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Resonance, oscillation and the intrinsic frequency preferences of neurons

Bruce Hutcheon and Yosef Yarom

The realization that different behavioural and perceptual states of the brain are associated with different brain rhythms has sparked growing interest in the oscillatory behaviours of neurons. Recent research has uncovered a close association between electrical oscillations and resonance in neurons. Resonance is an easily measurable property that describes the ability of neurons to respond selectively to inputs at preferred frequencies. A variety of ionic mechanisms support resonance and oscillation in neurons. Understanding the basic principles involved in the production of resonance allows for a simplified classification of these mechanisms. The characterization of resonance and frequency preference captures those essential properties of neurons that can serve as a substrate for coordinating network activity around a particular frequency in the brain.

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THE WORKING BRAIN is characterized by the rhythmic activation of large numbers of its neurons on characteristic temporal and spatial scales. These modes of coherent activity appear as the various brain rhythms. A series of firmly established empirical associations with the behavioural states of organisms provides compelling evidence that brain rhythms reflect basic modes of dynamical organization in the brain¹. However, the mechanisms that bind neurons into these rhythmical coherent ensembles are not well understood.

What determines the characteristic frequency range of each brain rhythm? Broadly speaking, there are two

types of explanation. One invokes patterns of connectivity between neurons and the dynamic properties of the intervening synapses. For example, reverberating activity within re-entrant neural circuits could result in the rhythmic activation of fundamentally non-oscillatory neurons within well-defined frequency bands². A different explanation states that network rhythmicity arises via the coupling of oscillatory sub-units, each of which possesses an intrinsically determined frequency preference³. These two explanations are not mutually exclusive (network connectivity could reinforce the patterns of excitation produced by coupled

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Box 1. Hunting resonance in circuits and cells

Physicists and engineers have long used frequency-domain techniques to describe the wave-like existence of particles, the motions of electrons in atoms, or the movement of a pendulum. These methods regard oscillation as a fundamental mode of behaviour and frequency as its natural unit of measure. For neurons, frequency-domain techniques provide an alternative to time-based descriptions of activity: a simpler and more-natural one for neurons that spend much of their existence immersed in sea of rhythmic inputs. Measurement of the electrical impedance characterizes the input–output relationship of neurons in a frequency-dependent way. Resonance is a property of the impedance. To explain further, it helps to explore first the principles of impedance and resonance in electrical circuit caricatures of neuronal behaviour.

Impedance is the frequency-domain extension of the concept of resistance for electrical circuits. Like resistance, it is a relationship between voltage and current. Unlike resistance, impedance is a frequency-dependent relationship between the amplitudes (and phases)

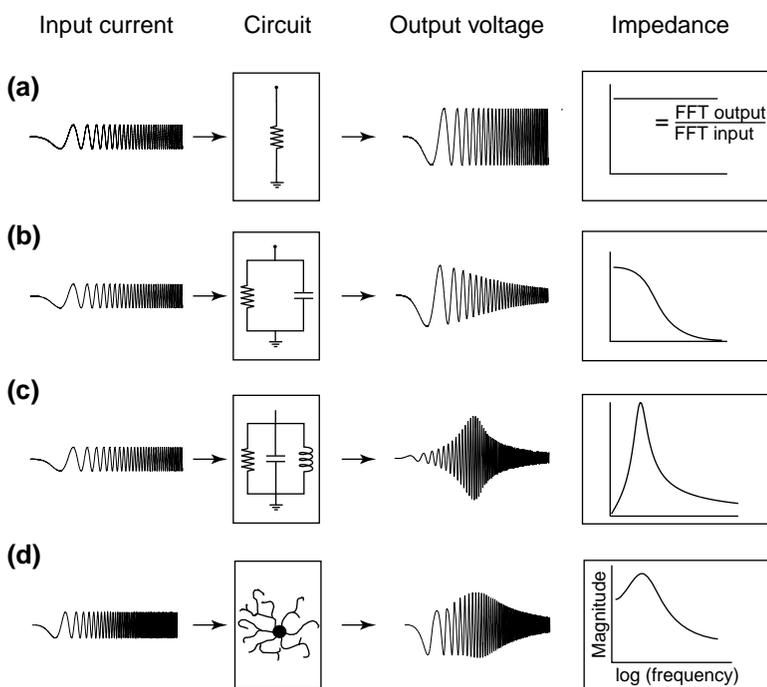
of oscillatory signals. The impedance of a simple circuit can be determined by probing it with an input current and observing the voltage response at each frequency. Although any input that has a known frequency composition can be used, the process is illustrated in this case using a signal that sweeps through many frequencies over time (the so called ‘ZAP’ input^a). This input is useful because it is poised almost equally between the time and frequency domains. Each frequency in the input is isolated briefly in time so that the frequency response can be judged by eye as well as by later analysis. For the experimentalist who is probing neuronal circuits this real-time feedback is valuable.

