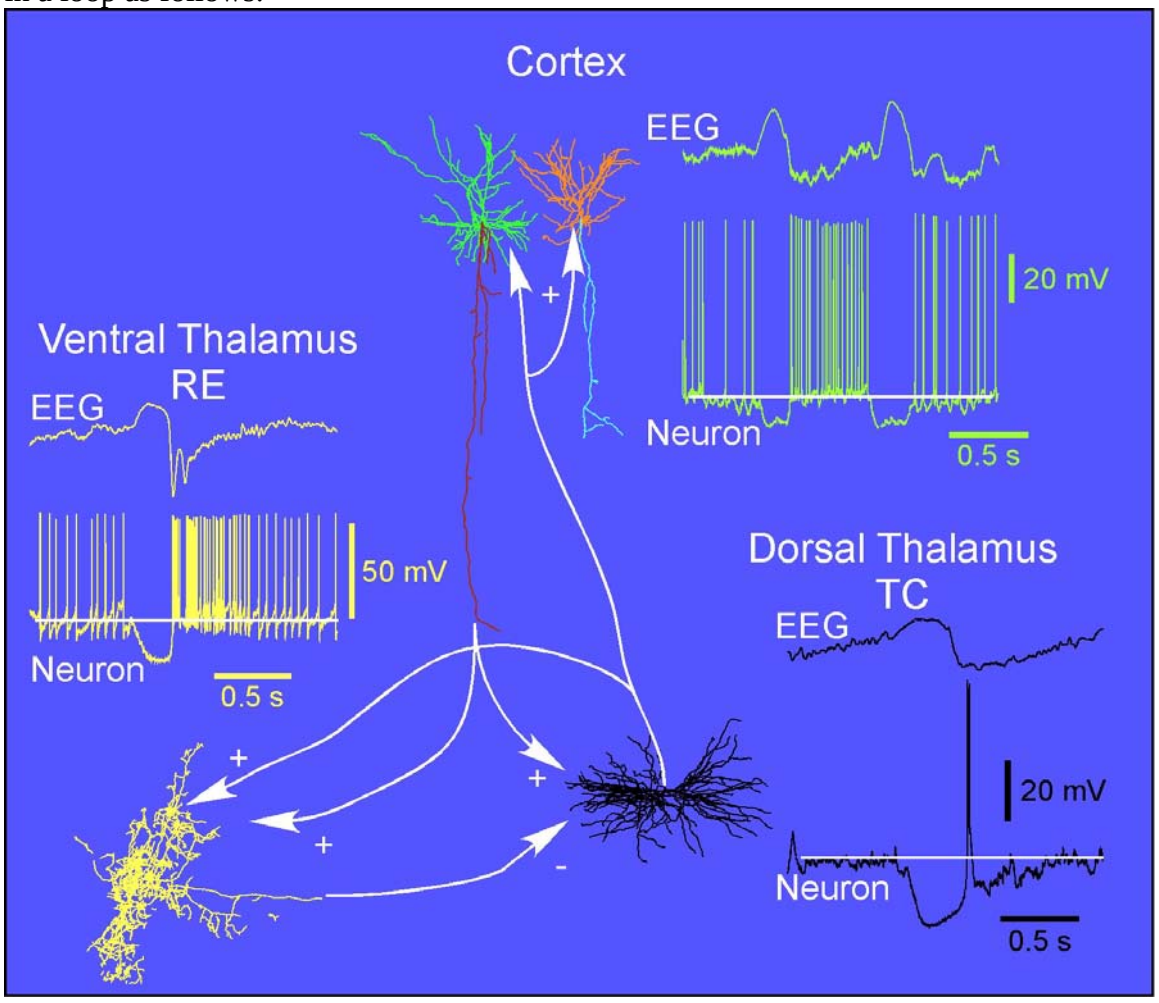
Three-time scale models of neurons and subthreshold oscillations

Biological neurons exhibit a wide range of ionic conductances in their soma and dendrites. These different currents are responsible for action potential generation and may also lead to complex dynamics including bursting, periodic oscillations, etc. Of a particular interest are Ca2+ conductance based on T-type Ca2+ channels, also called low-threshold Ca2+ current, and hyperpolarization-activated cation current, Ih. These channels are common across thalamic and cortical neurons and represent one of the well known mechanisms of self-sustained burst generation. In this chapter we will discuss kinetics of these currents and their role in periodic oscillations. We further will see examples of biological neurons expressing these currents.

