Nonlinear dynamics vs Neuronal Dynamics

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Cours de Methodes Mathematiques en Neurosciences

Brain and neuronal biological features

- Neuro-Computationnal properties of neurons
- Neuron Models and Dynamical Systems

A general Class of nonlinear integrate-and-fire models

- The class of models and their bifurcations
- Spike dynamics

Networks of oscillating neurons

Bifurcations and Neural Mass Models

- Cortical Column models
- Bifurcations & Behaviors
- Noise effects

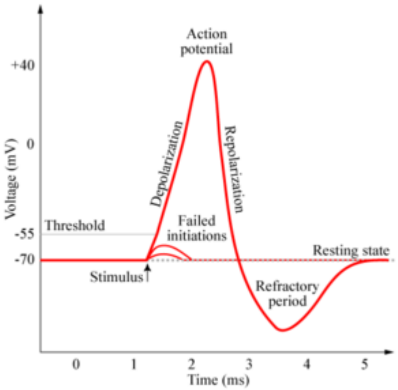
Neuronal Signal

Spikes

The elementary unit of the neuronal signal are stereotyped membrane potential electrical implulses.

Subthreshold behaviour

Small oscillations of the neuron's membrane potential are important features in some types of neuron for the robustness of rythmic patterns in the brain



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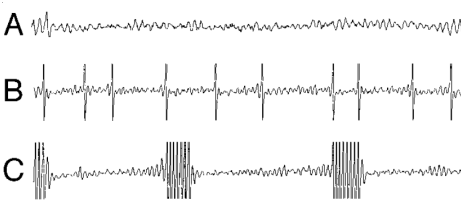
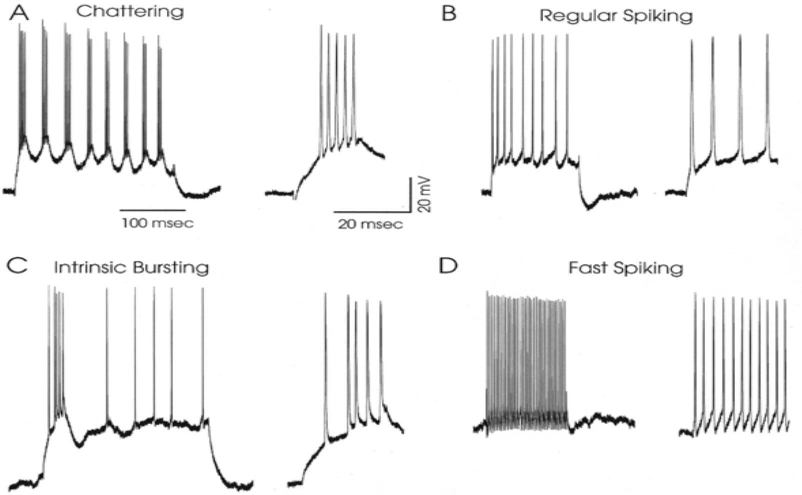


Neuronal *in vivo* behaviours



Neuro-Computationnal properties of neurons

Different points of view

In the neuroscience world, two points of view share the battlefield:

- Biologists consider that the main phenomena occuring in the spiking process are ion exchanges and channel dynamics.
- Many theoreticians consider this mechanism in terms of input-output processes.

Dynamical System point of view

In this talk we consider that the different behaviours of cortical neurons are strongly linked with the intrinsic non-linear dynamics of each individual neuron.

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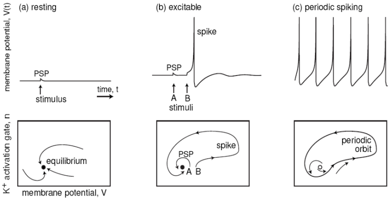
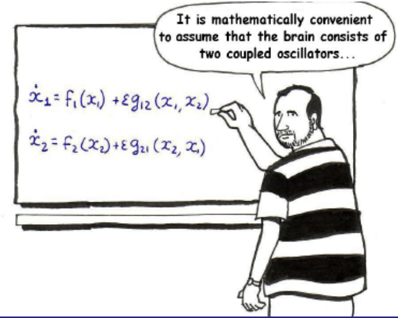
A simple dynamical system analysis



- The resting state corresponds to a stable equilibrium. Tonic spiking state corresponds to a limit cycle attractor
- Neurons are excitables because the equilibrium is near a bifurcation

Neurons from our point view

- Neurons are dynamical systems
- Phase plane analysis and bifurcations explain the neurocomputationnal behaviour of the neurons
- A good neuronal model must reproduce electrophysiology AND the bifurcation dynamics of neurons



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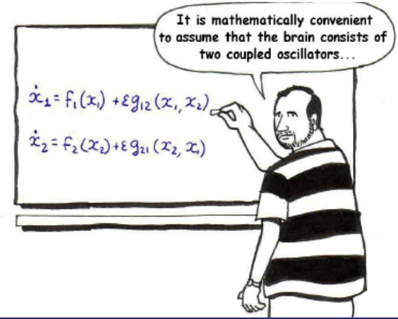

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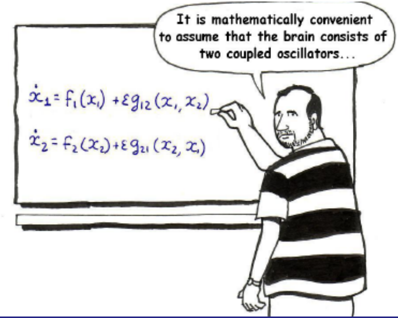

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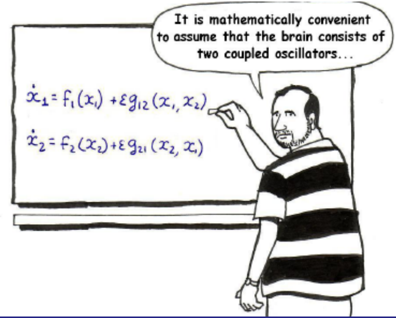
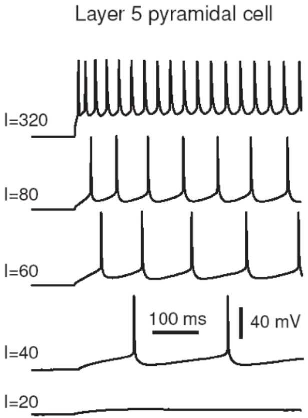
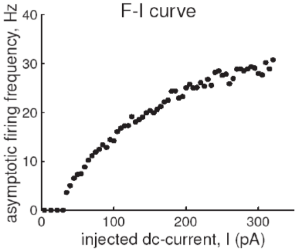


Excitabilité

La Classification de Hodgkin : classe 1





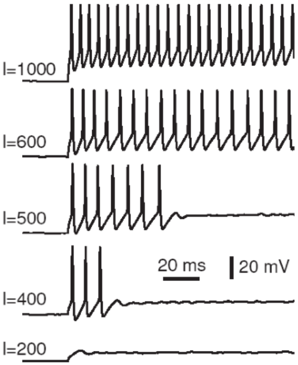
Izhikevich 2006

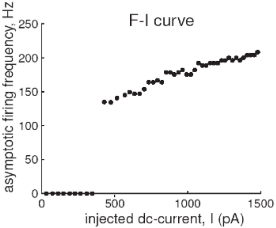
Courbe F-I.
Des trains de potentiels d'action de fréquence arbitrairement faible peuvent exister.