The simplest of impedance relationships occurs for the simplest of all circuits, a resistor connected to ground (see Fig. 1a). In this case, as in all others, the impedance is found by dividing the Fourier spectrum (calculated using the Fast Fourier Transform, or FFT) of the output by that of the input. In this example, the impedance is simply a constant with a value equal the resistance.

A slightly more-sophisticated circuit comprises a resistor and capacitor connected in parallel (Fig. 1b). This is a common model for the passive electrical properties of an isopotential neuron. In this case, the impedance is a more-complicated function, the decline in impedance with increasing frequency indicates that an oscillatory input current of unit amplitude produces a smaller and smaller voltage response as the frequency rises. This circuit, therefore, acts in a way that is similar to a low-pass filter, that is, current inputs arriving at low frequencies yield relatively large voltage responses but higher frequency inputs are attenuated or blocked. All neurons have some contribution from a low-pass mechanism such as this in their frequency response.

Finally, adding an inductive element to the circuit results in a qualitatively different impedance relation (Fig. 1c). A resonant peak appears so that instead of acting in the same way as a low-pass filter, the system responds like a bandpass. The meaning of this is seen in the time-domain response to the ZAP input. The system is activated preferentially as the input passes through the resonant frequencies. Thus, it exhibits a frequency preference: a frequency at which the response to inputs is best.

Like electrical circuits, neurons can exhibit resonance and therefore sustain a frequency preference (Fig. 1d). Resonant neurons produce large responses when driven by inputs near their resonant frequency and smaller responses at other frequencies. Functionally, such resonances constrain neurons to respond most powerfully to inputs at biologically important frequencies such as those associated with brain rhythms.



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Fig. 1. Frequency-dependent properties of electronic circuits and neurons: detection and analysis. The relationship between the current input (first column) and the voltage output (third column) of electrical circuits or neurons (second column) enables the calculation of the impedance as a function of frequency (fourth column). The use of a ZAP input function concentrates the analysis within a specific range of frequencies.

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oscillators); however, at present, we have no clear example of a centrally produced rhythm that relies on patterns of connectivity to determine its frequency. On the other hand, we now have good evidence that individual neurons can have frequency preferences that enable them to either generate spontaneous membrane-voltage oscillations, or respond best to inputs within a narrow frequency window (see below). Such intrinsically defined properties of individual neurons will have a role in determining the dynamics of coherent brain activity.

This article discusses the possibility that there is a common element underlying the diverse mechanisms of frequency preference in neurons. Resonance, a property that characterizes the frequency at which neurons

respond best to inputs of injected current (Box 1), provides one means to describe the frequency-dependent properties of different neurons on a common basis. Although resonance measurements assess only the small-signal responses of neurons (thus ignoring, or only approximating, their strongly nonlinear properties) this is usually adequate for understanding how neurons process oscillatory inputs at subthreshold potentials. Using resonance to reveal the similarities between oscillatory mechanisms of different neurons should lead to basic insights regarding the development and modulation of rhythms in the brain; understanding their differences should yield specific new targets for drug action in disorders as diverse as epilepsy and insomnia.

