Mathematical Foundations of Neuroscience - Lecture 10. Bursting.

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Introduction

- Up to now, we've seen that neurons may spike in response to input current
- We've studied the geometrical mechanisms that lead from resting to spiking
- But this is not the end of the story. Some neurons, instead of sending one spike, send a whole bunch of spikes. These spike packets are called bursts.
- It is not yet obvious what is bursting for - it may be more reliable in information exchange. Burst may also encode a channel (frequency modulation)
- Today we will look into the mechanisms responsible for bursting

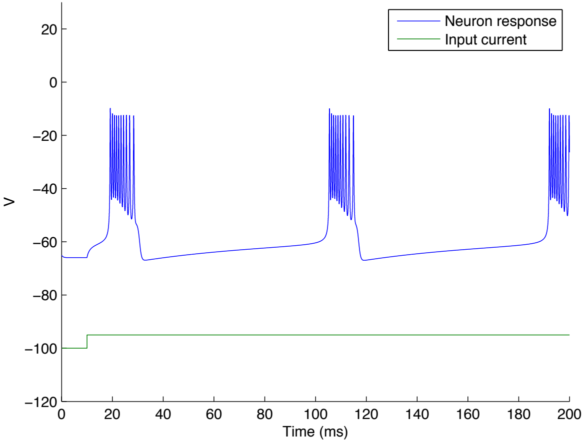


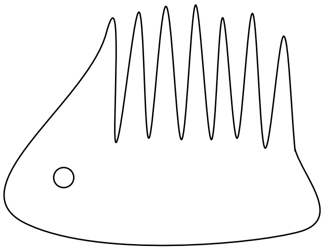
Figure: An example of a neuron bursting in response to a step current.

Definition

A **burster** *is a dynamical system which for some values of parameters autonomously alternates between periodic orbit and a stable resting state.*

As we will see bursters can vary from very simple to very complex multidimensional monsters.

- How could such a behavior occur in 2d system? The only possibility is that the trajectory will follow a very awkward cycle resembling a hedgehog:



- However this seems strange, such a model would not resemble any neural models we've seen!

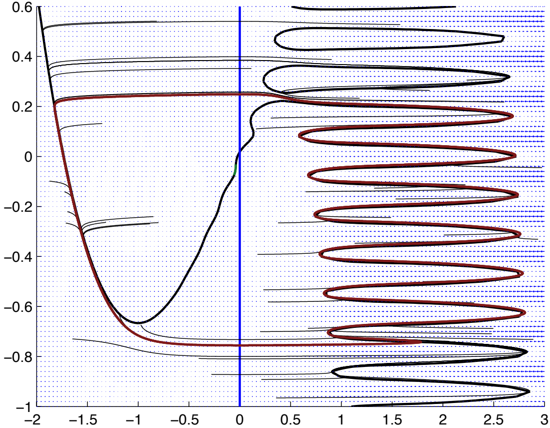


Figure: The system $\frac{dx}{dt} = x - x^3/3 - u + \frac{4}{1+e^{5(1-x)}} cos(40u)$, $\frac{du}{dt} = 0.01x$ is and example of a planar burster.

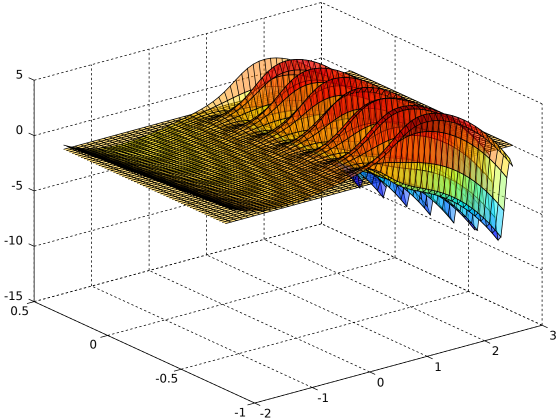


Figure: Vector field of the hedgehog system represented as plains.

- In neuronal models however we do not see any hedgehogs!
- When the input current steps up, the phase portrait instantly changes and remains fixed.
- The trajectory can either converge back to equilibrium (possibly firing one spike), or remain on the limit cycle indefinitely.
- The neuron can be bistable, but still there has to be a current pulse that switches from one regime to the other.
- Note that "bursting like" activity may be induced by stimulating a neuron with sinusoidal input current. However in a real burster something else has to oscillate and modulate the spiking.

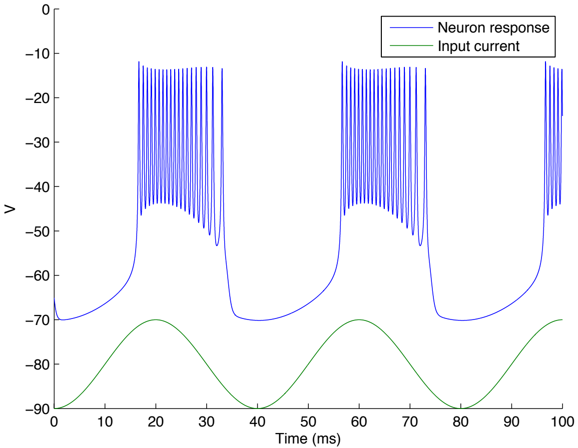


Figure: A sinusoidal current may elicit "bursting like" waveform ($I_{Na,p}$ - I_K bistable integrator)

Electrophysiology

- In neurons, there has to be some other mechanism responsible for spiking/quiescence alternation
- Spiking activates slow currents, which extinguish firing
- While the neuron remains quiet, the slow current deactivates, eventually destroying the stable equilibrium
- The neuron then fires another spike train, and so on...
- The exact neurophysiological mechanisms responsible for bursting can be of various types, voltage gated, calcium gated etc. The important thing to note, is that there is some slowly oscillating current modulating the fast spiking system.

