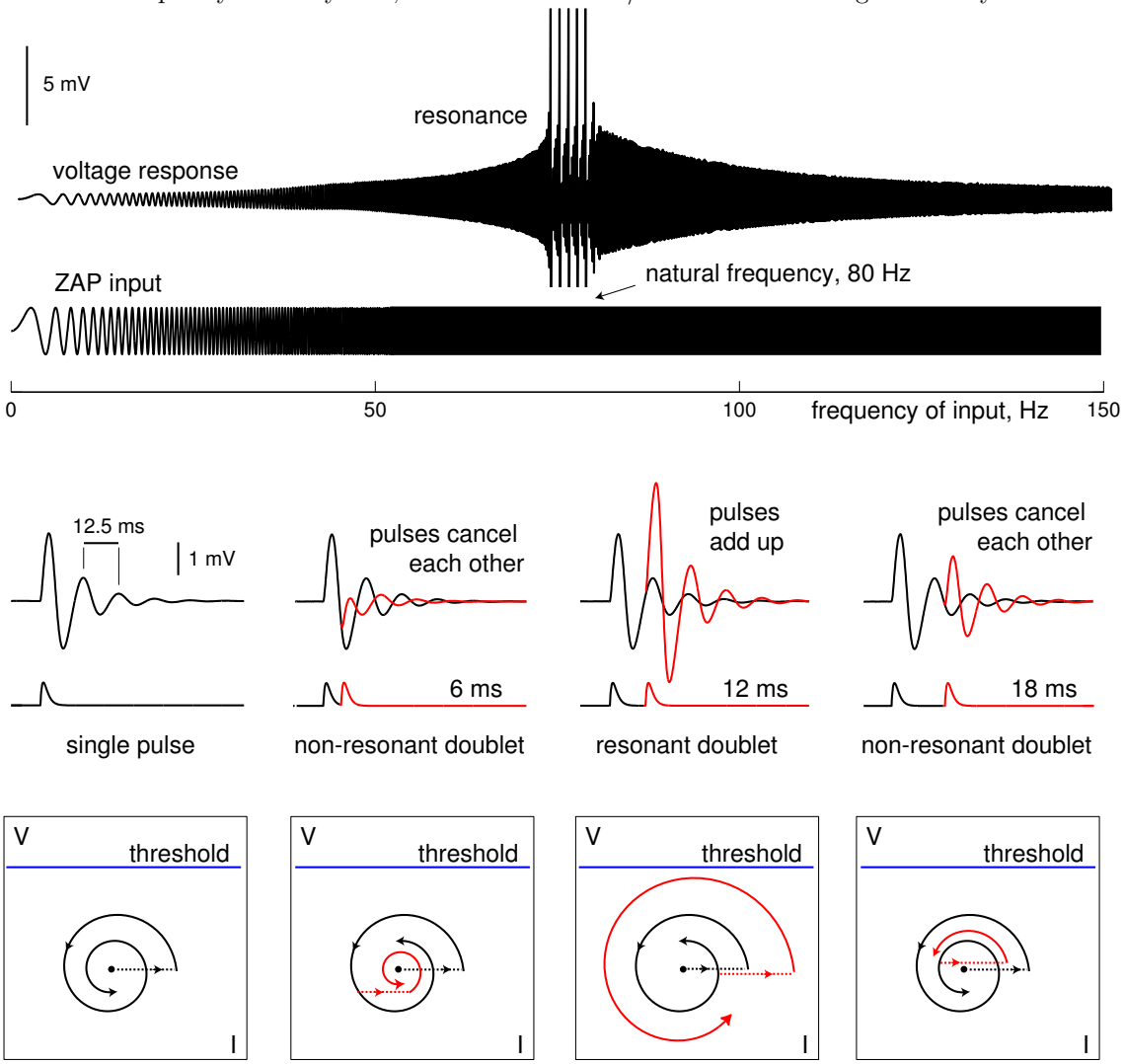
a Izhikevich E.M. (2003) Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting. Monograph in preparation.

b Rinzel J. and Ermentrout G.B. (1989) Analysis of Neural Excitability and Oscillations. In Koch C., Segev I. (eds) Methods in Neuronal Modeling, The MIT Press, Cambridge, Mass.

c Hodgkin A.L. (1948) The local electric changes associated with repetitive action in a non-medulated axon. Journal of Physiology 107:165–181.