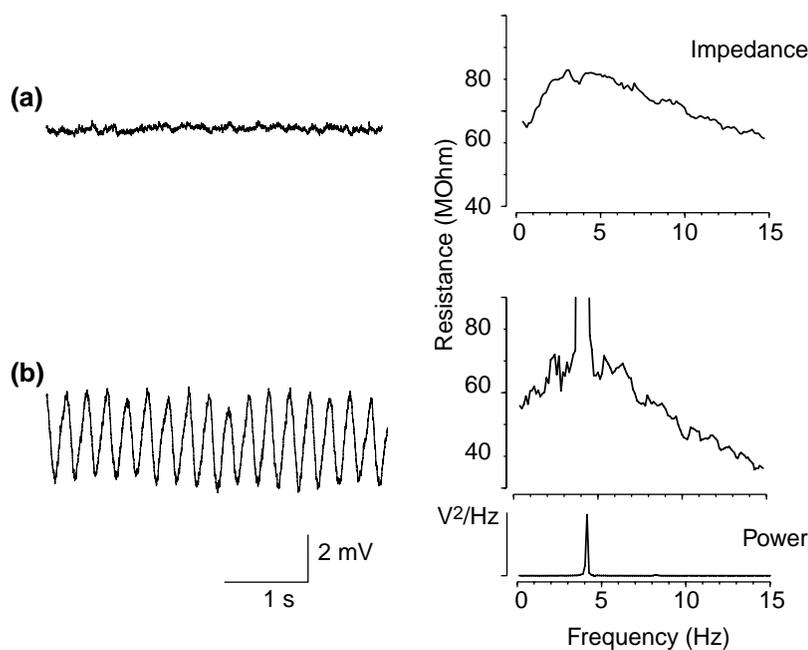


Fig. 1. Neurons of the inferior olive have an intrinsically determined frequency preference that is reflected in their network behaviour. (a) A whole-cell recording of an olivary neuron *in vitro* shows that it has a stable resting potential (left). The impedance profile of the same neuron (right) reveals a resonance at 4 Hz. The resonance is generated by the low-threshold Ca^{2+} current, I_T . (b) In a different olivary neuron, the membrane potential (left) oscillates steadily at 4 Hz as shown by the power spectrum (lower right). The impedance of this neuron also exhibits a resonance with a peak at the same frequency as the oscillations (the large truncated peak centered on the top of the resonance is due to the spontaneous oscillations). Oscillations in these neurons are partly intrinsic and partly caused by electrical coupling with other olivary neurons. Although the existence of oscillation is controlled by the strength of coupling and other modulatory factors such as the leak conductance, the frequency of the oscillations is determined by the resonance in the individual cells.

Resonance as a probe of frequency preference

The use of frequency-response analysis for understanding neuronal function was pioneered by Cole⁴, who used it, before the advent of voltage clamp techniques, to describe some of the basic events concerned with the generation of action potentials in the giant axon of the squid. Research using frequency-domain techniques was then carried forward by researchers who wished to study emergent electrical phenomena in single neurons by using Fourier techniques to tease apart the components of the response (for a review see Ref. 5). A distinctive property noted in some neurons using such techniques is a peak in the impedance curve, that is, a resonance (Box 1). The existence of a resonance in a neuron indicates that it is able to discriminate between its inputs, on the basis of their frequency content, so that oscillatory inputs near the resonant frequency produce the largest responses. Resonances have now been described in a number of excitable cell types such as cardiac cells⁵, hair cells of the inner ear⁶, and various peripheral⁷ and central^{8–14} neurons.

There are a few well-documented examples where frequency analysis has been used to demonstrate a close association between resonance and subthreshold oscillations of the membrane potential. In the neurons of the inferior olive, a coordinated subthreshold oscillation acts as a timing device to gate inputs^{15,16}. These oscillations require the presence of the low-voltage activated Ca^{2+} current (I_T)¹⁷. In slice recordings, impedance measurements show that all olivary neurons display resonance even if they do not oscillate (Fig. 1a). In neurons

with subthreshold oscillations, the peak of the resonance and the frequency of the oscillations coincide (Fig. 1b). As evidence of their intimate relationship, both the oscillations and the resonance are eliminated by pharmacological block of I_T (Ref. 13). In thalamic neurons, a similar mechanism involving I_T is responsible for a resonance near the same frequencies^{10,18}.

Pyramidal neurons in the neocortex have two resonances with different voltage dependence. A 1–2 Hz resonance that occurs near the resting membrane potential requires activation of the hyperpolarization-activated cation current, I_H (Ref. 12), whereas a 5–20 Hz resonance (the exact frequency is voltage dependent) is seen at potentials that are more positive than -55 mV (Ref. 19). Two ionic conductances are implicated in the generation of the more-depolarized resonance because it is abolished by TEA (tetraethylammonium; a K^+ channel blocker), and strongly attenuated, but not altered in frequency, by TTX (tetrodotoxin; a Na^+ channel blocker). Furthermore, this resonance is associated with the sporadic occurrence of self-sustained subthreshold oscillations of the membrane potential near the resonant frequency. The oscillations require the full integrity of both of the currents involved in the resonance because either TEA or TTX abolishes them. The oscillations are interpreted as arising from an interaction between a TEA-sensitive mechanism that generates a resonance and a TTX-sensitive mechanism that is capable of amplifying the resonance strongly to produce oscillations.

The possible functional importance of the resonance and oscillations observed in thalamic and cortical neurons lies in the known participation of these neurons in various brain rhythms. The low-frequency resonances in the cortex and thalamus appear suited to support the thalamocortical delta-wave oscillations that are particularly prominent during deep sleep. The higher-frequency oscillatory behaviour and underlying resonance in pyramidal and inhibitory²⁰ neurons of the neocortex might have some involvement with higher-frequency rhythms that appear in the cortex during cognition²¹.