Example - $I_{Na,p} + I_K + I_{K(M)}$ model

One can add a slow potassium current to the $I_{Na,p} + I_K$ model:

$$C_m \frac{dV}{dt} = -g_L(V - E_L) - g_{Na} m_\infty(V)(V - E_{Na}) - g_K n(V - E_K) + \\ - g_{Kslow} n_{slow}(V - E_{Kslow})$$

$$\frac{dn}{dt} = (n_\infty(V) - n)/\tau_n(V)$$

$$\frac{d n_{slow}}{dt} = (n_{\infty slow}(V) - n_{slow})/\tau_{slow}(V)$$

With $C_m = 1$, $E_L = -80$, $\tau(n) = 0.152$ $g_L = 8$, $g_{Na} = 20$, $g_K = 9$, $g_{Kslow} = 5$, $E_{Na} = 60$, $E_K = -90$, $E_{Kslow} = -90$, $\tau_{slow}(V) = 20$, $m_\infty(V) = \frac{1}{1+e^{\frac{-20-V}{15}}}$, $n_\infty(V) = \frac{1}{1+e^{\frac{-25-V}{5}}}$, $n_{\infty slow}(V) = \frac{1}{1+e^{\frac{-20-V}{5}}}$

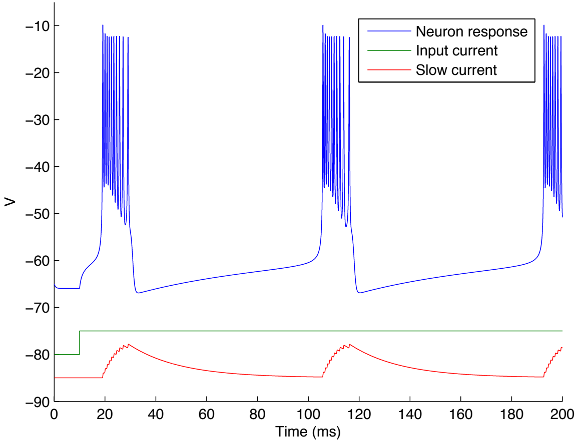


Figure: $I_{Na,p} + I_K + I_{K(M)}$ bursting.

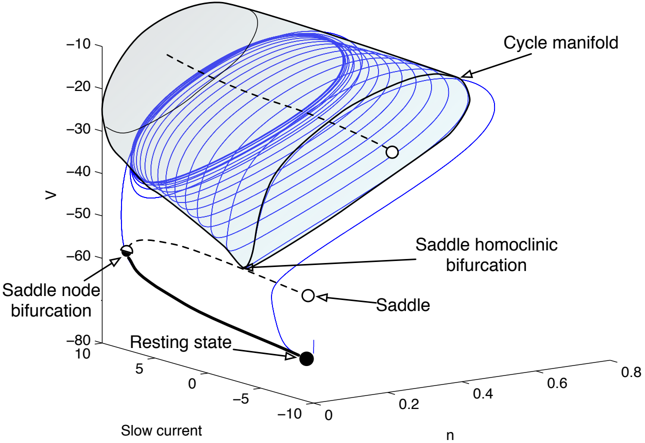


Figure: Phase space of a burster (one of many possible).

Fast-slow bursters

- A $m + k$ fast-slow burster is a system which can be described as:

$$\frac{d\vec{x}}{dt} = f(\vec{x}, \vec{u})$$
$$\frac{d\vec{u}}{dt} = \mu g(\vec{x}, \vec{u})$$

  where $\dim \vec{x} = m$, $\dim \vec{u} = k$ and μ is small, such that the two equations operate on different time scales. The first equation is the fast subsystem while the second is the slow one.

- In neural models the fast subsystem is usually the 2d system responsible for spiking. The slow system can be 1d or 2d and is responsible for modulating spike trains and induces bursts.

Dissecting a burster

- Fast-slow bursters are convenient for analysis, since they can be dissected.
- One can freeze the slow dynamics and analyze the fast subsystem, as the slow variable drives it through various bifurcations
- On the other hand one can assume the fast system is instantaneous (similarly to instantaneous gating variables in the simplifications of Hodgkin-Huxley model) and study the behavior (phase portrait) of the slow system.

Dissecting a burster

- In order to dissect a burster

$$\frac{d\vec{x}}{dt} = f(\vec{x}, \vec{u}) \qquad \frac{d\vec{u}}{dt} = \mu g(\vec{x}, \vec{u})$$

  we follow steps.

- If the neuron is resting, find the asymptotic resting value $\vec{x}_{\text{rest}}$ for fixed u. We obtain the function $\vec{x}_{\text{rest}}(u)$. We then study the reduced system:

$$\frac{d\vec{u}}{dt} = \mu g(\vec{x}_{\text{rest}}(u), \vec{u}) = \overline{g}(\vec{u})$$

- If the neuron spikes (folows a periodic orbit) the asymptotic $\vec{x}_{\infty}(u)$ hasn't a fixed value. We can however replace the periodic function with an appropriate average.

Dissecting a burster

- We replace $\vec{u}$ with some other variable $\vec{w} = \vec{u} + o(\mu)$ and put

$$\overline{g}(\vec{w}) = \frac{1}{n \cdot T(\vec{w})} \int_0^{n \cdot T(\vec{w})} g\left(\vec{x}_{\text{spike}}(t, \vec{w}), \vec{w}\right) dt$$

  where $T(\vec{w})$ is the spiking period of the fast subsystem at $\vec{w}$ and $\vec{x}_{\text{spike}}(t, \vec{w})$ is the value of the fast subsystem at t and $n \in \mathbb{N}$ is the number of cycles over which we compute the average (the more the better).
- Equilibria of the reduced slow system correspond to resting or spiking of the fast subsystem. Limit cycles may correspond to switching between spiking and resting (bursting behavior).
- The reduction fails for the points of transition from resting to spiking and vice versa (the period $T(\vec{w})$ may become infinite)!

