Ca2+ currents and bursts of action potentials (Physics 171/271)

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We previously discussed kinetics of low-threshold Ca2+ (T-type) current and its role in burst generation. Depolarization induced by IT may be enhanced by number of depolarization activated currents such as high-threshold Ca2+ current. This current is very common in cortical neurons and may be involved in generation of various oscillatory activities including, for example, paroxysmal oscillations observed during seizures. Since Ca2+ currents allows Ca2+ to enter a neuron, activation of Ca2+ currents is typically followed by activation of Ca2+ dependent K+ current and membrane hyperpolarization – the mechanism commonly involved in burst generation. In this chapter we will review kinetics properties of these currents and will discuss interaction of these currents in burst generation.

High-threshold Ca2+ current

Most Ca2+ channels (with exception of T-type current as we discussed earlier) are activated at membrane potentials positive to about -40mV; these currents are called *high-voltage (or high-threshold) activated* (HVA). High-threshold Ca2+ currents display both activation and inactivation properties:

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

where g_{max} is a maximal conductance, E_{Ca} is Ca^{2+} reversal potential, *m(t)* and *h(t)* are activation and inactivation variables:

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

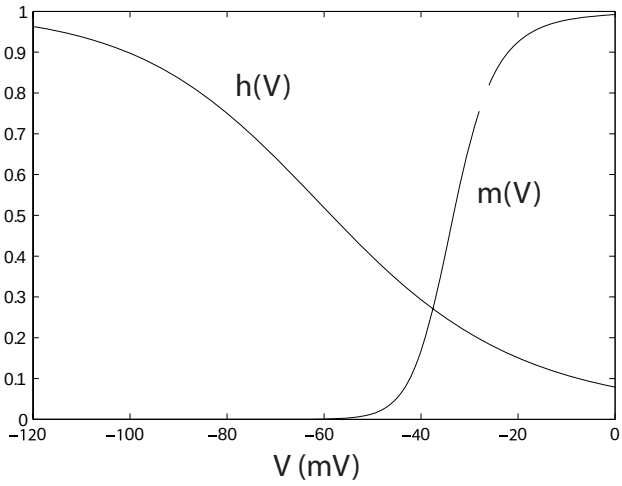
where V is membrane potential, $m_\infty(V)$ and $h_\infty(V)$ are steady-state activation and inactivation functions, respectably and $\tau_m(V), \tau_h(V)$ are time constants of activation and inactivation, respectably. Solving first ODE above will give us:

$$m(t) = m_\infty(V) - [m_\infty(V) - m_0]\exp(-t/\tau_m(V))$$
$$m(t=0) = m_0,$$
$$m(t \to \infty) = m_\infty(V)$$

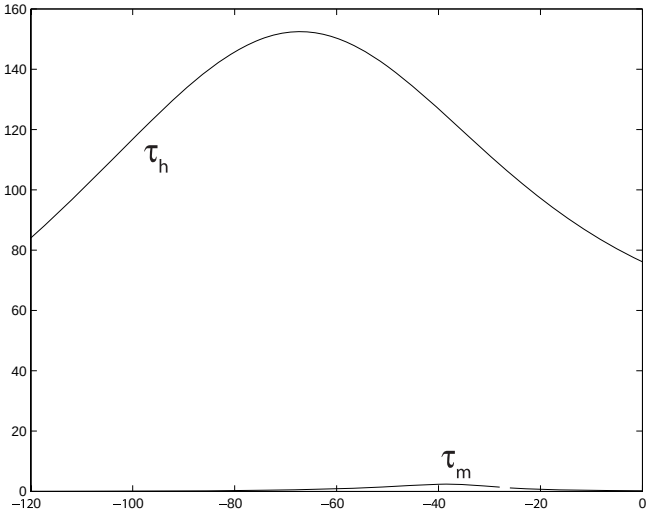
For neocortical neurons, for example, (Mainen and Sejnowski, 1996):

$m_\infty(V)$ = a/(a + b), $\tau_m(V)$ = (1/(a + b))/2.95
a(V) = 0.055(-27 - V)/(exp((-27 - V)/3.8) - 1), b(V) = 0.94exp((-75 - V)/17)

$h_\infty(V)$ = c/(c + d), $\tau_h(V)$ = (1/(c + d))/2.95
c(V) = 0.000457exp((-13 - V)/50); d(V) = 0.0065/(exp((-V - 15)/28) + 1);



Steady-state activation and inactivation properties of high-threshold Ca2+ current. Note shift to the right compare with IT current.