How to make resonance: rules of thumb

The examples above show there are diverse ways to create resonance and oscillations in neurons. Fortunately, there are some simple regularities that govern these processes. In particular, as in the dual mechanism that underlies the depolarized resonance in neocortical cells, there is often a dissociation between the basic mechanisms responsible for the existence of resonance and the subsequent amplification of resonance to generate oscillations. This allows the study of these processes in relative isolation. The basic mechanisms that establish resonance and how resonance can be amplified and turned into oscillation will now be considered.

Resonances in central neurons always arise from an interplay between their active and passive properties. In fact, to generate resonance it is necessary to combine in a neuron two mechanisms that have specific frequency-domain properties: one that attenuates voltage responses to inputs that occur at high frequencies and another that attenuates responses to inputs arriving at low frequencies. The resulting combination of low- and high-pass filtering behaviour effectively creates a notch filter that is capable of rejecting inputs at frequencies outside the pass-band.

There is no difficulty in locating which properties of neurons result in low-pass filtering characteristics. The mechanism is well known and ubiquitous. It is a fundamental property of all cells that the parallel leak conductance and capacitance of the outer membrane forms the equivalent of a filter that attenuates responses to inputs at high frequencies. The mechanism that underlies low-frequency attenuation, however, is less well known. Such mechanisms arise from the operation of specific classes of voltage-gated currents. There are two elementary rules for deciding which voltage-gated currents will act as high-pass filters and will therefore be capable of combining with the passive properties of neurons to produce resonance.

(1) Currents that actively oppose changes in membrane voltage can produce resonance. In Fig. 2a, this is demonstrated using a simulation model of an isopotential neuron with a voltage-gated current (I_K) that has properties similar to a delayed rectifier. As can be seen by comparing parts a and b in Fig. 2a, the voltage changes in response to a current pulse are greatly reduced by the addition of I_K . By definition, all voltage-gated currents whose reversal potential falls near the base of their activation curve will act in the same way to oppose changes in membrane voltage actively. Examples of such currents are outwardly rectifying K^+ currents and inwardly rectifying I_H (see Fig. 3a). The ability to oppose voltage changes, however, is not yet sufficient to produce resonance. One more requirement must be met.

(2) To produce resonance, currents that meet the criterion above must, in addition, activate slowly relative to the membrane time constant. This is demonstrated once again for a model neuron with I_K (Fig. 2a, part b). The model shows the damped oscillations that occur at the onset and offset of the response to an injected current pulse as the slow kinetics of I_K force it to turn on and off with a lag relative to the passive charging of the membrane. The damped oscillations, often called 'sag' and 'rebound' in neurons, are the time-domain signature of resonance. The same basic phenomenon is seen in the response to a 'ZAP' (see Box 1) current input where the slow kinetics of I_K result in it being most effective in tracking and opposing low-frequency changes in membrane voltage. The net result is that I_K attenuates low frequencies and acts as a high-pass filter with a corner frequency set by its activation time constant (Fig 2b). In addition, the low-pass filter formed by the passive properties of the membrane has a corner frequency set by the RC time constant. Resonance arises at intermediate frequencies where inputs induce voltage changes at frequencies too high to be opposed by I_K and too low to be counteracted by the passive properties of the membrane. If there is not enough of a gap between these high- and low-frequency regions of attenuation, resonance will be eliminated. As a general rule, the activation time constant for the voltage-gated current should be slower than the membrane time constant in order to produce resonance. If this criterion is fulfilled, the resonant frequency lies between these two time constants.

To summarize, slowly activating currents that actively oppose changes in membrane voltage produce resonance. The approximate frequency of the resonance can be estimated when the values of the activation and passive membrane time constants are known. Given that the kinetics of resonant currents are voltage dependent, the resonant frequency will also be voltage dependent.