Equivalent voltage

- The reduced system is useful, but it looses the connection with the fast subsystem and therefore my be not very informative
- With the neural models the slow system usually depends only on voltage V, and not the whole vector of values V, n, m etc...
- One may solve

$$g(V, \vec{u}) = \overline{g}(\vec{u})$$

  to find the equivalent voltage $V_{\text{equiv}}(\vec{u})$. Note that $V_{\text{equiv}}(\vec{u}) = V_{\text{rest}}(\vec{u})$ when the neuron is resting.
- That way we can get back to a more familiar phase space of $\vec{u}$ with V attached.

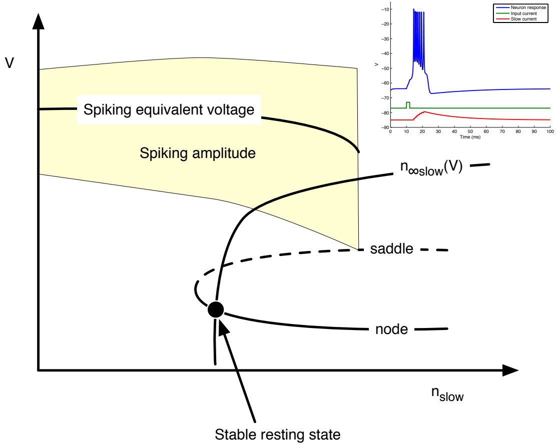
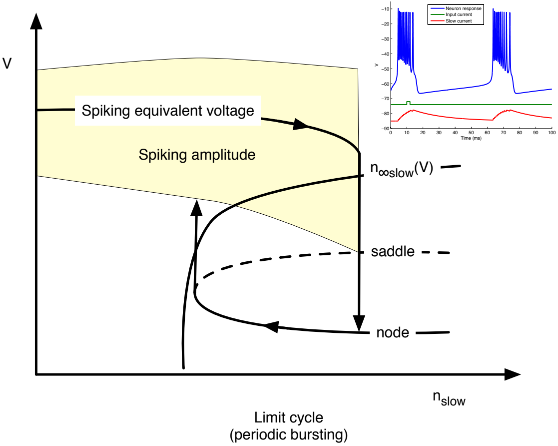


Figure: $I_{Na,p} + I_K + I_{K(M)}$ slow system phase portrait $I = 3, 6, 10$



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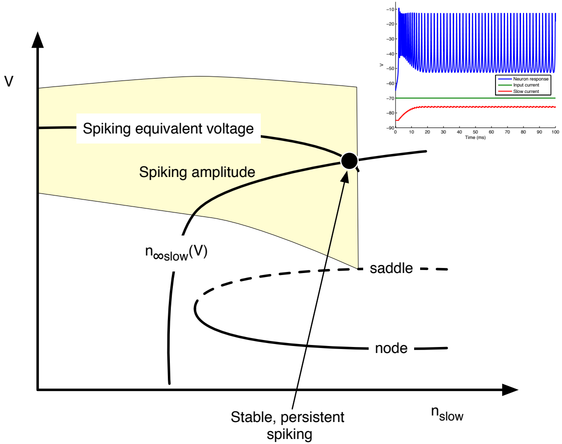


Figure: $I_{Na,p} + I_K + I_{K(M)}$ slow system phase portrait $I = 3, 6, 10$

Hysteresis loop and slow wave

- Lets get back for a minute to the interpretation of bursting in which the slow subsystem drives the fast one through a series of bifurcations, which ultimately initiate and extinguish spiking.
- Note that the slow system has to exhibit periodic behavior. Therefore the minimal dimension for the slow subsystem has to be two. But we've seen $1 + 1$ and $2 + 1$ bursters so far, how can they exist?
- The key is that the slow system is coupled with the fast one. If the fast system is bistable, it can drive the oscillations in the slow one via hysteresis loop.

Hysteresis loop and slow wave

- Consider a simple system:

$$\frac{dx}{dt} = -(x-1)x(x+1) - u$$
$$\frac{du}{dt} = 0.005x$$

- The fast system is bistable (stable states are positive and negative). When the fast system is at a positive state it slowly increases u, eventually reaching a point at which the equilibrium looses stability. At that point the system jumps to the negative equilibrium, and begins to decrease u. The process continues periodically, even though the slow system is 1d and cannot be periodic by itself.

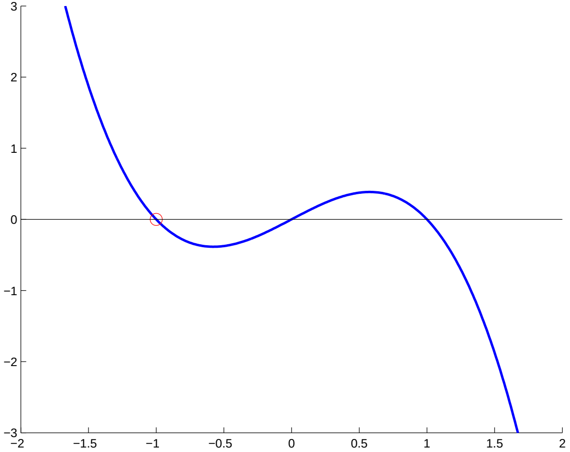
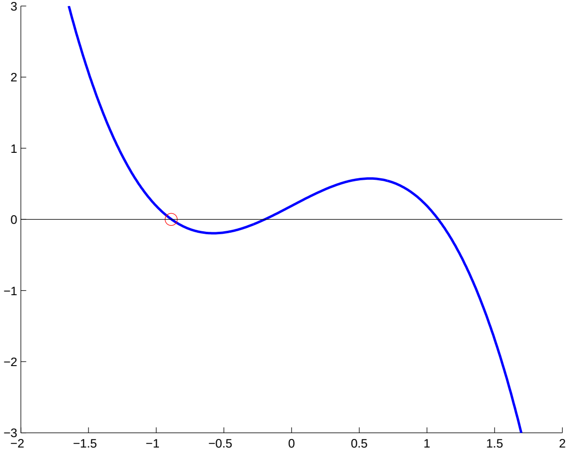


Figure: Hysteresis loop in a pair of coupled 1d systems.