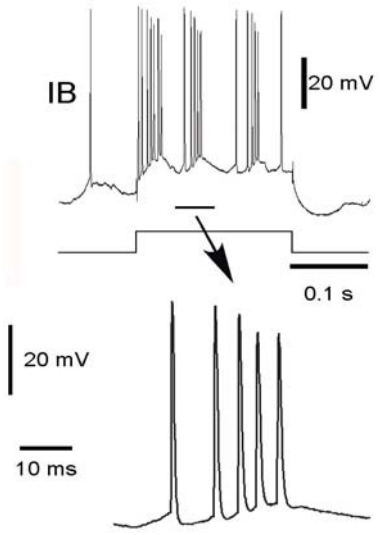
Activation and inactivation time constants of high-threshold Ca2+ current.

The Ca2+ reversal potential strongly depends on the intracellular Ca2+ concentration and can be calculated using Nernst equation:

$$E_{Ca} = (RT / 2F)\ \log[Ca]_o /[Ca]_i ,$$

where R=8.21441 J/mol^{o}K, T=309.15 ^{o}K, F= 96489 C/mol is Faraday constant, $[Ca]_i$ and $[Ca]_o$ are intracellular and extracellular Ca2+ concentrations, respectably. For typical values at rest $[Ca]_i = 2.4\ 10^{-4}$ mM and $[Ca]_o = 2$ mM, then $E_{Ca} = 120$ mV.

Because of its fast activation by depolarization, I_{HVA} current is involved in pattern generation in intrinsically bursting cortical neurons (see fig below). What is also important is that this current allows Ca2+ to enter the cell during depolarization, which may lead to activation of Ca2+ dependent hyperpolarizing currents which then terminate depolarization. This is one of the common mechanisms of burst generation and we will discuss it later in this chapter.



Responses of intrinsically-bursting neurons from area 4 to depolarizing current pulses (0.2 s, 0.8 nA). Bottom plot shows expanded fragment as indicated by horizontal lines and arrows.

Ca2+ dependent K+ channels

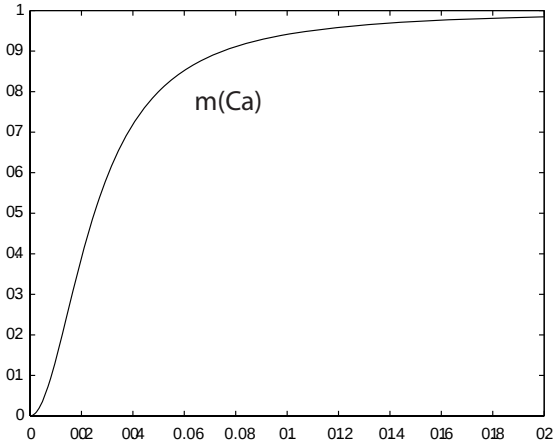
While many current are voltage dependent, there are others that are activation by increase of intracellular concentration of certain type of ions. One very common type of such current is Ca2+ dependent K+ current that is activated by increase in the intracellular concentration of unbounded Ca2+

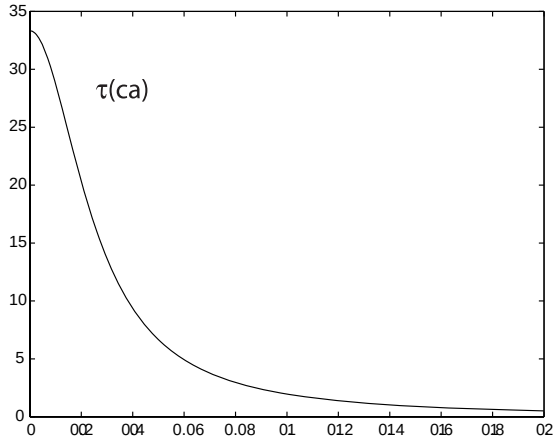
$$I_{KCa} = g_{\max} m^2 (V - E_K),$$

where g_{max} is a maximal conductance, E_K =-95mV is K^+ reversal potential and *m(t)* is activation variable:

$$\frac{dm}{dt} = (m_\infty(Ca) - m)/\tau_m(Ca)$$

Steady-state activation $m_\infty(Ca)$ and time constant $\tau_m(Ca)$ are both Ca2+ dependent:





First order kinetics of channel activation

Channels can not be half-open or half-closed. Then what, for example, does m=0.5 mean? It simply says that half of all the channels is in the open state at each time moment and another half is in the closed state. A large number of channels allows deterministic description of channel dynamics. Still each channel is stochastic and can be described by probability of being in open or closed state. Transitions between open and closed states of IKCa channels can be described by first order kinetics

$$(closed) + 2Ca^{2+} \underset{b}{\overset{a}{\rightleftharpoons}} (open)$$

where *a* and *b* are rate constants (probabilities). This equation simply shows that two Ca2+ ions are required to bind to the closed state of the channel to open it. Transition between open and closed states of the channel is stochastic process; at each time moment there is a fraction of the channels in closed and open states (this is also true for voltage dependent currents). Rate constant *a* defines the probability of the Ca2+ ions bind to the closed state of the channel producing the open state, *b* defines the probability of the open state of the channel switch back to closed state; ratio *b/a* gives the halfway activation concentration. The activation variable *m(t)* represents the fraction of the open channels. If binding two Ca2+ ions is required to open IKCa channels, then *m(t)* can be described by the linear differential equation:

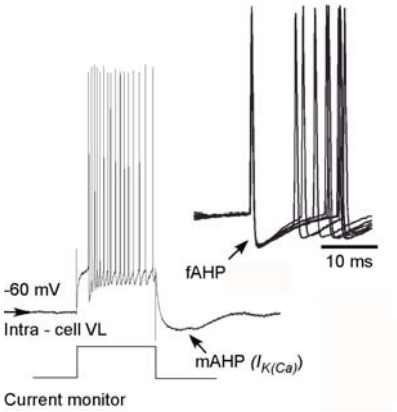
$$\frac{dm}{dt} = a(1-m)[Ca]_i^2 - bm$$

where $[Ca]_i$ is intracellular Ca2+ concentration. This equation is equivalent to

$$\frac{dm}{dt} = (m_\infty(Ca) - m)/\tau_m(Ca)$$

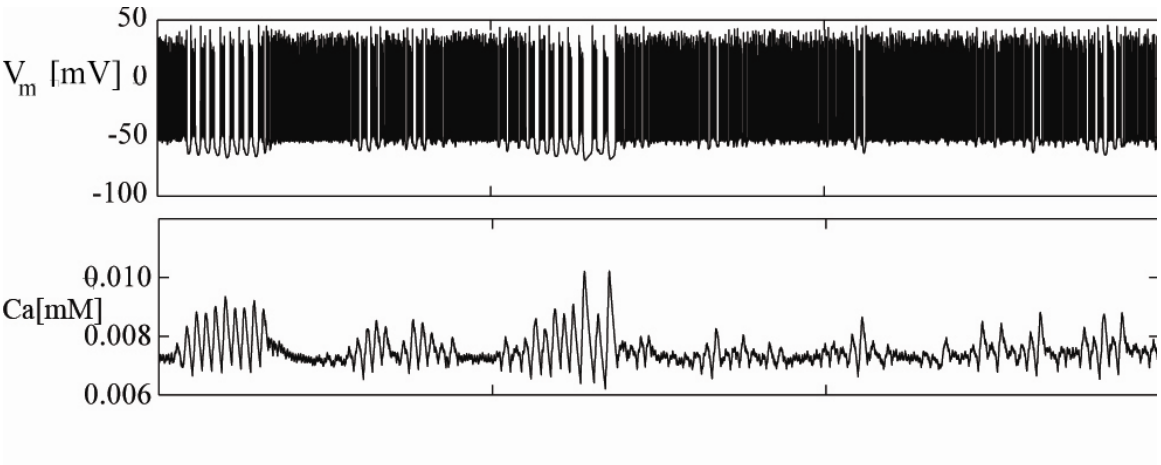
$$m_\infty(Ca) = a[Ca]_i^2/(a[Ca]_i^2 + b), \quad \tau_m(Ca) = (1/(a[Ca]_i^2 + b)).$$

The effect of IKCa is best seen after generation of a sequence of action potentials as prolonged hyperpolarization. This current also contributes significantly to the property of the many neurons (such as regular spiking cortical neurons) to decrease firing frequency during depolarization, a process known as *spike frequency adaptation*.



Intracellular recording from thalamocortical neuron in vivo. The resting membrane potential -60 mV. Depolarizing current pulse elicited tonic firing. Right, each action potential was followed by fast AHP (fAHP). Left, firing frequency decreases during depolarizing pulse. At the end of the current pulse a long-lasting AHP (mAHP) mediated by IKCa was generated. (modified from Timofeev and Bazhenov, 2005).

IKCa is often responsible for burst termination:



The figure above shows result of network simulations including alternating epochs of bursting and fast-spiking activity. Intracellular Ca+ was accumulated during each burst. That activated IKCa and led to the burst termination.

Ca2+ dynamics

To consider effects of Ca2+ dependent currents we have to describe the dynamic change of the intracellular Ca2+ concentration. Several mechanisms control $[Ca]_i$: influx of Ca2+ ions mediated by Ca2+ currents (such as, low- or high-threshold Ca2+ currents), Ca2+ pump, Ca2+ diffusion and Ca2+ buffering.