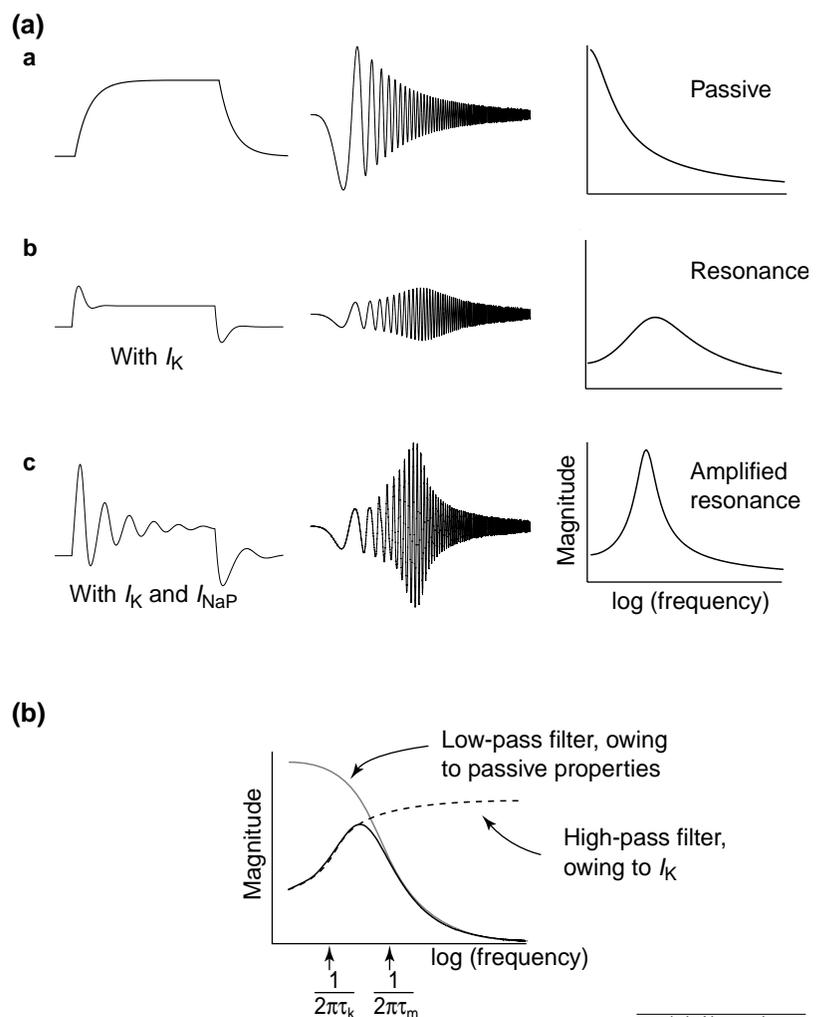


Fig. 2. Resonance is formed by the interaction of active and passive properties in a neuron. (a) Properties of three models that have passive properties only (part a), passive properties plus a resonant current, I_K (part b), and passive properties, a resonant current and an additional amplifying current, I_{NaP} (part c). For each model, the response to a pulse of current is shown on the left, the response to a 'ZAP' input in the middle and the corresponding impedance magnitude on the right. The amplified resonance results in oscillations, and an enlargement and narrowing of the resonant peak in the impedance magnitude. If the conductance of the amplifying current is increased much beyond the value shown, the oscillations become self-sustaining and the model acts like a pacemaker. (b) Demonstration of the separate contributions of the resonant current and passive properties to resonance in the impedance (unbroken line). The broken line shows the contribution of the resonant current (I_K) to the impedance. At low frequencies, the effectiveness of I_K at countering voltage changes is high, resulting in a small impedance. This effect is reduced at frequencies above $1/2\pi\tau_k$, where τ_k is the time constant for activation of I_K . On the other hand, the passive properties of the membrane (gray line) dominate the impedance at frequencies above $1/2\pi\tau_m$, where τ_m is the membrane time constant. The resonant peak occurs between these frequencies.

Amplifying currents, amplified resonance and oscillation

Although the rules for identifying resonant currents have been explained, the story is not yet complete. What is missing is the concept of an amplifying current. Such a current is essentially the inverse of a resonant current. Its reversal potential lies near the top, rather than the base, of its voltage-activation curve (Fig. 3); and it therefore actively potentiates, rather than opposes, voltage changes (cf. parts b and c in Fig. 2a). In addition, it activates quickly, rather than slowly, relative to the membrane time constant. Amplifying currents enhance voltage fluctuations through a weakly regenerative mechanism analogous to that responsible for the rising phase of action potentials. Examples of such

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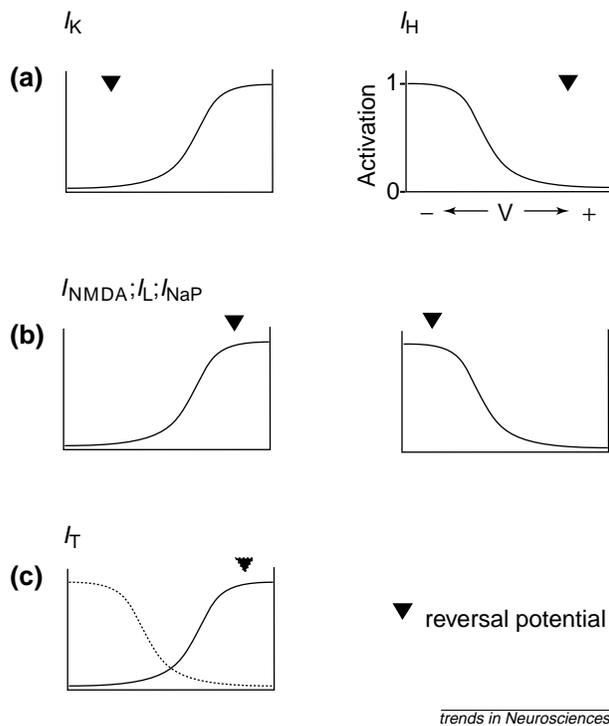