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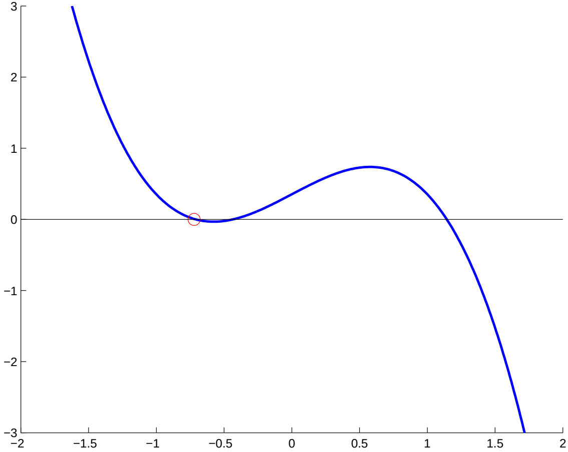

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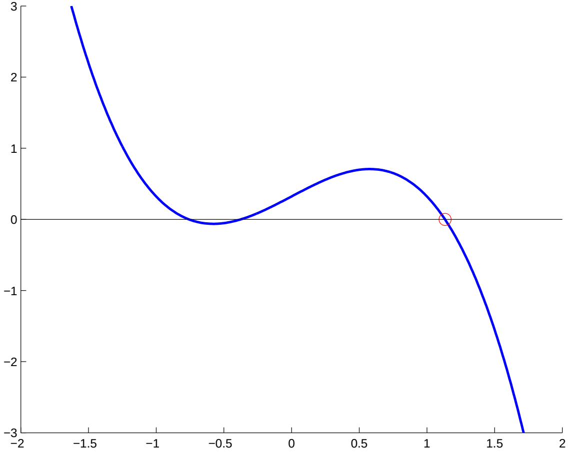

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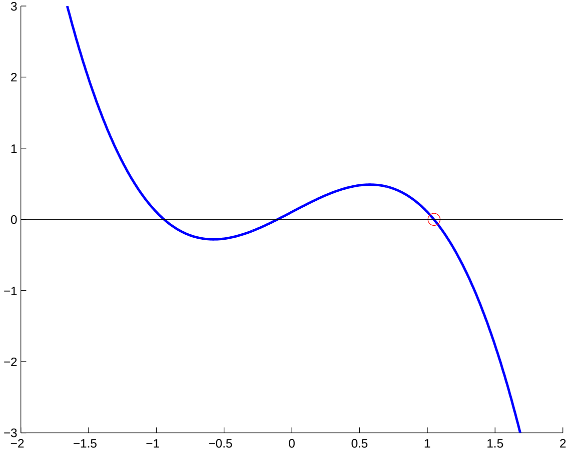

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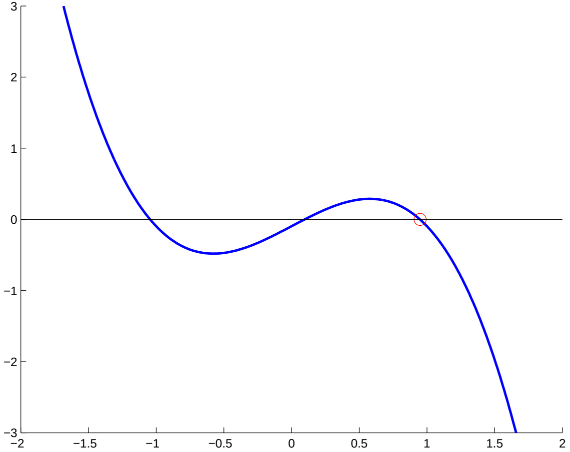

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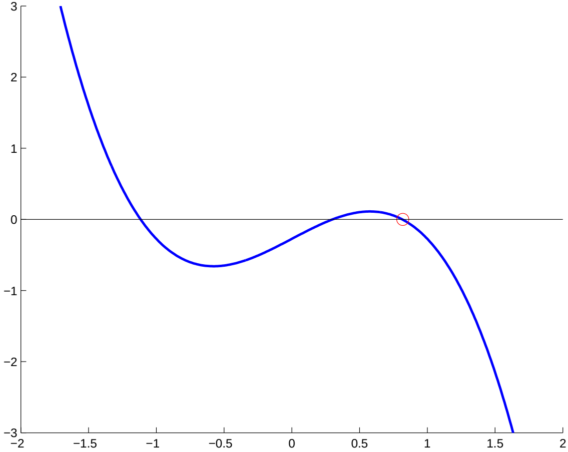

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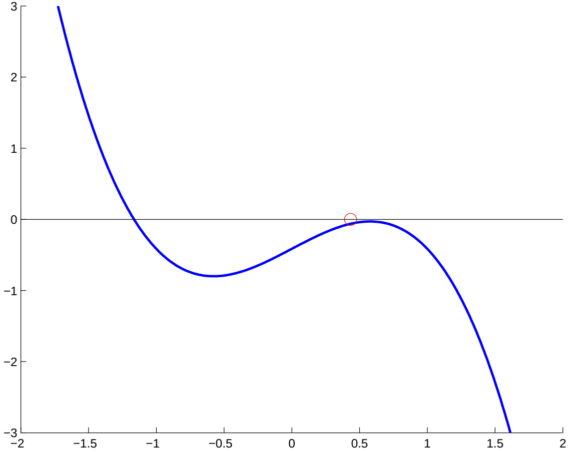