Box 4. 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 called the *natural frequency* or *eigenfrequency* of the system, and the period is called the *natural period*. For example, the Hodgkin-Huxley model [a] exhibits oscillatory potentials with natural period 12.5 ms when a single brief pulse of current is injected (see figure). If the injected current is sinusoidal sweeping through many frequencies (so called ZAP current), then the evoked 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 = 1/0.0125s in the Hodgkin-Huxley model.



Such an amplified response of the system when it is subjected to a periodic stimulation with frequency at or near its natural frequency is called *resonance*. Resonances can be destructive for mechanical or electrical systems. Many neurons exhibit oscillatory potentials (see Box 3) and hence resonance. In an excellent review paper [24], Hutcheon and Yarom use a band-pass filter formalism similar to the one in Fig. 1 to describe resonances in neurons. Here we present an alternative geometrical illustration why subthreshold oscillations lead to resonance and frequency preference.

Box 4. (continuation)

We stimulate the Hodgkin-Huxley model with doublets (pairs of pulses) having various inter-pulse periods and plot voltage traces in the middle of the figure. The first pulse (black) evokes damped oscillations of the membrane potential. The effect of the second pulse (red) depends on its timing relative to the timing of the first one. When the inter-pulse period is 6 ms, which is half of the natural period of the system, the second pulse arrives during the falling phase of oscillation, and it is essentially canceled by the first pulse. When the inter-pulse period is 12 ms, which is near the systems natural period, the second pulse arrives on the rising phase of oscillation, and the pulses essentially add up. Finally, when the inter-pulse period is 18 ms, which is 50% greater than the natural period, the second pulse arrives during the falling phase of oscillation, and it is again canceled by the first pulse.

In the bottom of the figure we present geometrical analysis of the "resonate-and-fire" model [b] whose dynamics can be depicted as trajectories on the (I, V) phase plane. Similarly 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 (black circle), and the model exhibits spiral damped oscillations toward the stable resting state (black trajectory) with the natural period 12.5 ms. The effect of the second pulse (red trajectory) depends on the timing of its arrival. If the interpulse interval is 6 ms, the trajectory is still in the left semi-plane, and the second pulse pushes it closer to the equilibrium, thereby canceling the effect of the first pulse. If the interpulse 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 interpulse interval is 18 ms, the trajectory is again in the left semi-plane, so the effect of the second pulse is small.

One can clearly see that the system's response is greatest when the input is resonant, i.e., its period is near the natural period of the system. In contrast, when the input is non-resonant, the response of the system to a doublet (or a burst of pulses) is smaller than its response to a single pulse.

a Hodgkin A.L. and Huxley A.F. (1954) A quantitative description of membrane current and application to conduction and excitation in nerve. Journal Physiol., 117:500–544.