Fig. 3. Classification of voltage-gated currents. Each panel shows, schematically, a possible arrangement of steady-state activation and reversal potential (arrowheads) that can lead to either resonant (a) or amplifying behaviour (b). The horizontal axes shows arbitrarily scaled membrane voltage with depolarized values on the right. (a) Currents that have their reversal potential at the base of their activation curves can produce resonance. Resonance is strongest where the slope of the steady-state activation curve is steep. There are two possible arrangements depending on whether the current is activated by depolarization or hyperpolarization. Examples of each possibility are listed above each panel. (b) Currents with a reversal potential at the top of the activation curve are amplifying. Examples of such currents that activate with depolarization are the persistent Na⁺ current (I_{NaP}), the L-type Ca²⁺ current (I_L) and the NMDA-receptor current (I_{NMDA}). To date, there is no clear-cut example of an amplifying current that is activated upon hyperpolarization. (c) The low-threshold Ca²⁺ current produces an amplified resonance and can be understood as made up of two active mechanisms. The inactivation process (broken line) produces a resonance, whereas the activation process (unbroken line) is amplifying. Abbreviations: I_H , hyperpolarization-activated cation current; I_K , outwardly rectifying K⁺ currents; I_T , low-threshold Ca²⁺ current.

currents (Fig. 3) are the persistent Na⁺ current, I_{NaP} , the current that flows through NMDA-receptor channels, I_{NMDA} , and the dihydropyridine-sensitive high-threshold Ca²⁺ current, I_L .

Amplifying currents interact with resonant currents to enhance resonance without greatly altering the resonant frequency. This is seen by comparing the ZAP responses or the impedance curves in parts b and c of Fig. 2a. If the resulting mechanism were to be described in terms of electronic circuits, we would speak of a band-pass amplifier rather than a band-pass filter. Amplified resonance has been demonstrated empirically for the interaction between I_{NaP} and I_H in somatosensory neocortical neurons from rats¹², and again for I_{NaP} and a slowly activating K⁺ current at depolarized potentials in neurons from the frontal cortex of guinea pigs¹⁹.

When amplifying currents are of sufficient strength, they are capable of coupling resonance to self-sustained oscillations of the membrane potential. This can be shown theoretically using simulation models but has also been demonstrated empirically by Gutfreund

*et al.*¹⁹(see Box 2). In such systems, two distinct currents interact to produce emergent phenomena: amplified resonances or spontaneous oscillations, whose frequency is set by one partner and whose strength is set by the other.

The oscillations and resonance caused by I_T in olivary and thalamic neurons can now be understood in the framework of resonant and amplifier currents. In brief, I_T is a special case where the resonant and amplifying mechanisms have been packaged together in the same current (Fig. 3c). The inactivation process of I_T meets all the requirements for producing resonance, whereas its fast activation mechanism acts as an amplifier. The resulting amplified resonance or spontaneous oscillations occur at voltages that are centered on the region of overlap of the steady state activation and inactivation curves (that is, the region of the 'window' current²²). The frequency is determined by the kinetics of I_T inactivation.

Concluding remarks

There are many different ways to construct a resonance or frequency preference in neurons. Despite the differences, however, an underlying theme emerges that allows a simple classification of the oscillatory characteristics of neurons. To summarize, there are three classes of frequency-dependent mechanism in central neurons: (1) solitary resonances caused by unaided resonant currents; (2) amplified resonances that arise from the interaction of resonant and amplifying mechanisms; and (3) spontaneous oscillations caused when a resonant current interacts so strongly with an amplifying current that the resting membrane potential becomes destabilized. Only in this last class is the frequency preference of the neuron overtly displayed as a pacemaker oscillation. In the first two classes the frequency preference of the neuron is latent and revealed only in the presence of inputs.

Given the large diversity of voltage-operated channels available, it is likely that every neuron in the brain has a resonance under some set of conditions and within some range of membrane voltages. A question therefore arises: are resonances used by neurons or are they simply epiphenomena?