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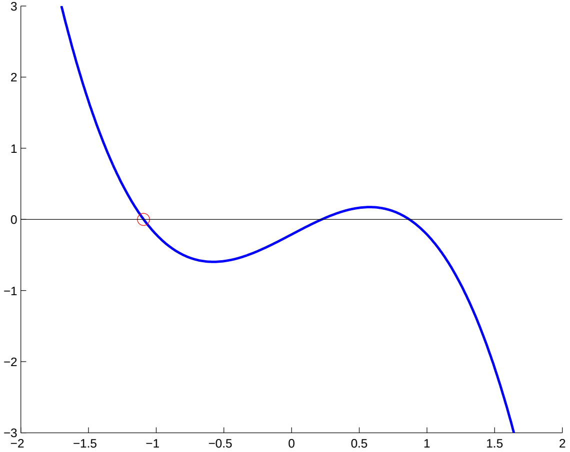

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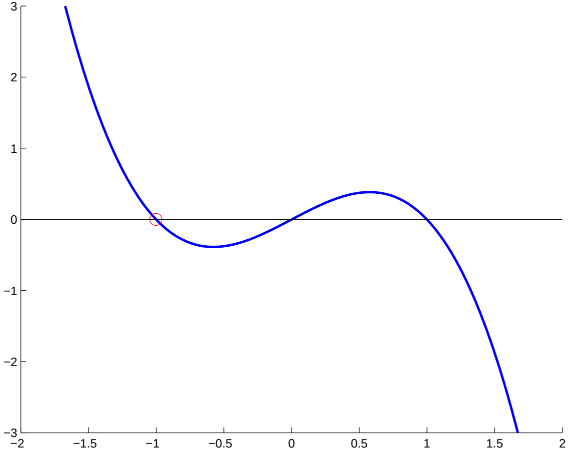

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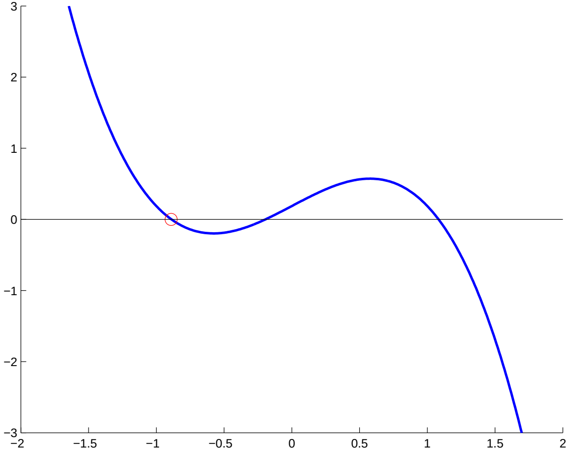

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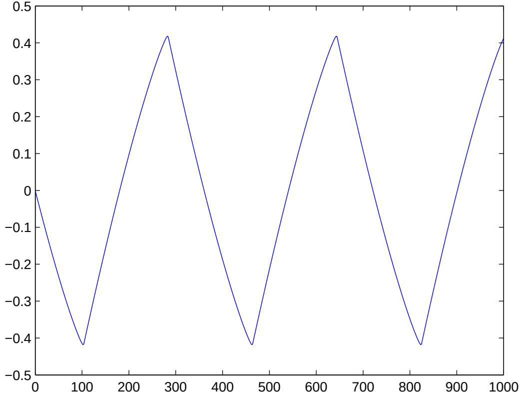

Figure: The slow subsystem (though 1d) exhibits periodic behavior due to hysteresis.

Hysteresis loop and slow wave

- The same thing applies to bursters - when the fast system is bistable (resting/spiking) then 1d slow system is sufficient for bursting and can be driven by the hysteresis loop.
- If the fast system is monostable, the slow subsystem has to have at least two variables, giving four in total. Recall that Hodgkin-Huxley model is 4d, therefore it is a minimal model for bursting.
- The slow system even when it is 2d may not be able to oscillate by itself! The only coupling of the equations may be through the voltage.
- Recall that bistability in neural models appears near saddle-node homoclinic orbit bifurcation and Bautin bifurcation.

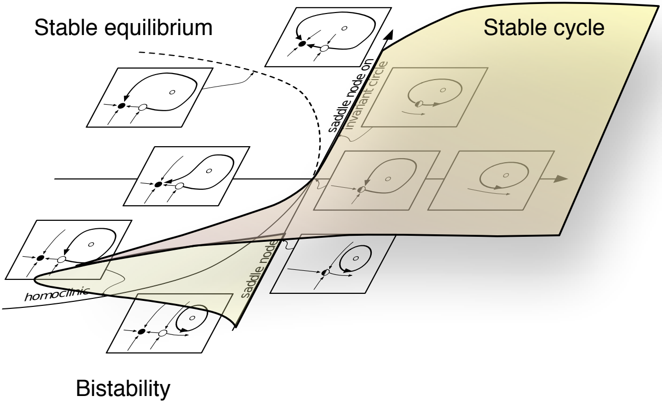

Figure: Bistability near saddle-node homoclinic orbit bifurcation

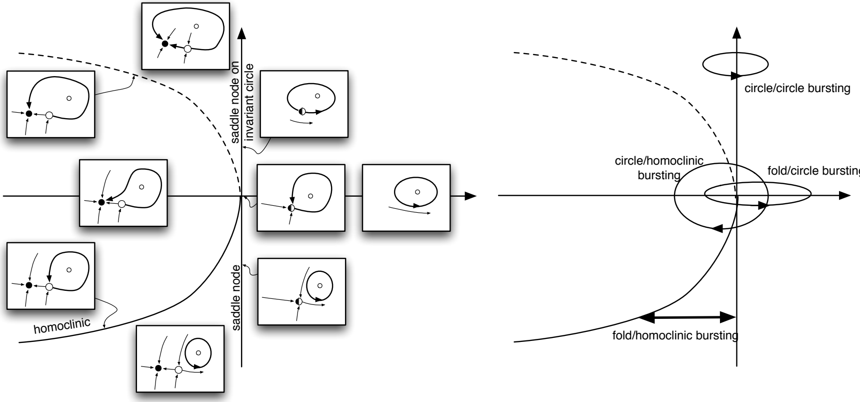

Figure: Possible ways that the slow system drives the fast one through bifurcations near saddle-node homoclinic orbit bifurcation.