Thalamocortical system

The thalamocortical (TC) network is a site of generation of different types of oscillatory activities with distinct mechanisms. The general architecture of TC network is organized in a loop as follows:



It includes: (1) two major classes of thalamic neurons – excitatory thalamicortical (TC) cells and inhibitory thalamic reticular (RE) neurons; and (2) two major cell types in the

neocortex – excitatory principal neurons (usually pyramidal cells) and inhibitory interneurons.

Oscillatory activity is an emerging property of the thalamocortical system. The various oscillatory rhythms generated in the thalamocortical system are mediated by two types of mechanisms:

- **intrinsic** mechanisms, which depend on the interplay between specific intrinsic currents.
- **extrinsic** or network mechanisms, which require the interaction of excitatory and inhibitory neurons within a population.

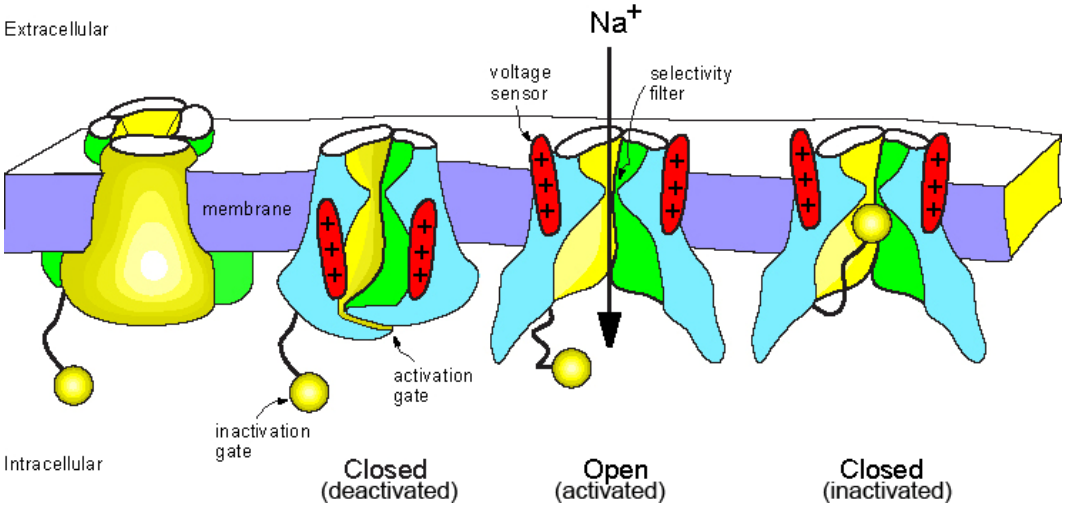
Intrinsic and network mechanisms can work alone (e.g., thalamic delta oscillations depend on the intrinsic properties of thalamic relay cells, cortical slow oscillation depends on network properties) or in combination (e.g., spindles depend on the interaction between thalamic relay and reticular neurons as well as on their intrinsic properties). The patterns and the dominant frequencies of thalamocortical oscillations depend on the functional state of the brain (e.g., sleep vs. wake).

Ionic channels.

Each ionic current is represented by particular type of ionic channels controlled by gating particles. These gating particles (gates) control the state of the channel: closed or open. While dynamics of the individual channels is stochastic, the large number of channels allows describing them using simple Hodgkin-Huxley formalism:

$$I = g_{\max} m^M h^N (V - E_{rev})$$

where g_{max} is a maximal conductance, M is the number of activation gates and N is the number of inactivation gates per channel, E_{rev} is reversal potential, $0 \le m(t) \le 1$ and $0 \le h(t) \le 1$ are activation and inactivation variables.



Activation and inactivation gates define the state of ionic channel (modified from Armstrong and Hille, 1998; see also Izhikevich, 2006).

All ionic currents can be divided into 2 large groups: *voltage-dependent* and *ion-dependent*. The first group includes currents those activation and inactivation is controlled by membrane voltage. Some of the examples include transient Na+ and delayed rectifier K+ currents involved in spike generation. The second group includes currents those activation properties are controlled by specific ions. Well known examples are Ca2+ activated and Na+ activated K+ currents. These currents become active when the internal concentration of Ca2+ ions is high enough. There are also currents that are both voltage- and ion-dependent.