(1) Ca2+ currents:
Dependence of the intracellular Ca2+ concentration on the Ca2+ currents can be described as following:

$$\frac{d[Ca]_i}{dt} = -I_{Ca} / 2FV_n ,$$

where F = 96489 C/mol is Faraday constant, $[Ca]_i$ is the Ca2+ concentration in the shell just below the membrane and V_n is the volume of the shell. Since $V_n = S\,d$, where S is membrane area and d is shell depth we can rewrite it as:

$$\frac{d[Ca]_i}{dt} = -i_{Ca} / 2Fd ,$$

where i_{Ca} is a current density (I/S) and d is the shell depth.

(2) Ca2+ pump:
The Ca2+ pump can be simply approximated as:

$$\frac{d[Ca]_i}{dt} = ([Ca]_\infty - [Ca]_i)/\tau(V) ,$$

where $[\mathrm{Ca}]_\infty$ is the equilibrium concentration of the pump, $[\mathrm{Ca}]_i$ is the concentration of the Ca2+ in the shell just below the membrane and $\tau(V)$ is the voltage-dependent time constant of the pump.

Combination of these 2 equations gives a simplest model of the intracellular Ca2+ dynamics. The next step to extend the model will be to introduce Ca2+ buffering.

(3) Ca2+ buffering:

Free Ca2+ inside the cell membrane can buffer to various calcium buffers. Since we are interested only in free Ca2+ dynamics (and not in buffer dynamics) we can assume that all the calcium bind to a single binding site on a single buffer. Then we can describe Ca2+ dynamics by first order kinetics in the form:

$$B + Ca^{2+} \underset{b}{\overset{a}{\rightleftarrows}} Ca \cdot B,$$

where forward (*a*) and backward (*b*) are rates of binding reactions. *B* is free buffer and $Ca \cdot B$ is calcium bound to buffer. The sum of free buffer and buffer bound to Ca2+ is constant representing total buffer available:

$$[B] + [Ca \cdot B] = [B]_{total}$$

If we rewrite kinetics eq above as differential equation, we will have:

$$\frac{d[Ca]}{dt} = \frac{dB}{dt} = -a[Ca][B] + b[Ca \cdot B]$$

This equation simply shows that: (1) the rate of Ca2+ concentration change is the same as the rate of buffer concentration change (because free Ca2+ binds to free buffer) and (2) the Ca2+ concentration decreases as a results of binding with rate *a* (-*a*[*Ca*][*B*]) and increases as a result of unbinding with rate *b* (+*b*[*Ca B*]).

Finally the intracellular Ca2+ concentration depends on intracellular Ca2+ diffusion. This diffusion dynamics will be discussed later in the course.

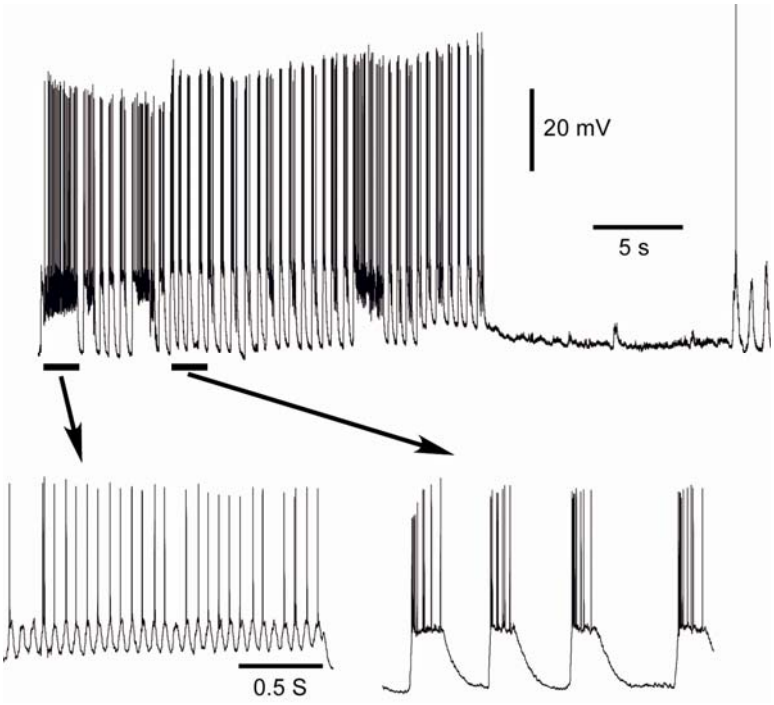
Taking into account all 3 mechanisms (currents, pump and buffering) we will get closed system of ODEs describing Ca2+ dynamics:

$$\frac{d[Ca]_i}{dt} = -I_{Ca} / 2FV_n + ([\mathrm{Ca}]_\infty - [\mathrm{Ca}]_i)/\tau(V) - a[Ca][B] + b[Ca \cdot B]$$

$$\frac{dB}{dt} = -a[Ca][B] + b[Ca \cdot B], \quad [B] + [Ca \cdot B] = [B]_{total}$$