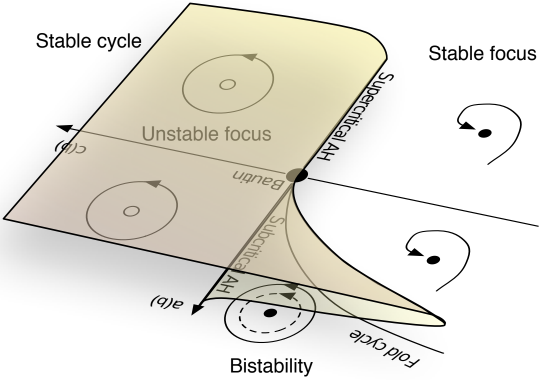

Figure: Bistability near Bautin bifurcation

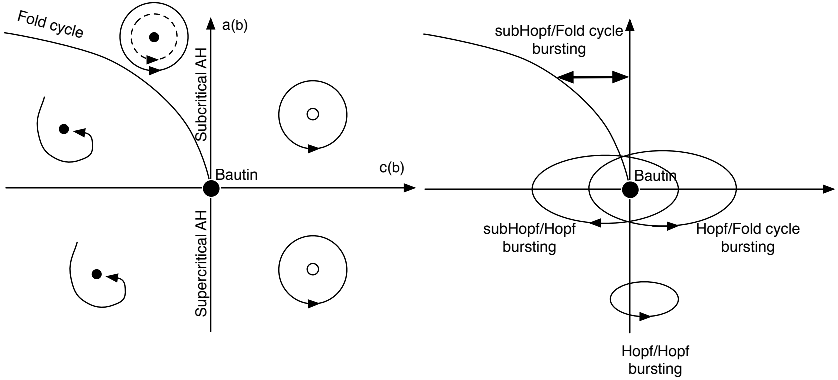

Figure: Possible ways that the slow system drives the fast one through bifurcations near Bautin bifurcation.

Types of bursting

- Any burst of spikes has two important stages - when it starts and when it ends. Each such an event corresponds to a bifurcation of the equilibrium and a limit cycle respectively.
- One can therefore classify bursters by the kind of bifurcation. Since we know there are four bifurcations of stable equilibria and for bifurcations of limit cycles, we end up with 16 possible bursters.
- Some of these bursters have been observed in real neurons, some are purely theoretical (perhaps they will be discovered in future).

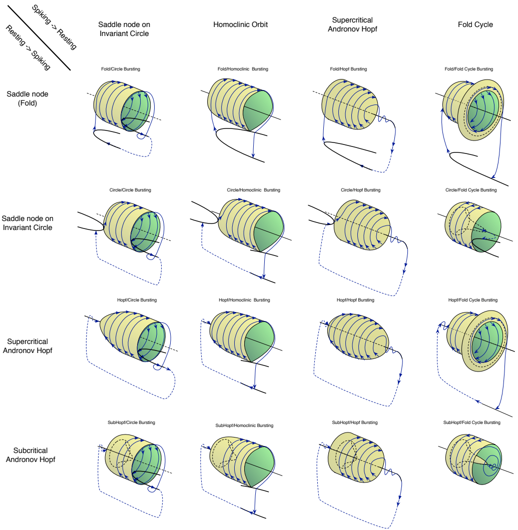

Figure: Diagram of major bursting types in neurons (see Izhikevich 2000).

Fold/Circle Bursting

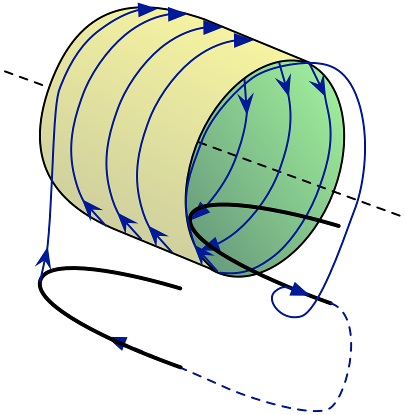

Figure: Fold-Circle bursting diagram. The slow system requires 2 dimensions.

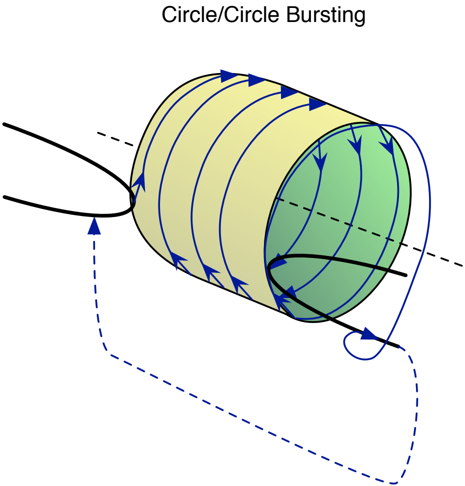

Figure: Circle-Circle bursting diagram. The slow system requires 2 dimensions.

Hopf/Circle Bursting

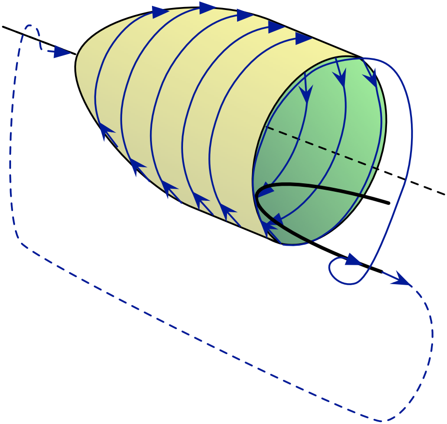

Figure: Supercritical Andronov-Hopf-Circle bursting diagram. The slow system requires 2 dimensions.