Excitabilité

La Classification de Hodgkin : classe 2

Brainstem mesV cell



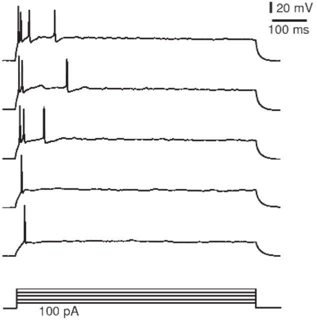


Izhikevich 2006

Courbe F-I.
Les fréquences des trains de potentiel d'action varient dans une bande limitée.
Le neurone agit comme un détecteur de seuil.

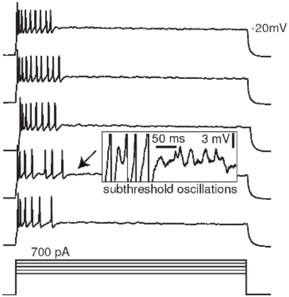
Excitabilité

La Classification de Hodgkin : classe 3



Izhikevich 2006

Neurone pyramidal de la couche 5 du cortex visuel chez le rat.



Izhikevich 2006

Un seul potentiel d'action est généré en réponse à une marche de courant. Une émission répétitive de potentiels d'action n'est possible que pour des courants injectés d'intensité très forte.

La naissance des cycles

Comment les cycles naissent?

Il y a 2 façons de faire naître un cycle:

- La bifurcation de Hopf (déjà étudiée)
- La saddle-node on invariant cycle (SNIC): mécanisme courant pour passer d'un point fixe à un cycle: une branche de cycle limite émerge d'un point de saddle-node au travers d'une orbite homocline.
- L'excitabilité de type 3 correspond à la présence d'un point fixe stable quel que soit la valeur du courant d'entrée.

Correspondance entre Bifurcations et Excitabilité

Rinzel et Ermentrout (1989) on fait le lien entre les deux types d'excitabilité et les deux bifurcations ci-dessus:

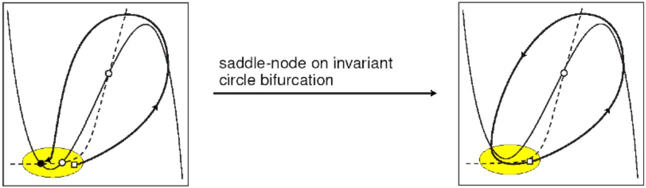
- Une bifurcation SNIC correspond à un phénomène d'excitabilité de type I
- Une bifurcation de Hopf correspond à un phénomène d'excitabilité de type II
- L'excitabilité de type 3 correspond à l'absence de bifurcation.

Attention:

La réciproque n'est bien sûr pas correcte.

La Classification de Hodgkin : classe 1

- L'excitabilité neurale de classe 1 correspond à la disparition de l'équilibre stable au travers d'une bifurcation noeud/col sur un cercle invariant.
- C'est la seule bifurcation d'équilibre de codimension 1 qui produit un cycle limite de fréquence arbitrairement faible.

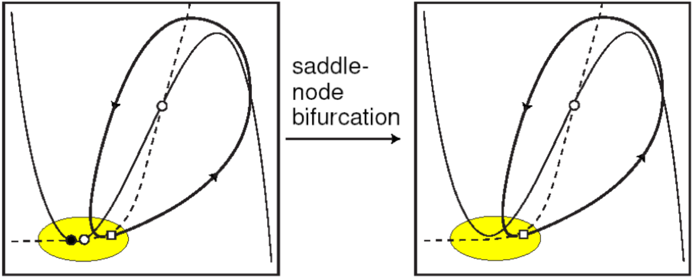


Izhikevich 2006

La Classification de Hodgkin : classe 2

L'excitabilité neurale de classe 2 correspond à la disparition de l'équilibre stable au travers

- d'une bifurcation noeud/col (en dehors d'un cercle invariant).
- d'une bifurcation d'Andronov-Hopf sur- ou sous-critique.



Izhikevich 2006

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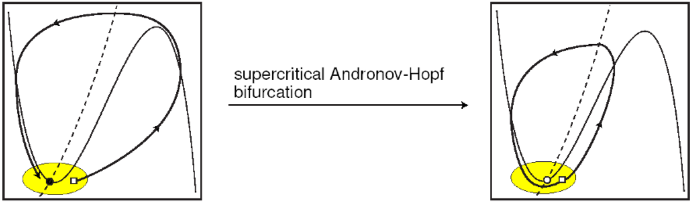

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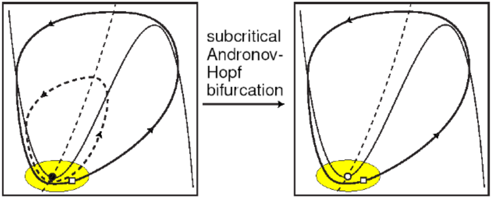
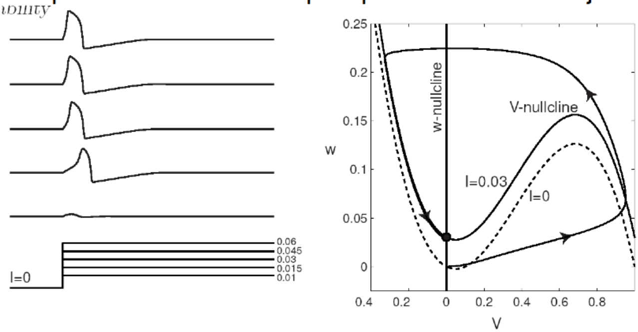


Izhikevich 2006

La Classification de Hodgkin : classe 3

L'excitabilité neuronale de classe 3 correspond au fait que l'équilibre stable le reste quel que soit le courant injecté.

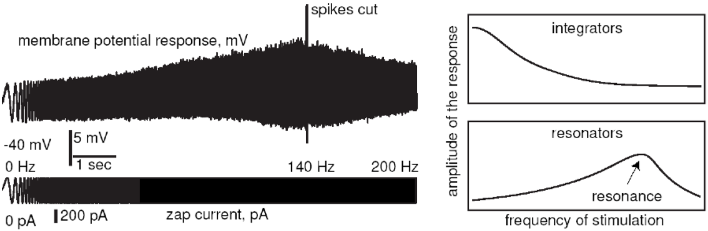


Izhikevich 2006

Exemple du modèle de FitzHugh-Nagumo :

$\dot{V} = V(a - V)(V - 1) - w + I \quad \dot{w} = bV - cw, \ a = 0.1, \ b = 0.01,$

Neurones intégrateurs ou résonateurs ?



Izhikevich 2006

Stimulation avec un courant “zap” (courant sinusoidal de fréquence croissante). Le neurone résonne à la fréquence de 140Hz.