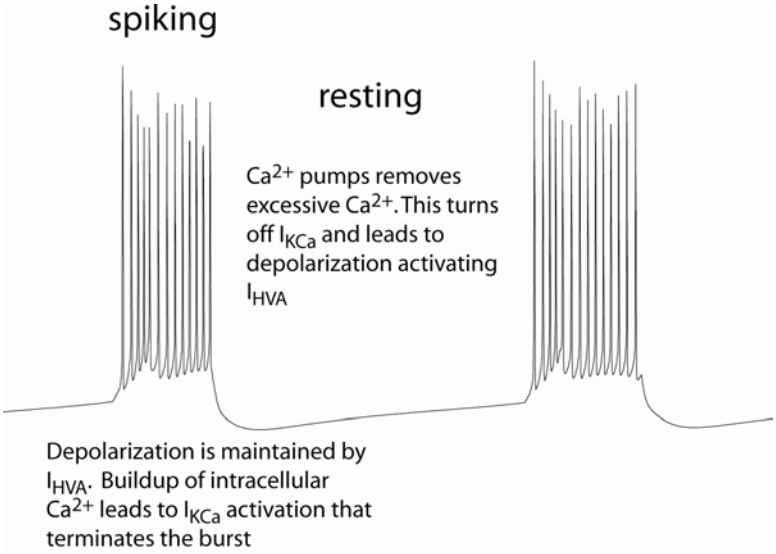
Burst generation

We previously described a mechanism of burst generation in thalamocortical neurons by interaction of low-threshold Ca2+ current and Ih current. Another common mechanism of bursting involve interplay of one or few depolarizing conductances such as high-threshold Ca2+ current with a hyperpolarizing currents such as Ca2+ dependent K+ current. Below is an example of bursting activity recorded in vivo during epileptic seizure.



Tonic spiking (left) and periodic bursting (right) during spike and wave seizure in anesthetized cat in vivo. (modified from Frohlich et al., 2006).

Burst generation mediated by interplay of Ca2+ current (such as I_{HVA}) and IKCa can be described as following (see fig below). Depolarization during burst is maintained by I_{HVA}. Progressive buildup of intracellular Ca2+ concentration mediated by I_{HVA} during depolarizing phase leads to slow IKCa activation that makes the neuron less and less excitable and eventually terminates the burst. During hyperpolarized phase, the I_{HVA} is deactivated and there is no Ca2+ influx to the cell. Slow IKCa deactivation and removal of Ca2+ (by pump) turn IKCa off that leads to depolarization and activation of I_{HVA} thus starting a new burst.



Burst generation in the model of neocortical neuron.

Reduced model of burst generation

The model shown above includes several currents and described by a high-dimensional system of ODEs. However, we can try to reduce the system dimensionality to study bifurcations leading to the bursting activity. Again, let's assume:

1) we can omit the fast dynamics responsible for spike generation. This assumption will allow us to eliminate 3 equations describing fast Na+ and delayed rectified K+ currents
2) we will assume that high-threshold Ca2+ current has instantaneous activation kinetics ($m_{HVA} = m_{HVA\_\infty}(V)$) and no inactivation at all ($h=1$).
3) finally we will assume that Ca2+ dependent K+ current has instantaneous activation kinetics ($m_{KCa} = m_{KCa\_\infty}(Ca^{2+})$)

With these assumptions we will reduce the original high-dimensional system to the systems of only 2 ODEs:

$$C\frac{dV}{dt} = -g_L(V - E_L) - g_{KCa}m^2_{KCa\_\infty}(V - E_K) - g_{HVA}m^2_{HVA\_\infty}(V - E_{Ca}) + I$$

$$\frac{d[Ca]_i}{dt} = -I_{Ca}/2FV_n + ([\mathrm{Ca}]_\infty - [\mathrm{Ca}]_\mathrm{i})/\tau(V) \qquad I_{Ca} = g_{HVA}m^2_{HVA\_\infty}(V - E_{Ca})$$