For voltage-dependent currents, the dynamics of the activation and inactivation variables is controlled by membrane voltage and may be described by the following first-order linear differential equations:

$$\frac{dm}{dt} = (m_\infty(V) - m)/\tau_m(V) \quad , \qquad \frac{dh}{dt} = (h_\infty(V) - h)/\tau_h(V) \, ,$$

where V is membrane potential, $m_\infty(V)$ and $h_\infty(V)$ are steady-state activation and inactivation functions, respectably and $\tau_m(V), \tau_h(V)$ are time constants of activation and inactivation, respectably. It is easy to see that $m_\infty(V)$ and $h_\infty(V)$ represent stable solutions of these ODEs. Indeed, for example, *dm/dt> 0* and therefore *m(t)* increases if $m < m_\infty(V)$. So, *m(t)* and *h(t)* always tend to reach their equilibriums $m_\infty(V)$ and $h_\infty(V)$, respectably. Since this is linear ODE we can solve them analytically and we will get:

$$\begin{aligned} &m(t) = m_\infty(V) - [m_\infty(V) - m_0]\exp(-t/\tau_m(V)) \\ &m(t=0) = m_0, \\ &m(t \to \infty) = m_\infty(V) \end{aligned}$$

These functions $m_\infty(V)$ and $h_\infty(V)$, $\tau_m(V), \tau_h(V)$ can be measured experimentally in voltage-clamp experiments. This is usually 2 step procedure: first, experimenter should block (ideally) all other channels except the one that will be measured. It can be achieved by combination of different drags and by choice of extracellular solution. Second, the kinetics properties are measured in voltage-clump experiments by applying depolarizing and hyperpolarizing current steps.

Basic Terminology

To understand effect of a given current for neuron dynamics, it is important to remember that the activation and inactivation variables $m_\infty(V)$ and $h_\infty(V)$ define 4 different possible states of this current:

Activated current	m->1
Deactivated current	m->0
Inactivated inactivated	h->0
Deinactivated deinactivated	h->1

To be different from zero, current should be **activated** (m->1) and **deinactivated** (h->1) at the same time. Strong hyperpolarization typically leads to **deactivation** (m=0) and **deinactivation** (h=1). Strong depolarization typically leads to **activation** (m=1) and **inactivation** (h=0). Usually, activation has much faster time constant than inactivation. So, for transient currents (including both activation and inactivation gates), rapid depolarization leads to nonzero current flow (fast activation) followed by current decay (slow inactivation).

Kinetics of low-threshold Ca2+ current (T-current).

T-current is inward current and it depolarizes the cell. It is controlled by voltage, however, it brings Ca2+ ions inside the cell, so this is why it is called "**Ca2+ current**". As we will see, it is activated at relatively hyperpolarized levels of membrane potential (-60 mV or less), this is why it is called "**low-threshold".** This current exhibits both activation and inactivation properties that are voltage dependent. Using Hodgkin-Huxley formalism this current can be represented in the following form:

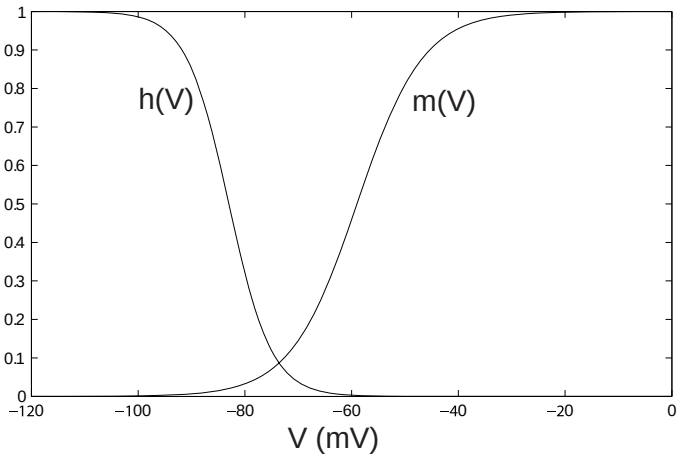
$$I_T = g_{\max} m^2 h \ (V - E_{Ca})$$

where g_{max} is a maximal conductance, E_{Ca} is Ca^{2+} reversal potential, $m(t)$ and $h(t)$ are activation and inactivation variables. For thalamocortical neurons, for example, the following expressions have been measured in slice experiments (Huguenard and McCormick 1992):