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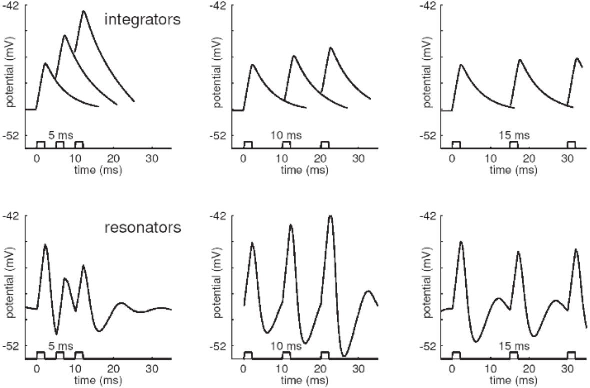


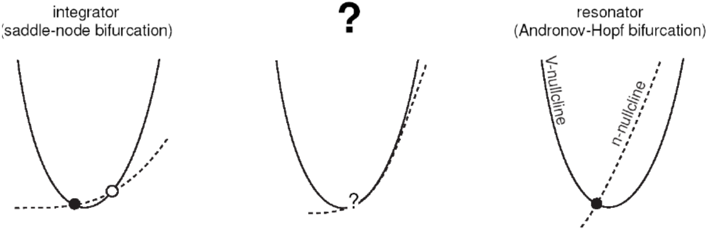
Izhikevich 2006

Les intégrateurs préfèrent les hautes fréquences : détecteurs de coïncidence.
Les résonateurs sont adaptés à une certaine bande de fréquence.

Coexistance des Type 1 and 2

Bogdanov-Takens

Il faut combiner en dimension 2 une bifurcation noeud-col avec une bifurcation d'Andronov-Hopf.

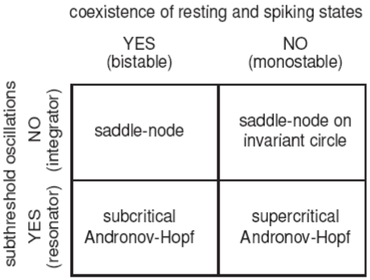


Izhikevich 2006

Spikes dans le modèle de Fitzhugh-Nagumo

- Présence d'un cycle via le théorème de Poincaré-Bendixon
- Quel type d'excitabilité?

Bifurcations and electrophysiological properties



(Ref: *Izhikevich* **2006***: Dynamical Systems in Neuroscience*)

Bifurcations and electrophysiological properties

properties	integrators		resonators	
bifurcation	saddle-node on invariant circle	saddle-node	subcritical Andronov-Hopf	supercritical Andronov-Hopf
excitability	class 1	class 2	class 2	class 2
oscillatory potentials	no		yes	
frequency preference	no		yes	
I-V relation at rest	non-monotone		monotone	
spike latency	large		small	
threshold and rheobase	well-defined		may not be defined	
all-or-none action potentials	yes		no	
co-existence of resting and spiking	no	yes	yes	no
post-inhibitory spike or facilitation (brief stimuli)	no		yes	
inhibition-induced spiking	no		possible	

(Ref: *Izhikevich* **2006**: *Dynamical Systems in Neuroscience*)

Problem

- Can we find a computationnaly simple phenomenological neuron model reproducing the main biological features of cortical neurons?
- Can we relate other neuronal behaviors to more complex bifurcations?

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Bidimensional spiking neuron models

Neurons, Dynamical Systems and Integrate-and-fire models

Neuron and Dynamical Systems

The main excitability properties can be linked with bifurcations of dynamical systems for

- Continuous dynamical systems: detailed neuron models and their reductions (Rinzel, Ermentrout, Guckenheimer, . . .).
- Discrete dynamical systems: map-based models (Caselles, Rulkov, . . .)

Hybrid dynamical systems

Integrate-and-fire neuron models combine:

- A continuous dynamical system (ordinary differential equations) accounting for input integration
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Classical Integrate-and-Fire Neurons

$$\frac{dv}{dt} = -v + I$$
$$v = \theta \Rightarrow \text{Spike!}$$

Izhikevich (2003) Brette & Gerstner (2005)

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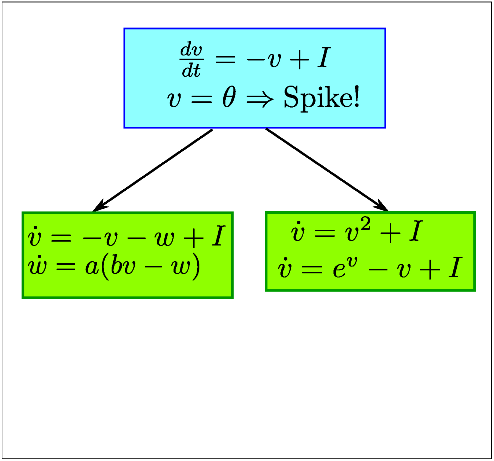

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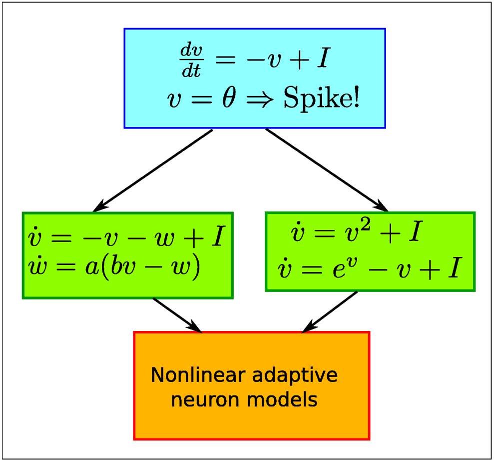

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A General class of models

Free (subthreshold) dynamics of the neuron

$$\begin{cases} \frac{dv}{dt} = F(v) - w + I \\ \frac{dw}{dt} = a(b\,v - w) \end{cases}$$

where

- v models the membrane potential of the neuron
- w is an adaptation variable.
- F is a real function
- a is the time scale of the adaptation variable with respect to the membrane potential
- b is the coupling strength.
- I is the (constant) input.

Technical assumptions on F:

Assumptions:

1. Regularity: F is at least three times continuously differentiable
2. Convexity: F is strictly convex
3. Shape of F:

$$\begin{cases} \lim_{x \to -\infty} F'(x) \leq 0 \\ \lim_{x \to +\infty} F'(x) = +\infty \end{cases}$$

Spiking Mechanism

Assumption 4 (Spikes)

$F(v) = R(v)\,v^{1+\varepsilon}$ for some $\varepsilon > 0$ and $R(v)$ is lowerbounded when $v \to \infty$.