b Izhikevich E.M. (2001) Resonate-and-Fire Neurons. Neural Networks, 14:883-894

References

1. Lisman J. (1997) Bursts as a unit of neural information: making unreliable synapses reliable, Trends Neurosci. 20:38–43
2. Henry Markram, Yun Wang, and Misha Tsodyks (1998) Differential signaling via the same axon of neocortical pyramidal neurons PNAS 95:5323-5328
3. Gupta A, Wang Y., Markram H. (2000) Organizing Principles for a Diversity of GABAergic Interneurons and Synapses in the Neocortex, Science 287:273–278
4. Fortune E.S. and Rose G.J. (2001) Short-term synaptic plasticity as a temporal filter, TINS, 24:381–385
5. Fortune E.S. and Rose G.J. (2000) Short-term synaptic plasticity contributes to the Temporal Filtering of Electrosensory Information, J. Neuroscience, 20:7122–7130
6. Dittman J.S., Kreitzer A.C., Regehr W.G. (2000) Interplay between Facilitation, Depression, and Residual Calcium at Three Presynaptic Terminals, J. Neuroscience, 20:1374-1385.
7. Abbott L.F., Varela J.A., Sen K., and Nelson S.B. (1997) Synaptic Depression and Cortical Gain Control, Science, 275:220–224
8. Thomson A.M. (2000) Molecular frequency filters at central synapses, Progress in Neurobiology 62:159-196.
9. Thomson Alex (2002) Frequency-filtering properties of 'dynamic' cortical synapses and their contributions to the behaviour of small networks. Computational Neuroscience (CNS) conference, invited talk, Chicago, July 23.
10. Thomas Natschlger and Wolfgang Maass (2001) Computing the Optimally Fitted Spike Train for a Synapse Neural Comp. 13: 2477-2494.
11. Izhikevich E.M., Desai N., and Walcott E.C. (2003) Subthreshold oscillations and selective interactions in rat brainstem mes V neurons *in vitro*, manuscript in preparations.
12. Izhikevich E.M. (2000) Neural Excitability, Spiking, and Bursting. International Journal of Bifurcation and Chaos, 10:1171–1266.
13. Izhikevich E.M. (2002) Resonance and Selective Communication Via Bursts in Neurons Having Subthreshold Oscillations. BioSystems, in press
14. Llinas R. R., Grace A.A., Yarom Y. (1991) In vitro neurons in mammalian cortical layer 4 exhibit intrinsic oscillatory activity in the 10- to 50-Hz frequency range, Proc. Natl. Acad. Sci. USA, 88:897–901.
15. Gutfreund Y., Yarom Y., Segev I. (1995) Subthreshold oscillations and resonant frequency in guinea-pig cortical neurons: Physiology and Modeling. J. Physiol. London 483:621–640
16. Hutcheon B., Miura R.M., Puil E. (1996a) Subthreshold Membrane Resonance in Neocortical Neurons, Journal of Neurophysiology, 76:683–697.
17. Hutcheon B., Miura R.M., Puil E. (1996b) Models of Subthreshold Membrane Resonance in Neocortical Neurons, Journal of Neurophysiology, 76:698–714.
18. Pedroarena C. and Llinas R. R. (1997) Dendritic calcium conductances generate high-frequency oscillation in thalamocortical neurons, Proc. Natl. Acad. Sci. USA, 94:724–728.
19. Hutcheon B., Miura R.M., Yarom Y., and Puil E. (1994) Low-threshold Calcium Current and Resonance in Thalamic Neurons: A Model of Frequency Preference. J. Neurophysiology 71:583–594.
20. Puil E., Meiri H., Yarom Y. (1994) Resonant Behavior and Frequency Preference of Thalamic Neurons. J. Neurophysiology 71:575–582.
21. Cobb S.R., Buhl E.H., Halasy K., Paulsen O., and Somogyl P. (1995) Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons, Nature 378:75–78.
22. Nanping Wu, Chie-Fang Hsiao, and Scott H. Chandler (2001) Membrane Resonance and Subthreshold Membrane Oscillations in Mesencephalic V Neurons: Participants in Burst Generation The Journal of Neuroscience, 21(11):3729-3739
23. Philip Heyward, Matthew Ennis, Asaf Keller, and Michael T. Shipley (2001) Membrane Bistability in Olfactory Bulb Mitral Cells The Journal of Neuroscience, 21(14):5311-5320
24. Hutcheon B. and Yarom Y. (2000) Resonance, oscillation and the intrinsic frequency preferences of neurons. Trends Neurosci. 23:216–222
25. Lampl I. and Yarom Y. (1997) Subthreshold Oscillations and Resonant Behavior: Two Manifestations of the Same Mechanism, Neuroscience, 78:325–341.
26. Lampl I. and Yarom Y. (1993) Subthreshold Oscillations of the Membrane Potential: A Functional Synchronizing and Timing Device, Journal of Neurophysiology, 70:2181–2186.
27. Desmaisons D., Vincent J.-D., Lledo P.M. (1999) Control of Action Potential Timing by Intrinsic Subthreshold Oscillation in Olfactory Bulb Output Neurons. The Journal of Neuroscience, 15:10727–10737.
28. Llinas R. R. (1988) The Intrinsic Electrophysiological Properties of Mammalian Neurons: Insights into Central Nervous System Function, Science, 242:1654–1664.
29. Dickson C. T., Magistretti J., Shalinsky M., Hamam B., and Alonso A. (2000) Oscillatory Activity in Entorhinal Neurons and Circuits. Annals of NY academy of Sciences, 911:127–150
30. White J.A., Klink R, Alonso A, and Kay AR (1998) Noise from voltage-gated ion channels may influence neuronal dynamics in the entorhinal cortex. J. Neurophysiol. 80: 262–269
31. Hodgkin A.L. and Huxley A.F. (1952) A quantitative description of membrane current and application to conduction and excitation in nerve, Journal of Physiology, 117:500–544.
32. Singer W. (1999) Time as Coding Space? Current Opinion in Neurobiology, 9:189–194.