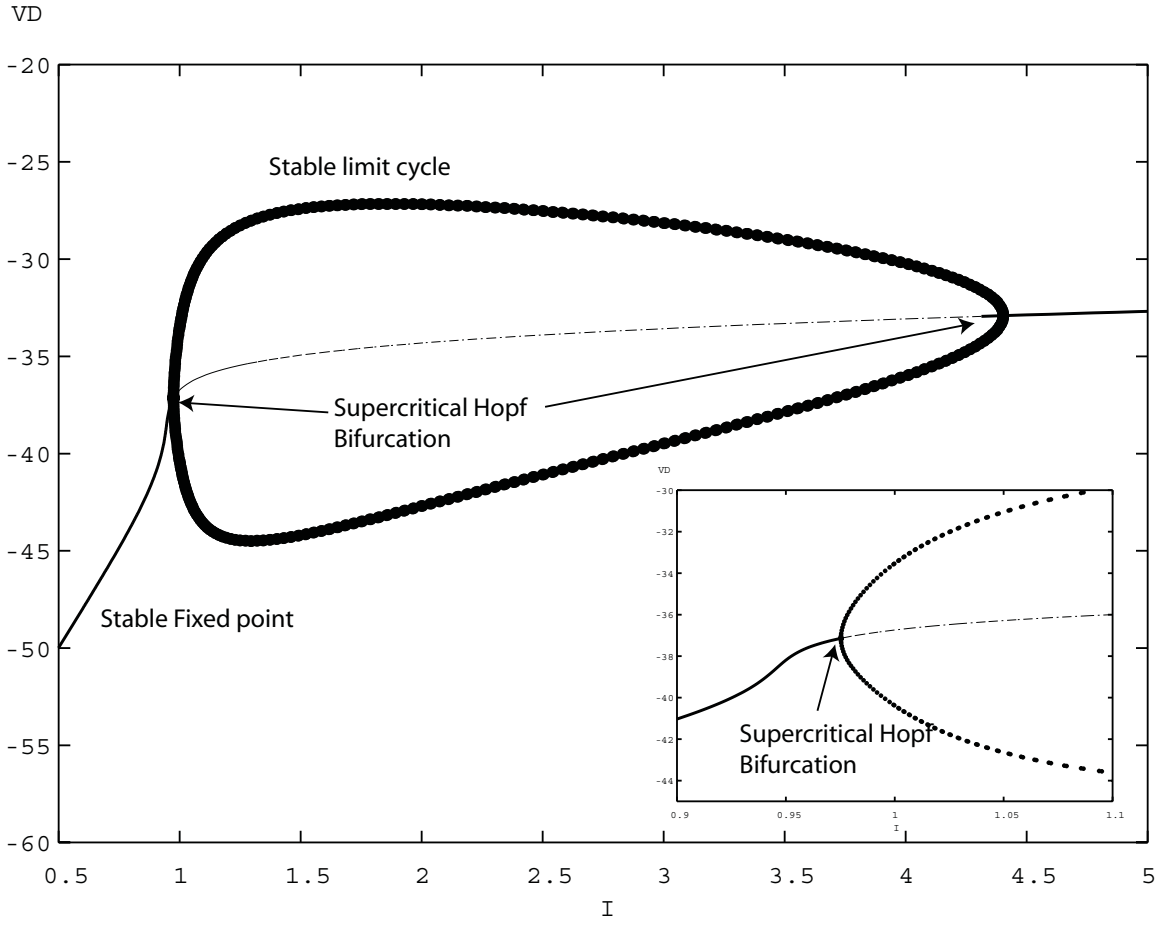
$$m_{HVA\_\infty}(V) = \mathrm{a}/(\mathrm{a} + \mathrm{b})$$

$$\mathrm{a(V)} = 0.055(-27 - \mathrm{V})/(\exp((-27 - \mathrm{V})/3.8) - 1), \quad \mathrm{b(V)} = 0.94\exp((-75 - \mathrm{V})/17)$$

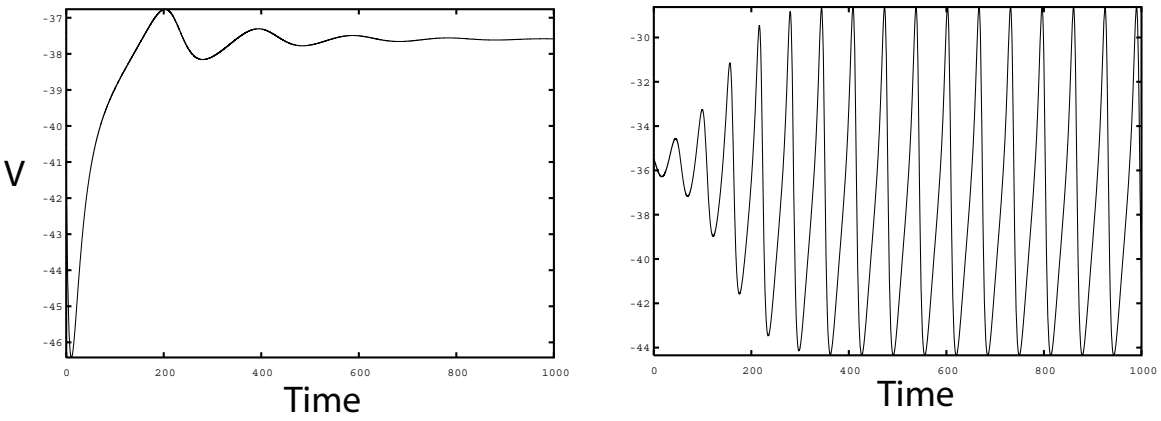
$$m_{KCa\_\infty}(Ca^{2+}) = \mathrm{a}[\mathrm{Ca}]_i^{\,2}/(\mathrm{a}[\mathrm{Ca}]_i^{\,2} + \mathrm{b}), \quad \tau_m(Ca^{2+}) = (1/(\mathrm{a}[\mathrm{Ca}]_i^{\,2} + \mathrm{b}))$$