Under these asumptions:

- The membrane potential blows up in finite time.
- A spike is emitted at the time t^* when the membrane potential blows up (or when it reaches a cutoff value).
- At this time, the membrane potential and the adaptation variable are reset:

$$\begin{cases} v(t^*) = v_r \\ w(t^*) = w(t^{*-}) + d \end{cases}$$

where v_r is the reset membrane potential and $d > 0$ is an adaptation parameter

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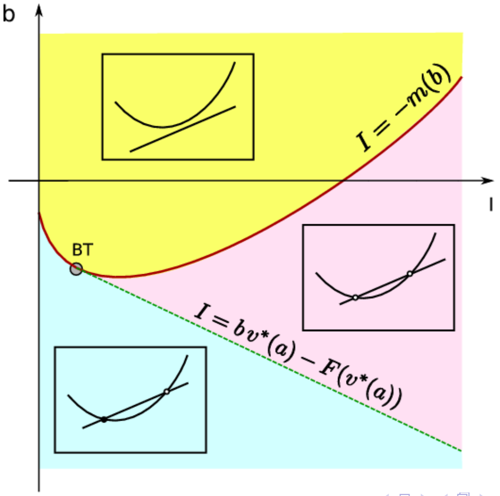
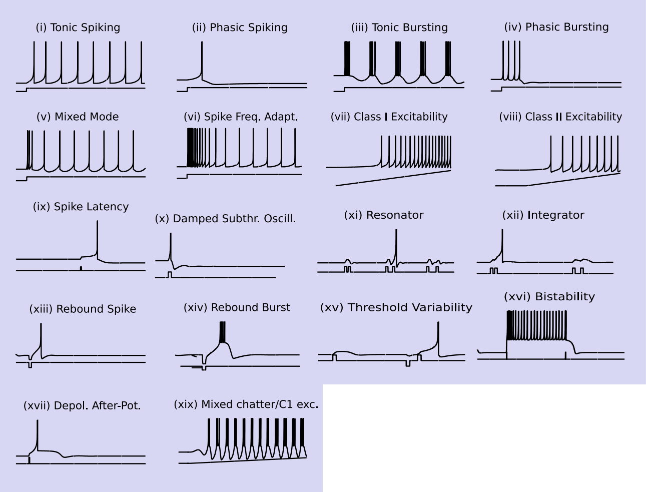
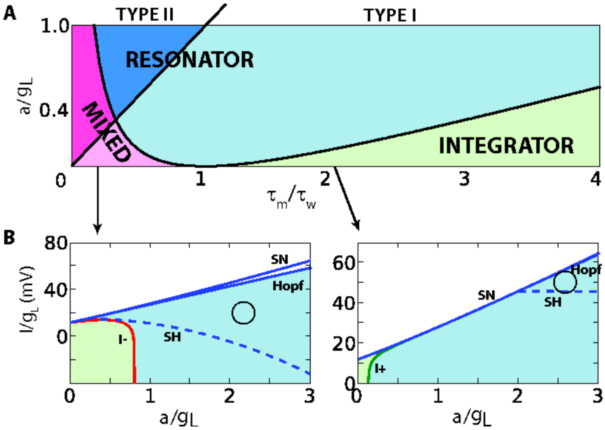
Interspike Behavior,
Mathematical Analysis

Bifurcations of the subthreshold system:




(i) Tonic Spiking
(ii) Phasic Spiking
(iii) Tonic Bursting
(iv) Phasic Bursting
(v) Mixed Mode
(vi) Spike Freq. Adapt.
(vii) Class I Excitability
(viii) Class II Excitability
(ix) Spike Latency
(x) Damped Subthr. Oscill.
(xi) Resonator
(xii) Integrator
(xiii) Rebound Spike
(xiv) Rebound Burst
(xv) Threshold Variability
(xvi) Bistability
(xvii) Depol. After-Pot.
(xix) Mixed chatter/C1 exc.

Electrophysiological classes



J.T., Romain Brette, Biol. Cybern. 2008.

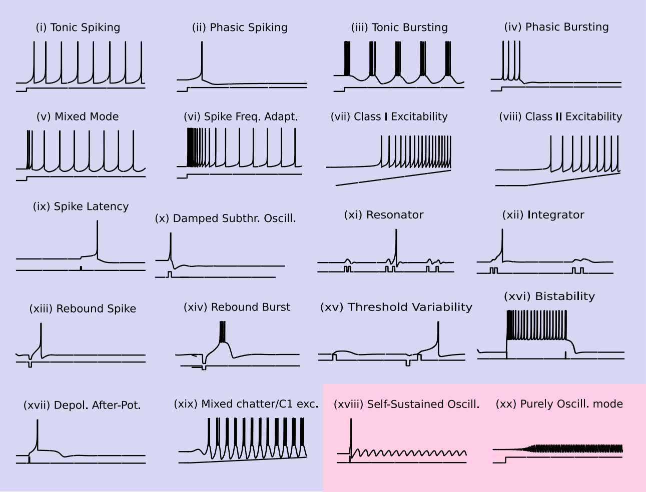
Problem: no subthreshold oscillations

- present in the the inferior olive nucleus, stellate cells in the enthorhinal cortex and dorsal root ganglia (DRG) neuron
- facilitate the generation of spike oscillations and shape specific forms of rhythmic activity vulnerable to the noise.

Solution

Bautin bifurcation

- Bautin bifurcation possible
- Occurs in the quartic model for instance: $F(v) = v^4 + 2a\, v$.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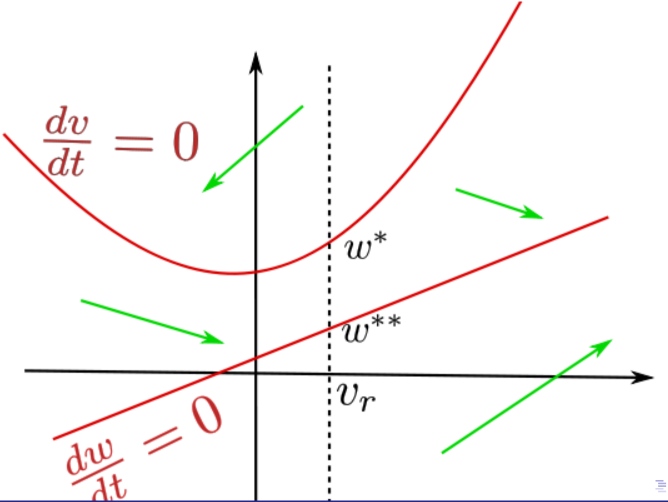
(xix) Mixed chatter/C1 exc.
(xviii) Self-Sustained Oscill.
(xx) Purely Oscill. mode

Spike Dynamics

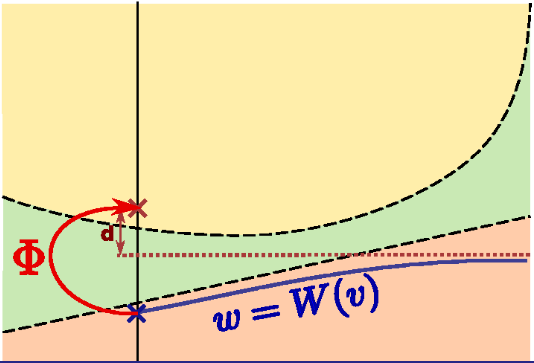
Dynamical objects



The Adaptation map

We define:

- $\mathcal{D}$ the set of w s.t. the solution starting from (v_r, w) spikes.
- $\Phi : \mathcal{D} \mapsto \mathbb{R}$ the function such that $\Phi(w)$ is the after-spike adaptation value.



A single case is considered

No fixed point

In this defense I only consider the case where $I > I_{SN}(b)$, i.e. the system has no fixed point

What if not?