$$m_\infty(V) = 1 / (1 + \exp(-(V+59)/6.2)) \qquad h_\infty(V) = 1 / (1 + \exp((V+83)/4))$$

$$\tau_m(V) = (1/(\exp(-(V+131.6)/16.7) + \exp((V+16.8)/18.2)) + 0.612) / 4.57$$

$$\tau_h(V) = (30.8 + (211.4 + \exp((V + 115.2)/5))/(1 + \exp((V + 86)/3.2))) / 3.74$$

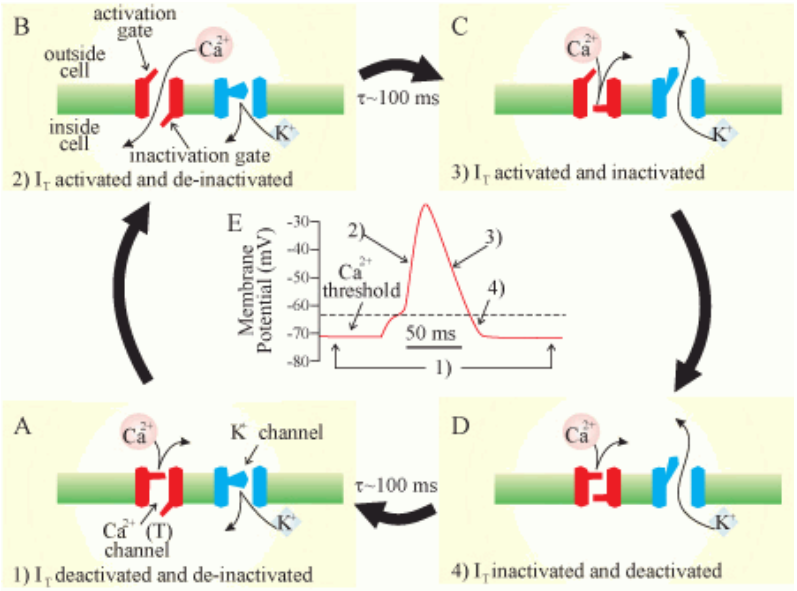


Steady-state activation and inactivation functions for T-current in thalamocortical neurons.

The plot above shows voltage dependence of the activation and inactivation variables. We can see that at relatively depolarized membrane potentials (such as above -60mV), the T-current is mainly inactivated (inactivation gates are closed, h~0) and makes very little contribution to the neuron dynamics. Hyperpolarization below -75mV deinactivates the current (h->1), but also deactivates it (activation gates are now closed, m~0), so it's still I_T~0. There is a small window of membrane potentials where both activation and inactivation variables are positive. However, both *m* and *h* are close to zero within this window that makes $I_T \sim 0$. So, how T-current can become sufficient to produce any significant effect on the membrane potential? The answer depends on the time constants of activation and inactivation. For T-current the inactivation is much slower than activation, especially at relatively hyperpolarized membrane potentials. Therefore, rapid depolarization from hyperpolarized state quickly activates the current (open activation gates, m->1). Since inactivation has a slower time constant, inactivation gates remain open (h~1) and the current produces depolarizing action to the membrane potential.

Low-threshold Ca2+ spike

Low-threshold Ca2+ current is responsible for so called *low-threshold Ca2+ spike (LTS)* commonly observed in thalamic neurons during sleep states. To understand mechanisms of its generation, let's assume that the neuron is hold at hyperpolarized potential (let's say, below -70 mV). At such negative resting potentials T-channels are deactivated (activation gates are closed) (panel A below, red). Rapid depolarization leads to opening T-channels and Ca2+ entry depolarizing the neurons. Both activation and inactivation gates remain open (panel B, red) that allows Ca2+ influx. It takes at least 100 msec to deinactivate T-channels (close inactivation gates) (panel C, red). During that time the neurons is depolarized above the threshold of Na+ spike generation, so LTS is usually crowned by a sequence of fast action potentials. Activation of various K+ conductances (panel C, blue) repolarize the membrane leading to the new state when T-channels are both deactivated and inactivated (both gates are closed) (panel D below, red). After few more hundreds msec the T-channels become deinactivated again making cell ready for another LTS.