A broad answer to this question is that, in nature, epiphenomena seldom remain epiphenomena for long; they are the raw material for evolutionary advances. It would be surprising to find that the brain has not found a use for a set of mechanisms capable of tuning neurons to specific frequencies, particularly in light of the prevalence of robust brain rhythms. On a more-specific level, it is obvious there are circumstances where strongly amplified resonances are used to coordinate the emergent pattern of network activity around a preferred frequency. This is the case in the inferior olive and it might also apply to the thalamic participation in delta- and spindle-wave generation^{23,24}. In other brain regions, functions for the subthreshold oscillations that are observed have not yet been found. However, this research is still in its infancy. Finally, for the weaker resonances, it can be argued that the widespread possession of a resonance of whatever strength aids neurons in the integration of their inputs. In effect, the establishment of even a weak resonance makes a neuron a good listener for activity within a specialized frequency band. A host of good listeners, mutually connected, should tune networks to operate in frequency ranges of special biological meaning.

Box 2. From resonance, to oscillation and back via phase-plane analysis

As in the case of resonance, spontaneous oscillations in neurons arise from an interplay of voltage-dependent conductances^{a,b}, where they might have important roles in the timing and integration of neuronal inputs and outputs^{c,d,e}. Moreover, resonance and spontaneous oscillations can coexist in the same system. A simple model, examined with the aid of tools developed for the branch of mathematical analysis known as dynamical systems theory, demonstrates that resonance and spontaneous oscillations are two aspects of the same basic phenomenon of frequency preference.

A mathematical model of an isopotential neuron with non-inactivating K⁺ and Na⁺ conductances (g_K and g_{Na} , respectively) is constructed according to the system of differential equations shown below. To simplify matters, a reduced system of parameters governing the kinetic and voltage behaviours of these conductances has been used. The Na⁺ conductance, for example, is assumed to activate instantaneously, and the maximal conductances of both the voltage-operated conductances are normalized by the amount of passive leak conductance. Given such a system, one can ask whether different combinations of the parameters result in oscillations or stable behaviours. The results of such a stability analysis (found by integrating the equations forward in time for each parameter set or using an analytical equation) are encoded in a stability diagram such as that shown in Fig 1a. It can be seen that specific combinations of g_K and g_{Na} values result in a stable resting potential (blue), whereas others result in destabilization of the resting potential and the consequent appearance of spontaneous oscillations (red).

$$\frac{dv}{dt} = -[v - v_{leak}] - g_{Na}(v)[v - v_{Na}] - g_K n [v - v_K] \quad (1)$$

$$\frac{dn}{dt} = \frac{n - n_\infty(v)}{\tau_K} \quad (2)$$

A closer look at the behaviour of the system when it is in the blue region in Fig. 1 shows that, although there are no spontaneous oscillations, the system nonetheless retains a disposition towards oscillation. This is seen by viewing so-called phase-plane diagrams of the system. For any combination of parameters, the phase-plane portrait shows the joint evolution of two or more dynamic variables of the system following a perturbation. In this case, the variables are the instantaneous values of the membrane voltage (v) and activation level of the K⁺ conductance (n). The arrowed lines in Fig. 1b represent trajectories or orbits the system might follow if the values of the variables were suddenly displaced and then released. The two phase-plane portraits on the left, which correspond to the parameter com-

binations at positions 1 and 2 in the stability diagram at the top, both show the system eventually approaching a stable point (the resting potential) after a perturbation. The spiral nature of these trajectories reveals that the return to resting potential is oscillatory in these systems. The more-pronounced spirals in the phase-plane portrait in the middle panel indicate that the system is strongly oscillatory owing to the interaction of the resonant conductance (g_K), and the amplifying conductance (g_{Na}) whose value is high relative to that of the system in the portrait on the left. Thus, even when the system is in the stable blue region in the stability diagram, the model neuron can be oscillatory to differing degrees. The intrinsic tendency to oscillate is revealed as damped oscillations in the response to inputs such as the modeled synaptic-like current inputs shown below each diagram. Equivalently, if these stable systems are probed with oscillatory inputs, a resonance is observed.

If the value of amplifying (g_{Na}) conductance is raised more, the system enters the red area of the stability diagram, the stability of the resting potential is lost, and any perturbation of the system variables eventually results in the system entering an orbit around a so-called limit cycle. The limit cycle, which corresponds to a spontaneous, self-sustained oscillation, is seen in the rightmost phase-plane diagram. The time-domain trace below the diagram shows that the oscillation has about the same frequency as the damped oscillations in the stable systems. Moreover, an oscillatory current input to this spontaneously active system will reveal a resonance near the frequency of the oscillation. Thus, damped and spontaneous oscillations are seen as arising from a single fundamental mechanism involving interactions between voltage- and time-dependent conductances. As resonance measurements are capable of probing such interactions independent of whether the system lies in the stable or unstable regions of the stability diagram (Fig 1a), they provide the most convenient way of investigating the frequency preferences of neurons on a common basis.