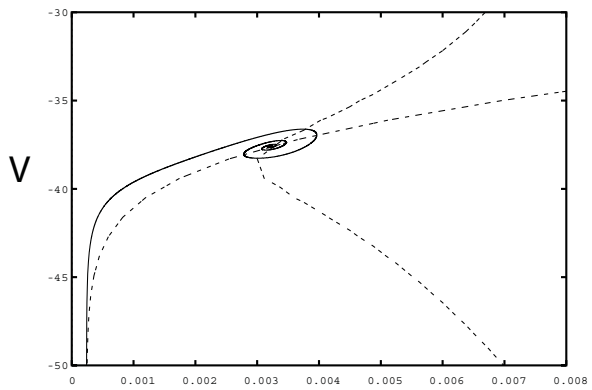
a=*48 ms*$^{-1}$*mM*$^{-2}$, b=*0.03 ms*$^{-1}$.

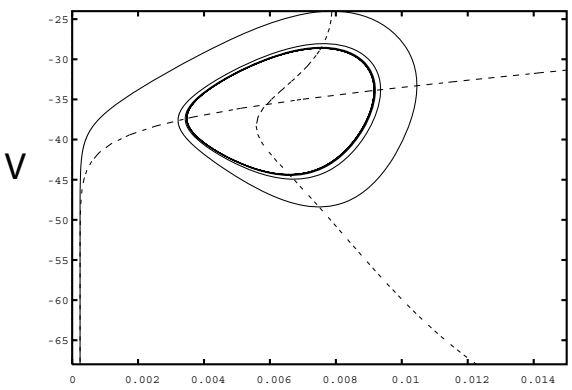
We will use external current I as a bifurcation parameter and we will find:

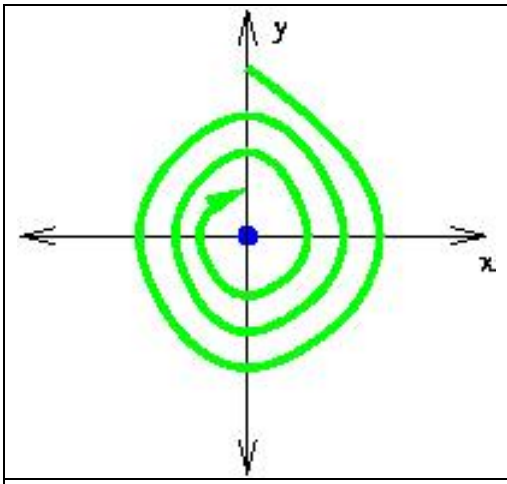
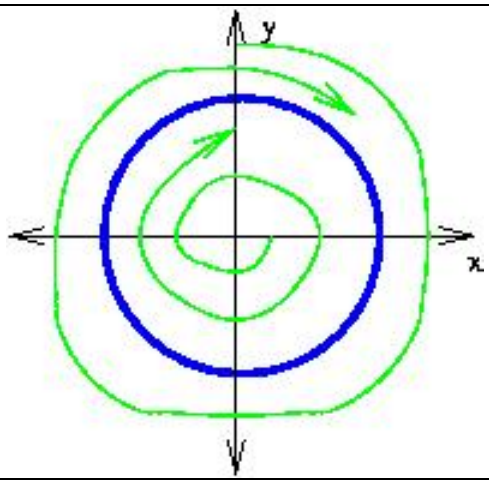


Thus, the stable fixed point corresponding to the rest state is stable below bifurcation point I~0.98 (I=0.96; below, left). As the current I increases beyond this point the stable fixed point becomes unstable and lead to birth of the stable periodic orbit corresponding to the periodic bursting that we are looking for (I=1.2; below, right).