Low-threshold spike generation mediated by T-channels (modified from Sherman and Guillery, 2006)

Kinetics of hyperpolarization-activated cation current, Ih.

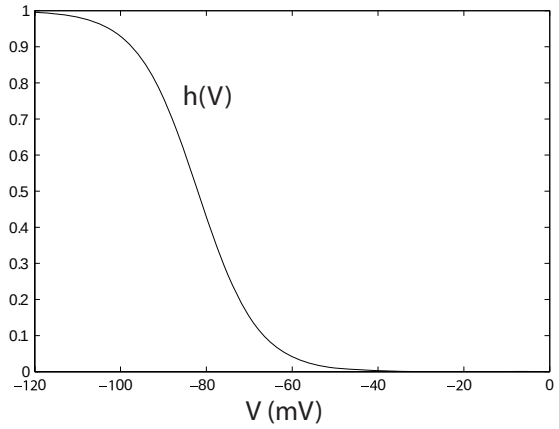
A variety of neurons have a class of cation channels that are activated slowly by hyperpolarization. Such currents are generally called "hyperpolarization-activated" currents. In the frameworks of Hodgkin-Huxley formalism these currents can be viewed as a "persistent" current that is always activated (m=1) and which kinetics is controlled by inactivation variable alone:

$$I_h = g_{\max} h (V - E_{rev}) .$$

Based on this, we should say that Ih is *deinactivated* at hyperpolarized potentials but more common terminology is that Ih is *activated* by hyperpolarization and we will follow it in this chapter. Thus, Ih increases (activates) at hyperpolarized potentials (h->1) and disappears (deactivates) upon depolarization (h~0). Ih channels are permeable to both Na+ and K+ ions and its reversal potential defined by Nernst equation is about -40 mV. Since the resting potential is usually lower than -40 mV, the Ih current depolarizes the cell membrane potential from rest. Ih has relatively slow kinetics. The following set of equations give an example of Ih kinetics in neocortical neurons:

$$\frac{dh}{dt} = (h_\infty(V) - h) / \tau_h(V) \ , \quad h_\infty(V) = 1 / (1 + \exp((V+82)/7)) \ , \quad \tau = 38$$

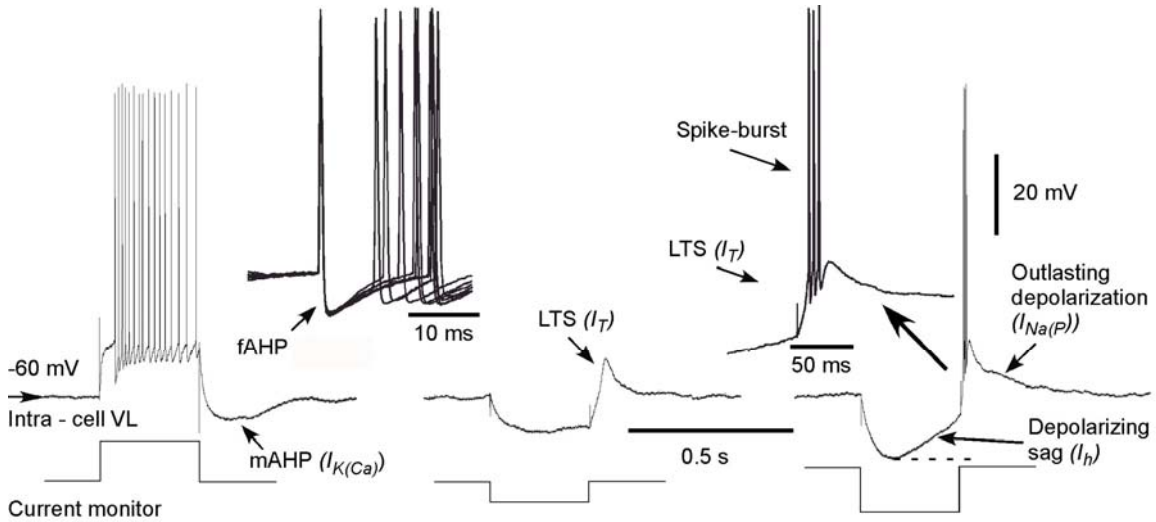
As we can see, for this particular type of Ih current, the time constant is voltage-independent. The steady-state "activation" calculated based on the eqs shown above is described by the curve:



Steady-state "activation" kinetics of hyperpolarization activated Ih current in cortical cells.