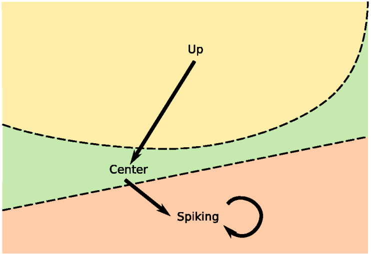
The other cases are more intricate and fully treated in the manuscript.

Mathematical study of Φ

- We define a Markov partition of the dynamics.
- In the spiking zone, $w(t) = W(v(t))$ where the function W is the solution of the differential equation:

$$\begin{cases} \frac{dW}{dv} = \frac{a(bv-w)}{F(v)-w+I} \\ W(v_0) = w_0 \end{cases}$$

- The map Φ is defined by $\lim_{v\to\infty} W(v) + d$.



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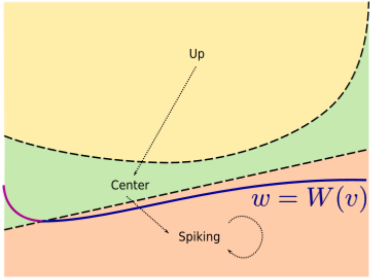

Mathematical study of Φ

- We define a Markov partition of the dynamics.
- In the spiking zone, $w(t) = W(v(t))$ where the function W is the solution of the differential equation:

$$\begin{cases} \frac{dW}{dv} = \frac{a\,(b\,v - w)}{F(v) - w + I} \\ W(v_0) = w_0 \end{cases}$$

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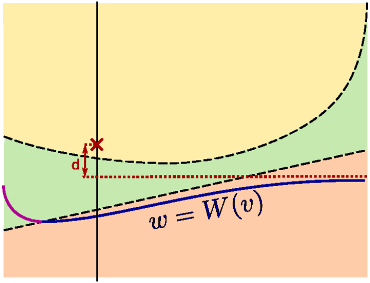

Well-posedness of the model

Adaptation variable at the times of the spikes

In order for this sytem to be well posed, the value of the adaptation at the times of the spike must be well defined.

Result

- We show that the adaptation variable at the times of the spikes is well defined in the quartic and the exponential models
- And in the quadratic models it blows up!

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Sketch of the proof

- Any spiking trajectory will enter a region stable under the dynamics included in $\{w < bv\}$ and where $F(v) - w + I$ never vanishes.
- Therefore the membrane potential will blow up in this zone ($\dot{v} \geq F(v) - bv + I$ + Gronwall).
- Moreover, the orbit satisfies the equation $\frac{dW}{dv} = \frac{a\,(b\,v - W)}{F(v) - W + I}$ and w is increasing hence

$$\frac{a\,(b\,v - W_0)}{F(v) - b\,v + I} \geq \frac{dW}{dv} \geq \frac{a\,(b\,v - W)}{F(v) - W_0 + I}$$

- Gronwall's lemma leads to the conclusion: the adaptation value is bounded at the times of the spikes if and only if $\frac{v}{F(v)}$ is integrable.

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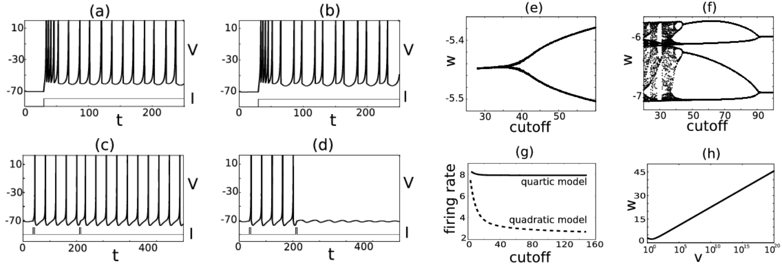
Consequences

Classical Models

Izhikevich model is ill-posed, the Quartic and the Exponential well-posed.

- Izhikevich model has a strict voltage threshold, the cutoff θ.
- The adaptation value at the times of the spike reads $W(\theta)$ and diverges when $\theta \to \infty$.
- Therefore spike patterns depend on the cutoff value, and in a very sensitive way.
- It has important consequences on numerical simulations.

Sensitivity to cutoff of Izhikevich model



J.T., Submitted to Neural Computation

Spike Dynamics

Well-posedness assumption

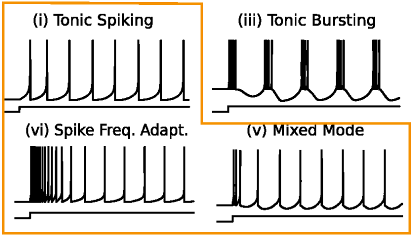
Assumption 5 (Well-posedness)

$F(v) = R(v)\, v^{2+\varepsilon}$ for some $\varepsilon > 0$ and $R(v)$ is lowerbounded when $v \to \infty$.

Mathematical remark

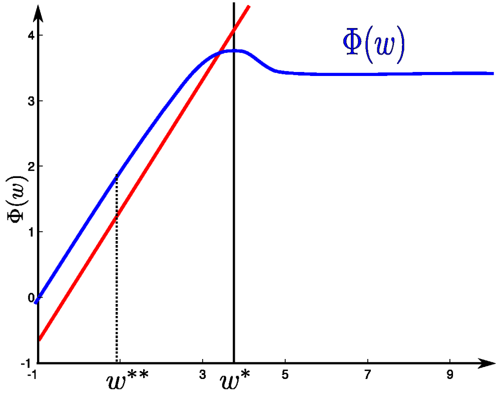
In this case the map Φ corresponds to a generalization of a Poincaré map.

Spiking signature



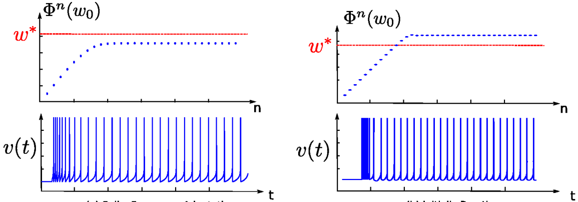
The spike pattern fired is directly linked with the sequence of reset value of the adaptation, called the adaptation sequence $\left(\Phi^n(w_0)\right)_{n\geq 0}$.

Description of the adaptation map



Regular Spiking

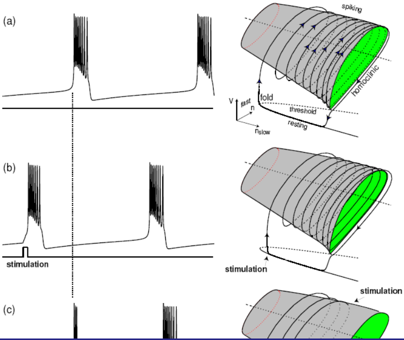
- Regular spiking corresponds to the convergence of the sequence $\Phi^n(w)$ to the fixed point of Φ noted w_{fp}.
- $w_{fp} \leq w^* \Leftrightarrow$ spike frequency adaptation.
- $w_{fp} \geq w^* \Leftrightarrow$ initial bursting.
- Theorem: If $\Phi(w^*) \leq w^*$, the system presents regular spiking with spike frequency adaptation.