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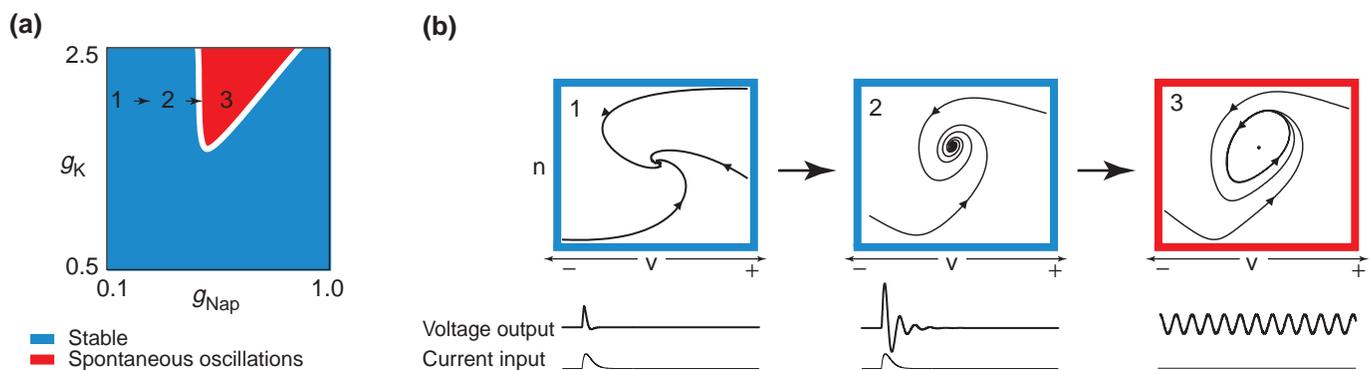


Fig. 1. Theoretical analysis of a resonant model neuron. (a) Stability diagram showing combinations of resonant (g_K) and amplifying (g_{NaP}) maximal conductance values where the system has a stable resting potential (blue) or exhibits spontaneous oscillations (red). (b) Phase-plane diagrams showing details of the system response at the three positions indicated by the numbers in the stability diagram at top. These diagrams show how a resonant system evolves continuously into a spontaneously oscillatory system as the amplifying conductance is increased. The frequency of the oscillations of resonance is set by the properties of the resonant conductance.

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Calcium signaling in the ER: its role in neuronal plasticity and neurodegenerative disorders

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Endoplasmic reticulum (ER) is a multifaceted organelle that regulates protein synthesis and trafficking, cellular responses to stress, and intracellular Ca^{2+} levels. In neurons, it is distributed between the cellular compartments that regulate plasticity and survival, which include axons, dendrites, growth cones and synaptic terminals. Intriguing communication networks between ER, mitochondria and plasma membrane are being revealed that provide mechanisms for the precise regulation of temporal and spatial aspects of Ca^{2+} signaling. Alterations in Ca^{2+} homeostasis in ER contribute to neuronal apoptosis and excitotoxicity, and are being linked to the pathogenesis of several different neurodegenerative disorders, including Alzheimer's disease and stroke.

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ENDOPLASMIC RETICULUM (ER) is widely distributed within neurons, being present in dendrites and dendritic spines, axons and presynaptic nerve terminals, and in growth cones (Fig. 1)^{1–5}. It is highly motile, rapidly extending into and retracting from distal regions of growth cones⁵, and congregating in stack-like structures within dendrites in response to stimulation of metabotropic glutamate receptors⁶. Microtubules and actin filaments appear to have key roles in controlling ER motility, as well as in its structure and function^{7,8}. ER is continuous with the outer nuclear membrane and is often associated intimately with plasma membrane and mitochondria, which suggests functional coupling be-

tween these structures⁹. It is classically divided into two subtypes: 'rough' ER, which contains ribosomes and is responsible for protein synthesis, and 'smooth' ER, which can serve a particularly important role in Ca^{2+} signaling. Although smooth and rough ER coexist in neuronal cell bodies and proximal regions of axons and dendrites, the specialized endings of neurites (growth cones, axon terminals and dendritic spines) contain mainly smooth ER. Emerging evidence suggests that, by controlling levels of cytoplasmic free Ca^{2+} locally in growth cones and synaptic compartments, ER regulates functional and structural changes in nerve cell circuits in both the developing and adult nervous systems.