SubHopf/Circle Bursting

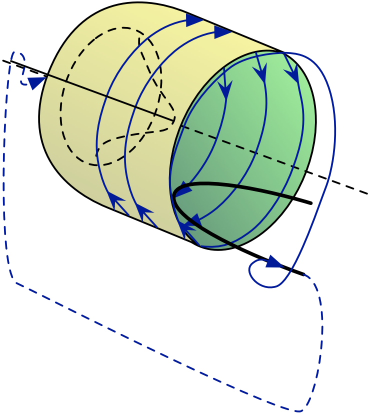

Figure: Subcritical Andronov-Hopf-Circle bursting diagram. The slow system requires 2 dimensions.

Fold/Homoclinic Bursting

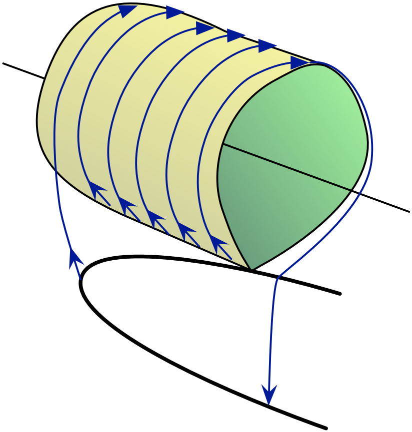

Figure: Fold-Homoclinic bursting diagram. The slow system may be one dimensional due to hysteresis loop..

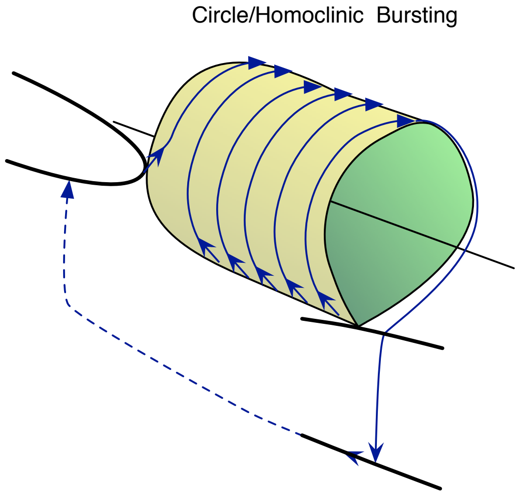

Figure: Circle-Homoclinic bursting diagram. The slow system requires 2 dimensions.

Hopf/Homoclinic Bursting

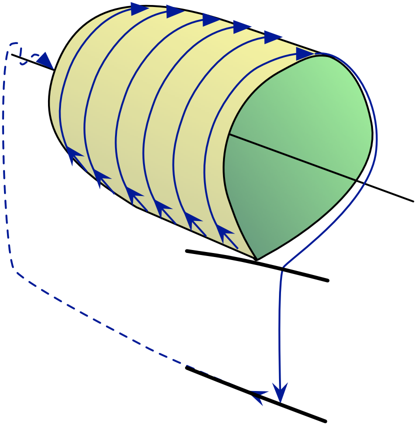

Figure: Supercritical Andronov-Hopf-Homoclinic bursting diagram. The slow system requires 2 dimensions.

SubHopf/Homoclinic Bursting

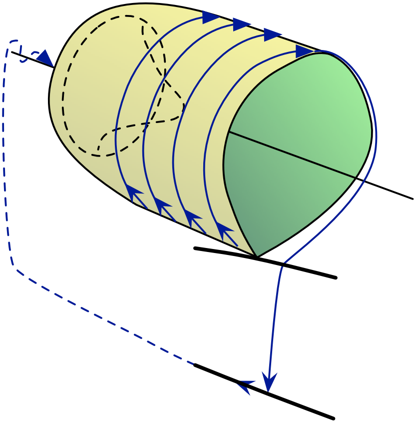

Figure: Subcritical Andronov-Hopf-Homoclinic bursting diagram. The slow system requires 2 dimensions.

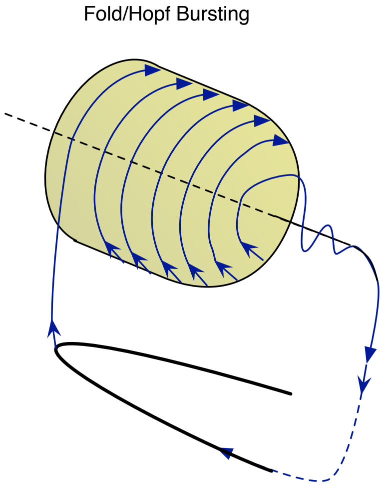

Figure: Fold-Supercritical Andronov-Hopf bursting diagram.The slow system requires 2 dimensions.

Circle/Hopf Bursting

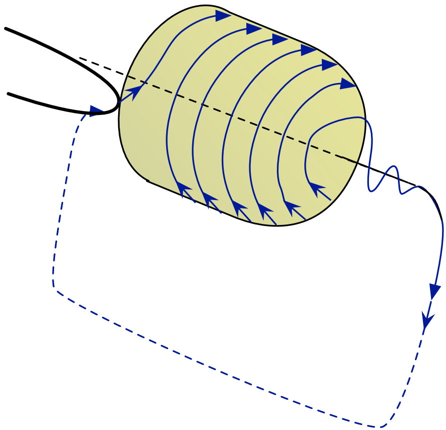

Figure: Circle-Supercritical Andronov-Hopf bursting diagram. The slow system requires 2 dimensions.

Hopf/Hopf Bursting

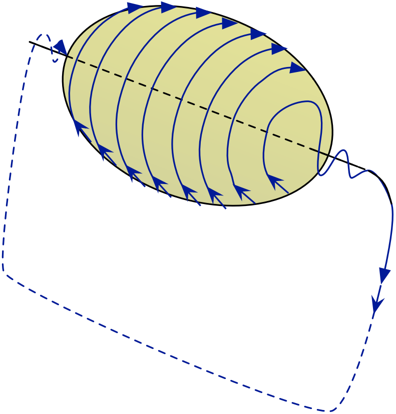

Figure: Supercritical Andronov-Hopf-Supercritical Andronov-Hopf bursting diagram. The slow system requires 2 dimensions.