(a) Spike Frequency Adaptation (b) Initially Bursting

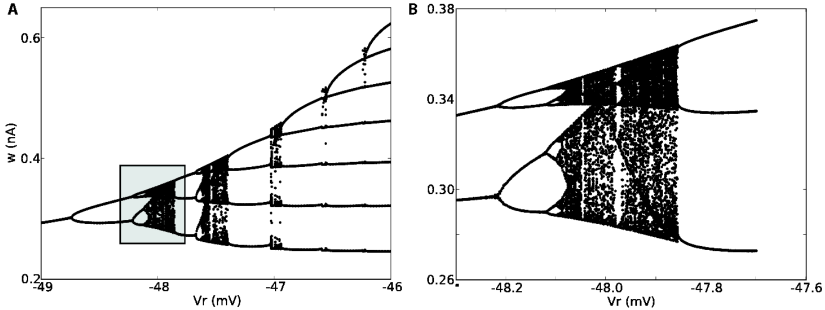
Regular Bursting:

- Bursts correspond to cycles in the sequence.
- Simple conditions on the values of Φ account for the existence of cycles, e.g. cycles of period three (hence cycles of any period).



Bifurcations with respect to v_r:

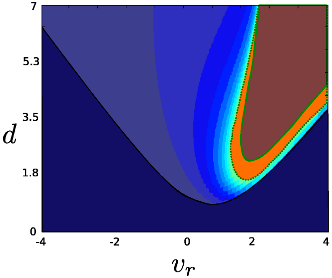
The parameter v_r sharpens the map Φ.



Plausibility of chaos?

It has been observed in the Purkinje cell a period doubling route to chaos in vivo and in vitro, by varying the temperature (which could result in varying v_r). It is also observed in the Hogkin Huxley's model with temperature.

Electrophysiological Classes



J.T., Romain Brette, Submitted at SIAM Appl. Dyn. Syst.

Contributions

1. We introduced a unified framework allowing to study and compare planar spiking neuron models.
2. We proved that Izhikevich model differred from other models because of the necessary presence of a strict voltage threshold.
3. We studied the interplay between continuous and discrete nonlinear dynamics resulting in producing different spike patterns.
4. Our study provides classifications in the parameter space of different electrophysiological behaviors.

Weakly coupled neural oscillators

Oscillations

- Oscillations is one of the most prominent brain activity type
- Responsible of repetitive activity such as locomotion, feeding, breathing, epileptic seizures, ...
- We aim at understanding how the spikes of one neuron affects the timing of the others.

Mathematical Theory

It is therefore important to develop t he theory of coupled oscillators.

Living around a cycle

Stability properties of the perturbations around a cycle

Floquet theory of linear ODEs with periodic coefficients.

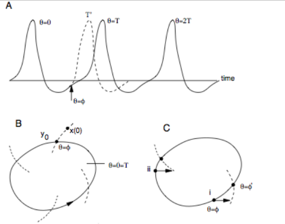
Phase Parametrization

- Consider the dynamical system $\dot{X} = F(X)$ and assume it has a T-periodic limit cycle Γ which is orbitally asymptotically stable.
- Γ can be parametrized by the time modulo the period T which defines a phase $\theta \in [0, T[$ along the limit cycle, and denote $\Theta(x)$ the phase of $x \in \Gamma$.
- When a cycle is asymptotically stable, it is possible to define a phase $\Theta(y)$ for y in a neighborhood of Γ, since there exists $x \in \Gamma$ such that $\|X(t, y) - X(t, x)\| \to 0$ when $t \to \infty$, and $\Theta(y) := \Theta(x)$

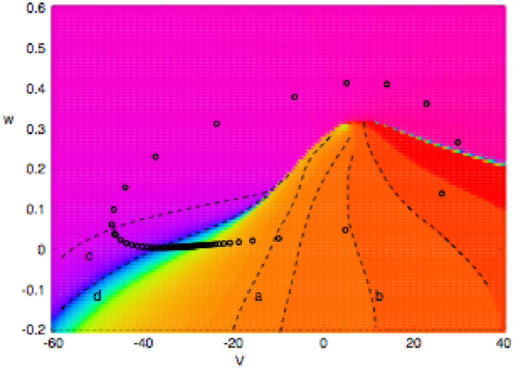
Isochrons

Phase Parametrization

- The set of points that have the same phase are called isochrons of the limit cycles, denoted $N(x)$
- The isochrons are local sections: if $y \in N(x)$, $X(T, y) \in N(x)$.
- In practice, isochron can be computed numerically.
- Isochrons form a partition of the neighborhood of Γ



Isochrons for Morris-Lecar Model



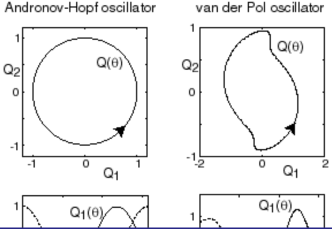
Phase Transition Curve

Weak coupling: We consider the forced oscillator $\dot{X} = F(X) + \varepsilon s(t)$. It can be remapped in terms of phase as:

$$\dot{\theta} = 1 + \varepsilon Q(\theta) \cdot s(x)$$

where $\cdot$ is the scalar product. $Q(\theta)$ is the linear response curve, or phase response curve (PRC).

Example: SNIC oscillator: $Q(\theta) = 1 - cos(\theta)^2$, Hopf oscillator: $Q(\theta) = sin(\theta - \Psi)$ where Ψ is a constant phase shift



Networks of weak coupled oscillators

$$\dot{X}_i = F_i(X_i) + \varepsilon \sum_{j=1}^{n} g_{ij}(X_i, X_j)$$

can be mapped in terms of phase onto:

$$\dot{\theta}_i = 1 + \varepsilon Q_i(\theta_i) \sum_{j=1}^{N} g_{ij}(\gamma(\theta_i), \gamma(\theta_j)).$$

Interest

Allows studying the dynamics of complex oscillators in terms of simple ODE.

Cortical Column modeling

Coritical column models

Assumptions

- Individual spikes do not constitute the cortical column signal
- BUT the signal of a cortical column arises from the mean firing rate of the neurons projecting towards the different cortical areas it is connected to.
- Two main cortical populations contribute to the phenomenon under investigation: Pyramidal neurons and inhibitory interneurons

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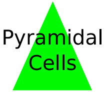
Jansen and Rit's model of EEG signal



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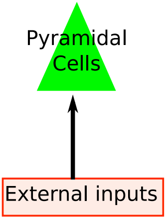

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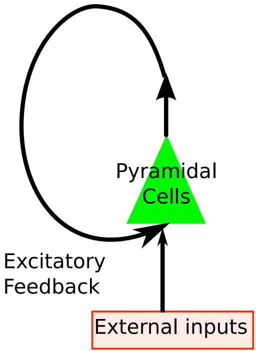