So, Ih current becomes negligible for membrane potentials more depolarized than ~ -60 mV. However, it has substantial depolarizing effect below -60 mV and especially below -70 mV. A very typical "signature" of this current is *depolarizing sag* triggered by hyperpolarizing current pulse (see fig below).

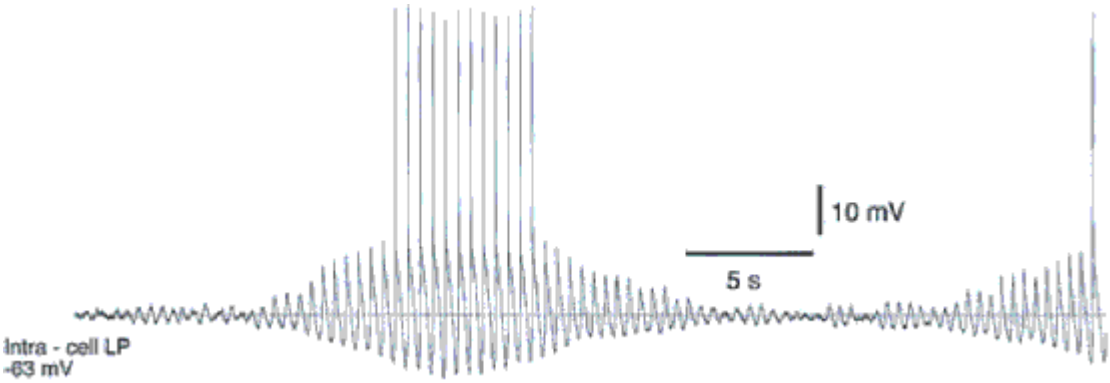
Properties of thalamocortical neurons in vivo



Response properties of thalamocortical neuron in vivo. Barbiturate anesthesia. The membrane potential for this neuron was -60 mV. Depolarizing current pulse elicited tonic firing (left). At the end of small amplitude hyperpolarizing current pulse the neuron generated a low-threshold spike (LTS) in isolation (middle). During large amplitude hyperpolarizing current pulse (right) depolarizing sag was obvious. At the end of the current pulse the neuron generated an LTS accompanied with spike-burst. (modified from Timofeev and Bazhenov, 2005).

Thalamocortical **(**TC) neurons posses a large set of intrinsic currents that enable them to contribute to the various oscillatory activities. The electrophysiological identification of a TC neuron is shown in the figure below. Usually, a small depolarization of TC neuron with intracellular current pulse produces passive response (not shown). Progressive increase in the intensity of the depolarizing current leads to the generation of action potentials followed by increase in their discharge frequency (below, left). This firing mode of TC neurons is called *tonic*. Each fast spike produced by TC neuron is followed by an afterhyperpolarizing potential (AHP). Application of low-amplitude hyperpolarizing current pulse results in passive responses (not shown). An increase in the pulse amplitude hyperpolarizes TC neuron to the level of deinactivation of T-current. At the offset of the hyperpolarizing current pulse, TC neuron generates a depolarizing response, LTS (below, middle) that we discussed earlier in this chapter. An increase in the amplitude of the hyperpolarizing current pulse activates Ih current. This produces the depolarizing sag and increases rebound excitation that leads to a burst of Na^+ spikes (up to eight spikes in the experiment shown in the figure, right). This type of response is called *bursting*. Thus, both excitatory and inhibitory inputs are able to induce firing of TC neurons. Excitatory inputs lead a generation of firing in a tonic firing mode, while LTSs are generated at the end of inhibitory responses and TC neurons fire in the bursting mode.