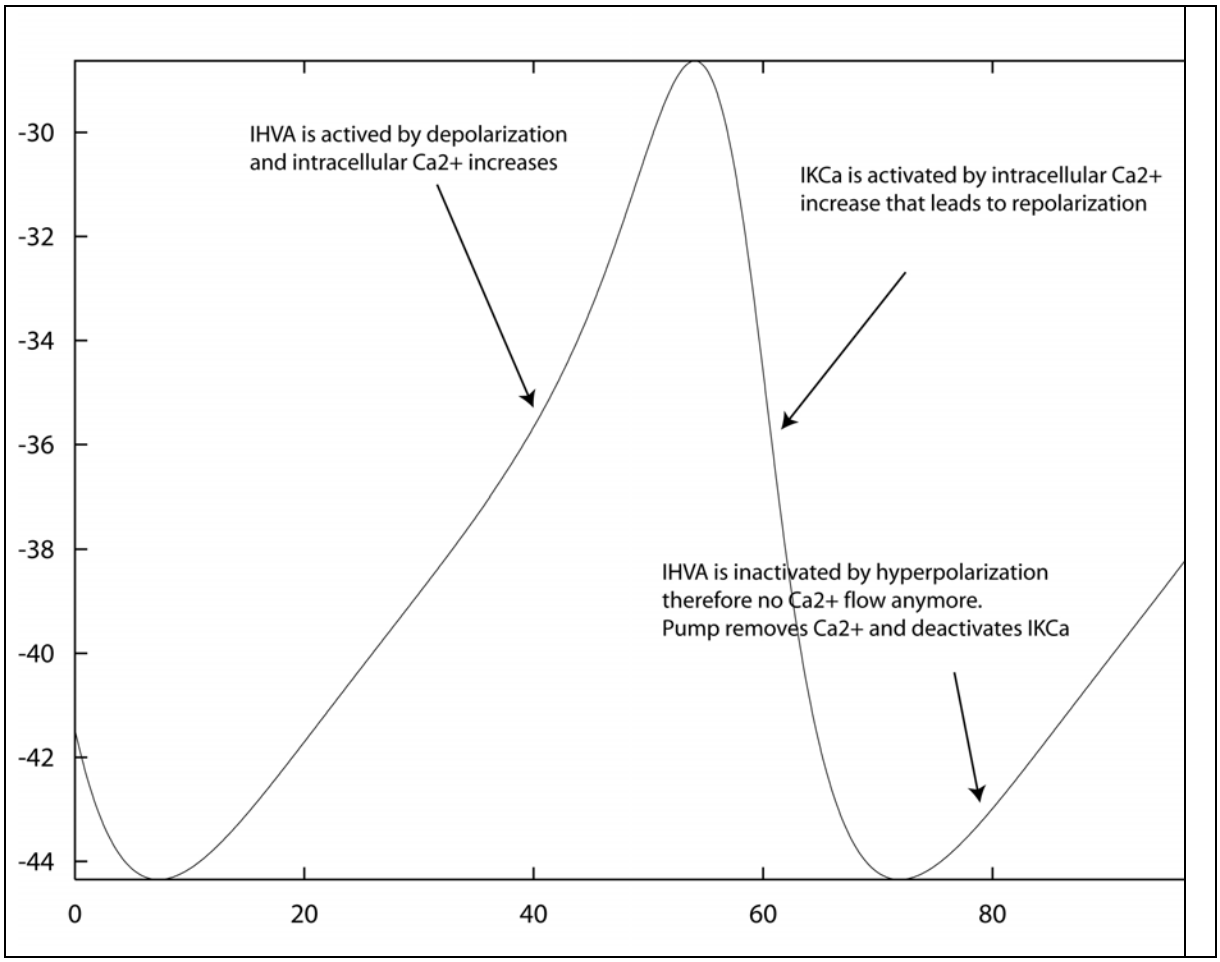



V
-30
-35
-40
-45
-50
0
0.001
0.002
0.003
0.004
0.005
0.006
0.007
0.008
[Ca]i


V
-25
-30
-35
-40
-45
-50
-55
-60
-65
0
0.002
0.004
0.006
0.008
0.01
0.012
0.014
[Ca]i

	
I < 0.98	I > 0.98

y
x
V



In this simple model the burst generation occurs as following:

(1) activation of IHVA leads to depolarization and increase of intracellular Ca2+ concentration;

(2) Ca2+ increase activates IKCa. It produces negative force that hyperpolarizes the cell.

(3) Hyperpolarization deactivates IHVA that stops Ca2+ entry to the cell.

(4) Slow Ca2+ pump (2d equation) removes Ca2+ and therefore deactivates IKCa. It terminates hyperpolarization and starts a new cycle of oscillations.