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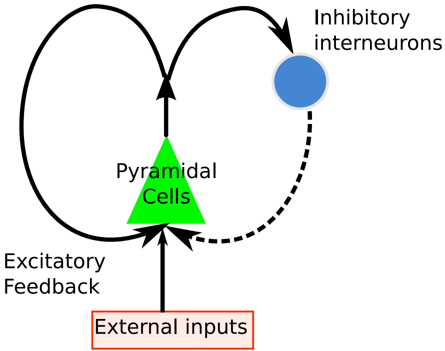
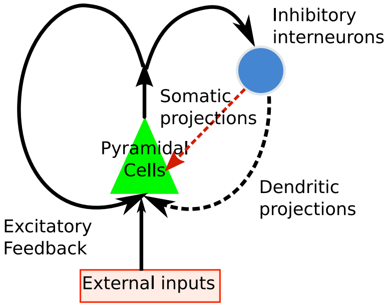
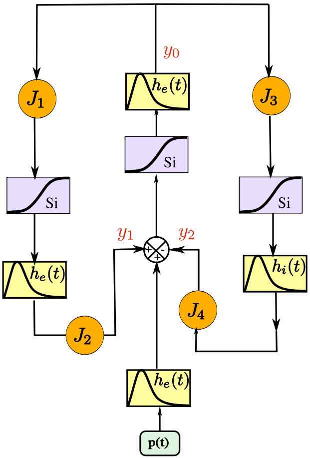


Wendling & Chauvel's model



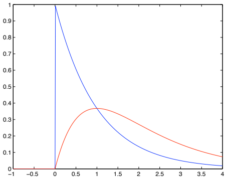
Block Diagram



Two Main processes

- Synaptic integration: modelled as linear
- the nonlinear voltage to firing rate transformation S

Block Diagram



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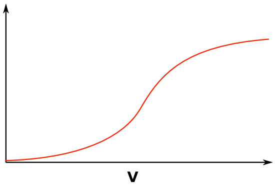

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- the nonlinear voltage to firing rate transformation S

Resulting Equations

$$\begin{cases} \ddot{y}_0(t) & = A\, a Si\left(y_1(t) - y_2(t)\right) - 2\, a\, \dot{y}_0(t) - a^2\, y_0(t) \\ \ddot{y}_1(t) & = A\, a\left\{p(t) + J_2 Si\left(J_1 y_0(t)\right)\right\} - 2\, a\, \dot{y}_1(t) - a^2\, y_1(t) \\ \ddot{y}_2(t) & = B\, b\, J_4 Si\left(J_3 y_0(t)\right) - 2\, b\, \dot{y}_2(t) - b^2\, y_2(t). \end{cases}$$

Conclusion

We are led to study properties of a nonlinear dynamical system. The first thing to do for understanding the behavior of the system, we study the bifurcations of the system

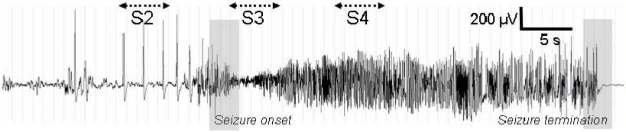
Theoretical Aspects

What do we want to do?

A correspondence catalogue between bifurcations and neuronal behaviors

We aim at relating neuronal behaviors and bifurcations properties of the underlying dynamical system.
Main interest: genericity property.

Epileptic-related phenomena



Phenomena of interest

- Oscillatory activity (mostly alpha rhythms)
- Fast onset activity (seizure onset)
- Slow high amplitude epileptic spikes

Bifurcations

- Normal behavior is linked with the presence of a fixed point in the system
- Oscillatory activity is linked with the presence of periodic solutions (limit cycles).

More complex structures need more profound analysis of mathematical structures.

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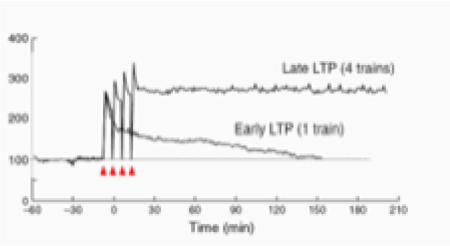
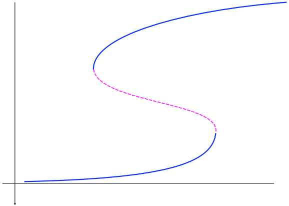
Bistability



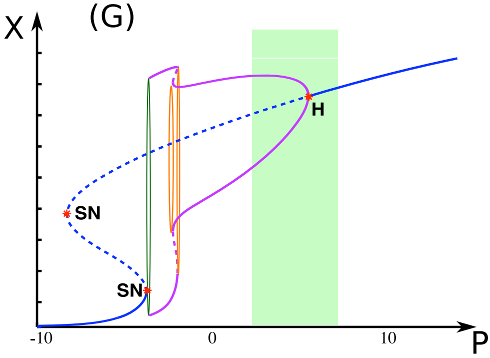


Conclusion

Bi-stability and Bi-rhythmicity can arise from cusp bifurcations of fixed points (resp. cusps of limit cycle)

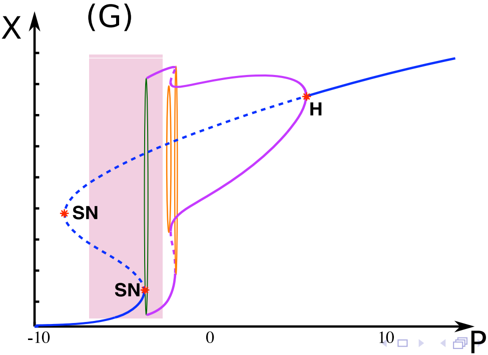
Alpha, Beta, Theta rhythms

Can be linked with the presence of Hopf bifurcation



Epileptic activity

Epileptic spikes correspond to low frequency, large amplitude, oscillations that appear suddenly. A simple bifurcation giving rise to large amplitude slow waves is the saddle homoclinic orbit, that can arise from what is called *Bogdanov-Takens* bifurcation.



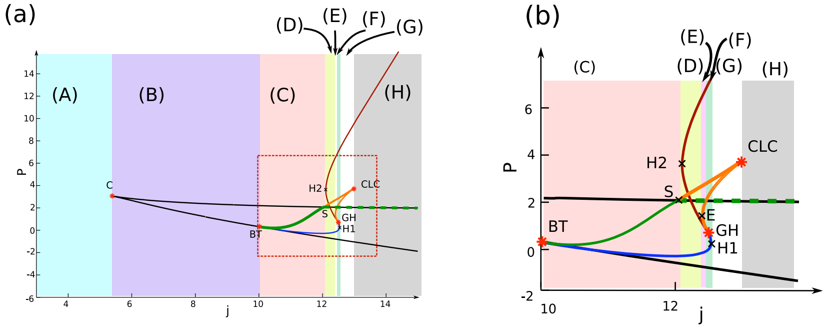
Conclusion

Codimension 2 bifurcations are of interest

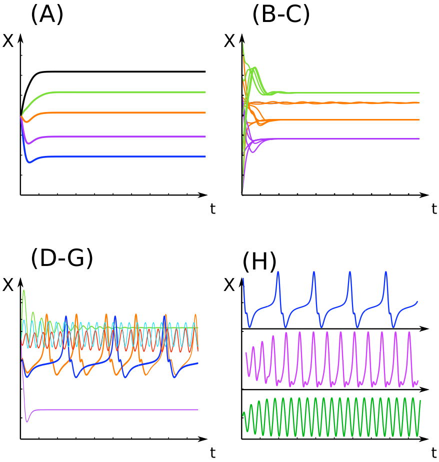
The study of cortical models such as Jansen and Rit models can be closely related to codimension two bifurcations of the underlying dynamical system and allows to understand and predict conditions that can lead to epileptic behaviors.