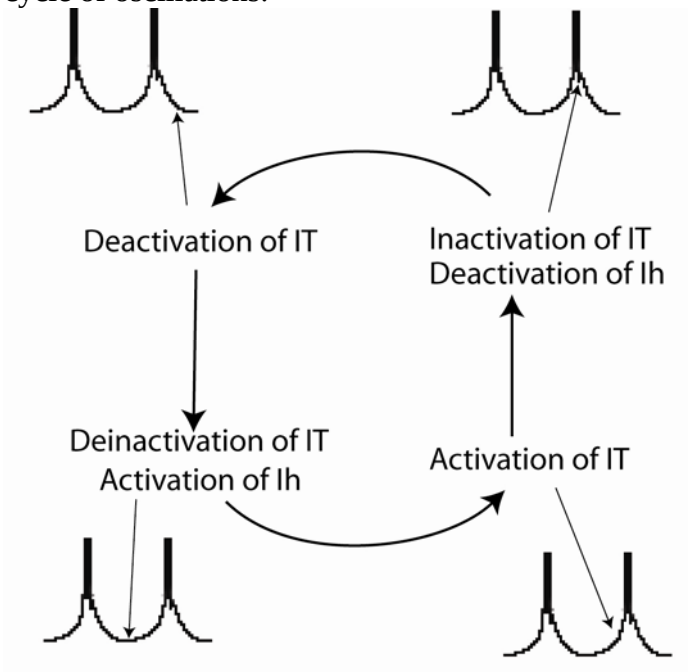
Oscillations mediated by interaction of IT and Ih in thalamocortical neurons

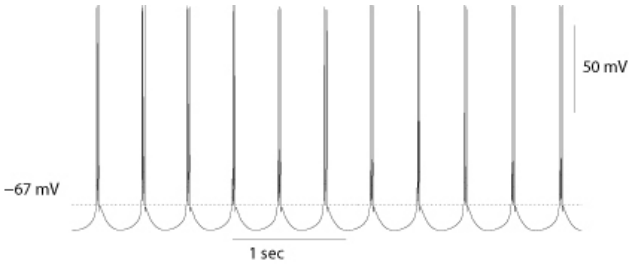


Waxing and waning delta activity (2.2 Hz) in LP thalamo-cortical neuron in decorticated cats (Ketamine-xylazine anesthesia; modified from Timofeev and Bazhenov 2005).

Thalamic delta (1-4 Hz) oscillation is well known example of rhythmic activity generated intrinsically in thalamic relay neurons. These oscillations arise as an interplay of low-threshold Ca^{2+} current (I_T) and hyperpolarization activated cation current (I_h) and may be observed during deep sleep when TC neurons are hyperpolarized sufficiently to deinactivate I_T. As we discussed before, long and deep hyperpolarization removes I_T inactivation and makes possible rebound burst generation triggered by a depolarized input. Hyperpolarization of TC neuron also leads to slow I_h activation that provides this depolarizing input triggering rebound burst. Both I_h and I_T disappear during burst, so membrane potential becomes hyperpolarized again after burst termination. This

afterhyperpolarization leads to deinactivation of IT and activation of Ih, starting next cycle of oscillations:





Self-sustained periodic oscillations in the model of thalamocortical neuron mediated by interaction of intrinsic currents.

Reduced model of delta oscillations

A complete Hodgkin-Huxley type model that is capable to produce oscillations shown in the fig above has to include at least 5 ionic currents (IT, Ih, fast Na+, delayed rectifier K+ and leak current). This will make the total dimensionality of the system D=7. We can design reduced system capable to capture the underlying dynamics of these oscillations.

Let's assume:

1) Fast Na+ and delayed rectifier K+ currents responsible for spike generation can be omitted to study only subthreshold delta oscillations;
2) Activation of IT is very fast and can be approximated as instantaneous
3) Voltage-dependent inactivation time constant of IT can be approximated by constant value.

With these assumptions we can reduce a complete 7-dimensional ODE system to the system of only 3 equations:

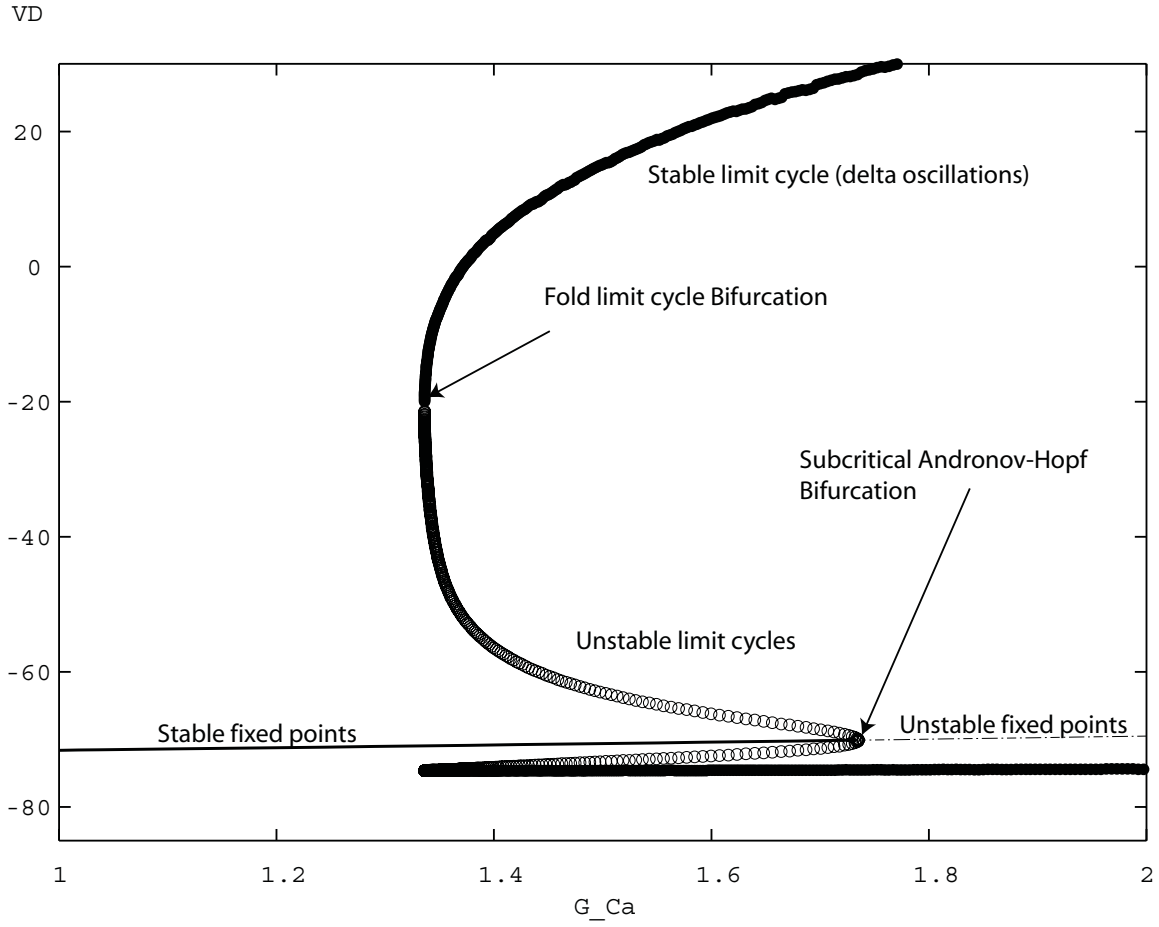
$$C\frac{dV}{dt} = -g_L(V - E_L) - g_{Ih}h_{Ih}(V - E_{Ih}) - g_{Ca}m^2_{Ca\_\infty}h_{Ca}(V - E_{Ca})$$
$$\frac{dh_{Ih}}{dt} = (h_{Ih\_\infty}(V) - h_{Ih})/38$$
$$\frac{dh_{Ca}}{dt} = (h_{Ca\_\infty}(V) - h_{Ca})/38$$

where

$$h_{Ih\_\infty}(V) = 1/(1+\exp((V+82)/7)), \quad h_{Ca\_\infty}(V) = 1/(1+\exp((V+83)/4)),$$
$$m_{Ca\_\infty}(V) = 1/(1+\exp(-(V+59)/6.2))$$

E_L = -80mV, E_{Ih} = -43mV, E_{Ca} = 140mV, g_L, g_{Ih}, g_{Ca} are the maximal conductances of the leak, Ih and IT currents, respectably.

The bifurcation diagram for this system:



Below bifurcation point (g_{Ca}<1.75) the fixed point corresponding to the rest state is stable, so the trajectories from the small vicinity converge to this fixed point (below, left). It becomes unstable above this bifurcation point (g_{Ca}>1.75) and the system approachs the limit cycle corresponding to the delta oscillation (below, right).