SubHopf/Hopf Bursting

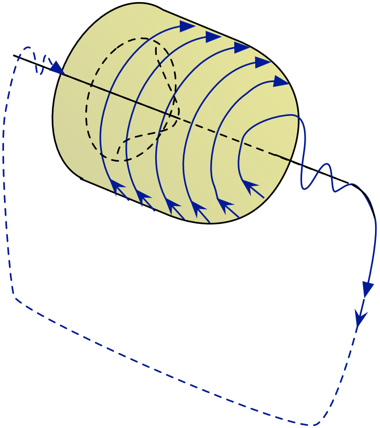

Figure: Subcritical Andronov-Hopf-Supercritical Andronov-Hopf bursting diagram. The slow system requires 2 dimensions.

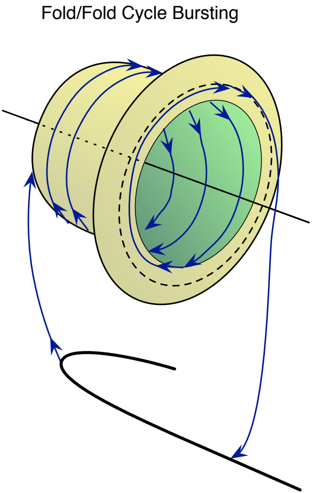

Figure: Fold-Fold Cycle bursting diagram. The slow system requires 2 dimensions.

Circle/Fold Cycle Bursting

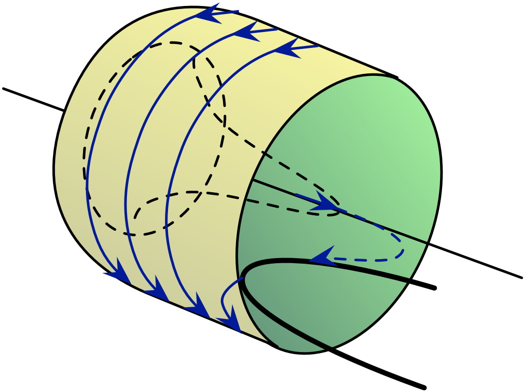

Figure: Circle-Fold Cycle bursting diagram. The slow system requires 2 dimensions.

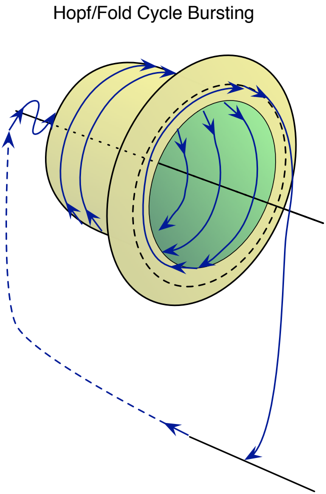

Figure: Supercritical Andronov-Fold Cycle bursting diagram. The slow system requires 2 dimensions.

SubHopf/Fold Cycle Bursting

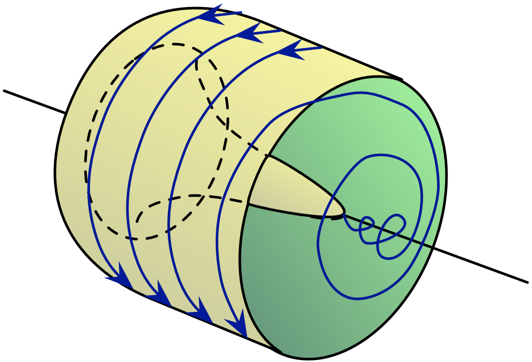

Figure: Subcritical Andronov-Fold Cycle bursting diagram. The slow system may be one dimensional due to hysteresis loop.

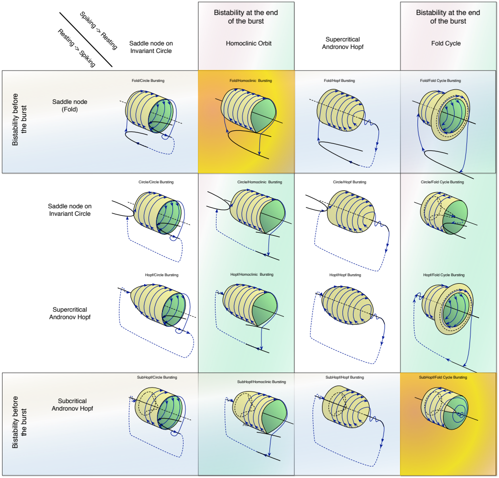

Figure: Bistability at the beginning and end of the burst. Marked are models which are bistable during the whole burst (which can have 1d slow system). Are there any other bursters which can be bistable during the whole burst?

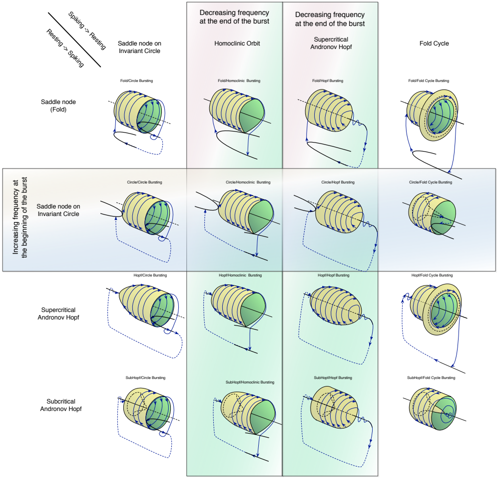

Figure: Classification of bursters based on their spike frequency at the beginning and end of the burst.

Recapitulation

- Bursting is a series of spikes alternating with a period of quiescence.
- In the general dynamical system sense, it is a system which autonomously alternates between period orbit and a resting state.
- Fast-slow bursters can be dissected into independent systems and studied theoretically
- Not all bursters are of the fast-slow type. These are very difficult to study.
- The slow system can be 1d (driven by the hysteresis loop - only when the fast system is bistable) or > 1d (slow wave type).