Application to Jansen and Rit's model

Full study of codimension two bifurcations in Jansen and Rit's model (with respect to total connectivity and input)



Four different behavior zones



Dependency on the excitation and inhibition balance

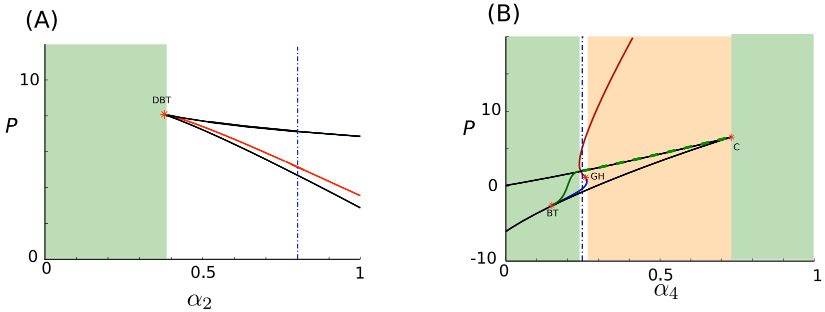
So Far

We studied the possible behaviors and the bifurcations as the input and the total connectivity varies. This corroborates for instance observations that neo-synaptogenesis, i.e. increased total connectivity, favors the apparition of epileptic behavior.

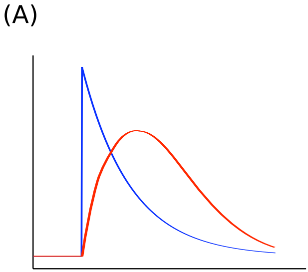
What we want to do

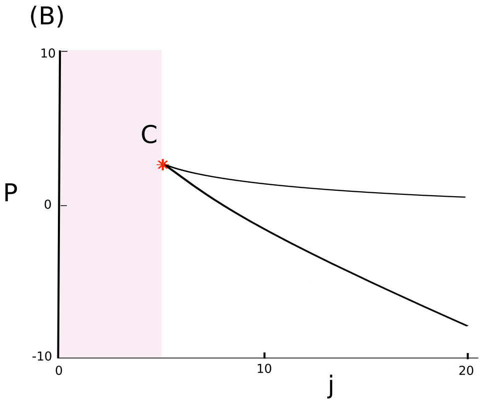
Most anticonvulsant drugs act either on excitatory or inhibitory connections (either acting on channels or on neutransmitter). Hence we aim at addressing the effect of changing the balance of excitatory and inhibitory connections: α_2 controls the excitation and α_4 the inhibition

Dependency on the excitation and inhibition balance



Importance of Delays





What we are left explaining

What we can explain through bifurcation analysis

We explain the emergence of

- alpha, beta and theta activity
- rhythmic spikes
- importance of delays and of a safe balance between excitation and inhibition

What we cannot explain

- Fast onset activity
- interictal spikes and bursts

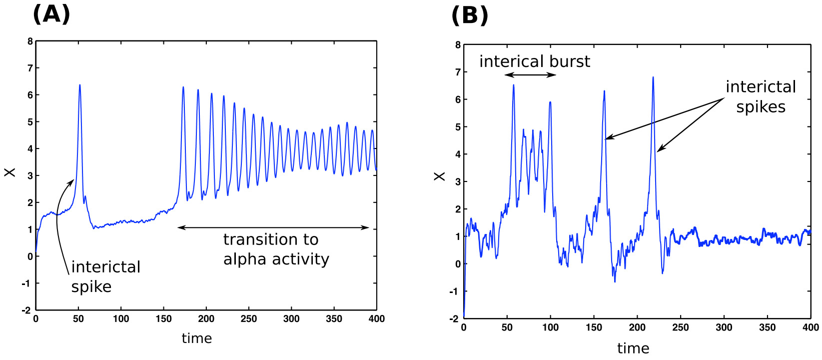
Bifurcations and Neural Mass Models

Interictal spikes and Bursts

Theoretical interpretation

The presence of a saddle-homoclinic bifurcation and noise in the input directly generates the important interictal spikes, that are of particular interest and that lacked models. Interictal spikes on which rapid discharges (interictal bursts) are predictors of rapid discharge (according to Patrick Chauvel) that was not modelled or interpreted so far, and understanding it can improve seizure predictions.

Interictal spikes and Bursts Simulations



Fast Onset Activity

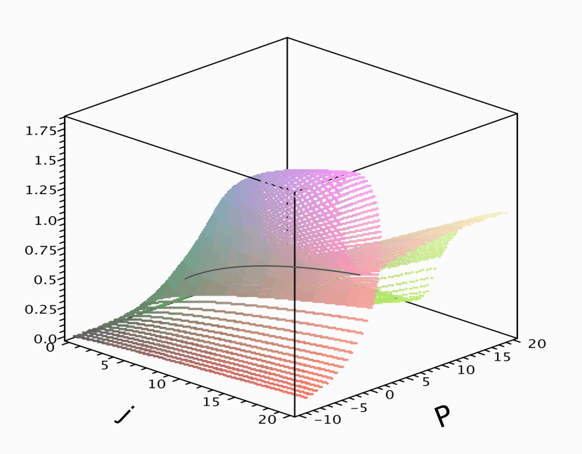
No cycle for FOA

In the analysis of JR's (and WC's) models, no rapid cycle appeared. However, noise can explain this phenomenon.

Mathematical Interpretation

Close to the epileptic zone, we observe that the imaginary part of the eigenvalues of the Jacobian matrix are characterized by a high value. Therefore, convolution with noisy input will generate fast rhythms.

Fast Onset Activity



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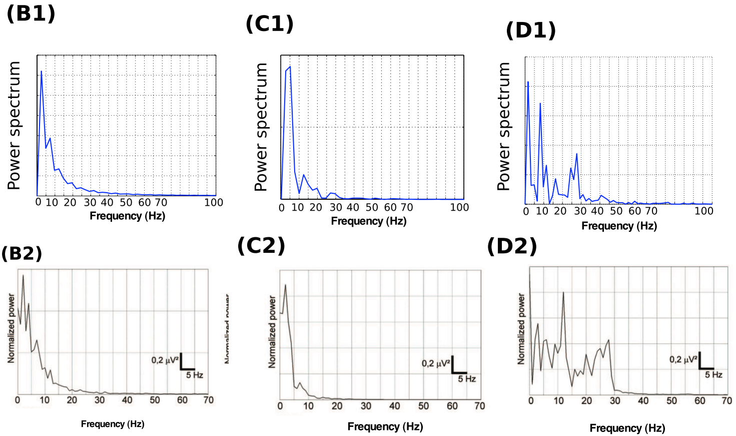

A path towards seizures

Let us assume that, in an epileptic column, that a process results in the regular increase of total input (that can for instance be triggered by oscillatory activity). In that case, Jansen and Rit's model shows all the phases towards seizure. We can also model the injection of anticonvulsant and the termination of the crisis.

A path towards seizures