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.

Bruce Hutcheon is at the Institute for Biological Science, National Research Council of Canada, Ottawa, Canada E1A 0B8, and Yosef Yarom is at the Department of Neuroscience, and the Center for Neurocomputation, Hebrew University, Jerusalem, Israel 91904.

56 Pisu, P. et al. (1997) Brain Res. 754, 163–170
61 Ciani, L. et al. (1996) Inhibition of free radical production or free radical scavenging protects from the excitotoxic cell death mediated by glutamate in cultures of cerebellar granule cells. Brain Res. 728, 1–6
66 Majewska, M.D. et al. (1998) Regulation of the NMDA receptor by redox phenomena: inhibitory role of ascorbate. Brain Res. 537, 528–552
69 Greenough, W.C. (1987) The role of ascorbic acid in the biosynthesis of the neuroendocrine peptides u-MSH and TRH. Brain Res. 414, 311–318

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 brain. However, the mechanisms that bind rhythms into these rhythmic 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 bands. A different explanation states that network rhythmicity arises via the coupling of oscillatory sub-units, each of which possesses an intrinsically determined frequency preference. These two explanations are not mutually exclusive network connectivity could reinforce the patterns of excitation produced by coupled
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 manner. Resonance is a property of the impedance: 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). 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 circuits, a resistor connected to ground (see Fig. Ia). 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 to the resistance.

A slightly more-sophisticated circuit comprises a resistor and capacitor connected in parallel (Fig. Ib). This is a common model for the passive electrical properties of an individual 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. Ic). A resonant peak appears so that instead of acting in the same way as a low-pass filter, the system responds like a band-pass. 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. Id). 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.

**Box 1. Hunting resonance in circuits and cells**

![Input current Circuit Output voltage Impedance](image)

**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.

---

**Reference**

Oscillations in these neurons are partly intrinsic and partly caused by electrical coupling with cated peak centered on the top of the resonance is due to the spontaneous oscillations). The Ca2
neuron (right) reveals a resonance at 4 Hz. The impedance of this neuron shows that it has a stable resting potential (left). The impedance profile of the same 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 cells, hair cells of the inner ear, and various peripheral and central 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 inputs10,11. These oscillations require the presence of the low-voltage activated Ca2 current (iL). 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 iL (Ref. 13). In thalamic neurons, a similar mechanism involving iL is responsible for a resonance near the same frequencies14,15.

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 (iH) (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 TTX (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 inhibitory neurons of the neocortex might have some involvement with higher-frequency rhythms that appear in the cortex during cognition.

**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 ion-potential 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_NaP (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.

Resonance is formed by the interaction of active and passive properties in a neuron. The properties of three models that have passive properties only (part a), passive properties plus a resonant current, I_K (part b), and passive properties plus 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. 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 1/2πτm where τm is the time constant for activation of I_K. On the other hand, the passive properties of the membrane (gray line) dominate the impedance of frequencies above 1/2πτm where τm 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
All these currents (Fig. 3) are the persistent Na\(^+\) current, \(I_{\text{NaP}}\), the current that flows through NMDA-receptor channels, \(I_{\text{NMDA}}\), and the dihydropyridine-sensitive high-threshold Ca\(^{2+}\) current, \(I_{\text{CaP}}\).

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 \(I_{\text{NaP}}\) and \(I_{\text{Ca}}\) in somatosensory neocortical neurons from rats\(^1\), and again for \(I_{\text{Ca}}\) and a slowly activating K\(^+\) current at depolarized potentials in neurons from the frontal cortex of guinea pigs\(^2\).

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 Gutfr...
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\(^a\), where they might have important roles in the timing and integration of neuronal inputs and outputs\(^b\). 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 \(g_{Na}^p\) 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 Ia.

It can be seen that specific combinations of \(g_K\) and \(g_{Na}^p\) result in a stable resting potential (blue), whereas others result in destabilization of the resting potential and the consequent appearance of spontaneous oscillations (red):

\[
\frac{d}{dt}v = -\left[(0.1v + 1.2) - g_K(v - v_K) - g_{Na}^p(v - v_{Na})\right]
\]

\[
\frac{d}{dt}g_K = 0.01v - g_K(v - v_K)
\]

A closer look at the behaviour of the system when it is in the blue region in Fig I 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 Ib 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 combinations 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 \((g_{Na}^p)\) 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 \((g_{Na}^p)\) 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 Ia), they provide the most convenient way of investigating the frequency preferences of neurons on a common basis.

References


![Fig. 1. Theoretical analysis of a resonant model neuron. (a) Stability diagram showing combinations of resonant \((g_K)\) and amplifying \((g_{Na}^p)\) 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.](image-url)
Calcium signaling in the ER: its role in neuronal plasticity and neurodegenerative disorders

Mark P. Mattson, Frank M. LaFerla, Sic L. Chan, Malcolm A. Leisring, P. Nickolas Shepel and Jonathan D. Geiger

Endoplasmic reticulum (ER) is a multifaceted organelle that regulates protein synthesis and trafficking, cellular responses to stress, and intracellular Ca\textsuperscript{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\textsuperscript{2+} signaling. Alterations in Ca\textsuperscript{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.