some mathematical methods for neurosciences, lecture 1

Romain Veltz / Etienne Tanré

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Details about the lecture

Website of the lectures: **http://romainveltz.pythonanywhere.com/teaching/**

Go to **https://sympa.inria.fr/sympa/info/cours_mmn_paris_2022_23** to subscribe to the mailing list

Research axis:

- Mathematical modeling: mean field, interplay between noise and dynamics, space dependent neural networks (waves,...)
- Emphasis on biology: modeling the synapse, pain. [postdoc]
- Dynamics of spiking neurons with additional details: homeoplasticity, dendritic compartment
- Effect of plasticity on network dynamics
- Bio-inspired Machine Learning

Overall goal of lectures on (deterministic) methods

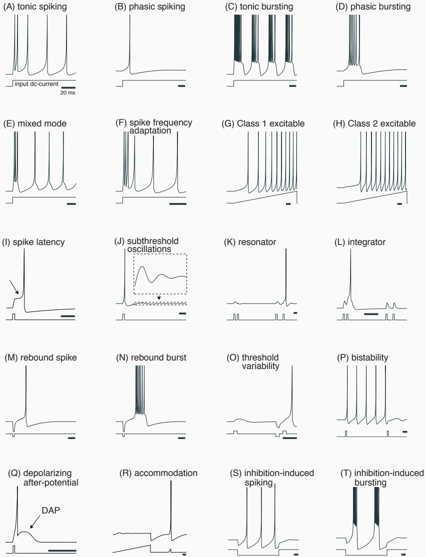
To understand dynamical behaviors of models from neuroscience.

What is the working regime of the phenomenon?

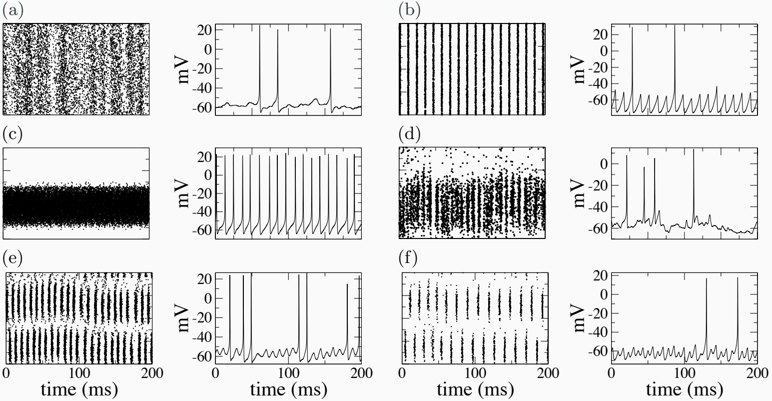
Emphasis on spiking neurons.

- Reduction of these models (locally) to simple low dimensional ODE
- Reduction of these models (locally) based on a difference of time scales?
- Understand the algorithms / maths behind the numerical tools to investigate these models.
- To be able to build models that match a behavior.

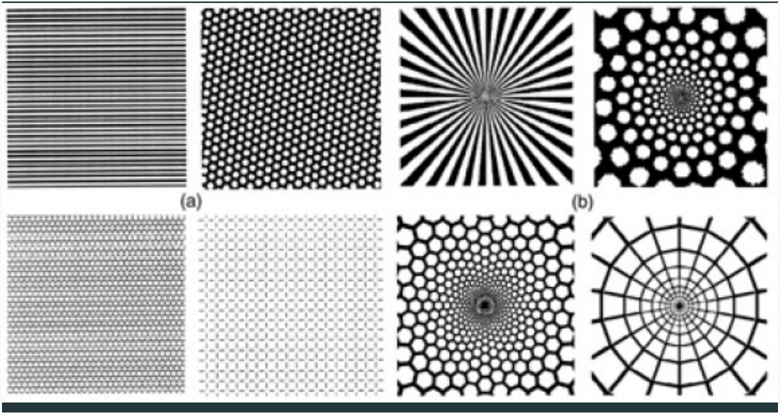
Spiking behaviors



Example of network dynamics [Roxin-etal:06]

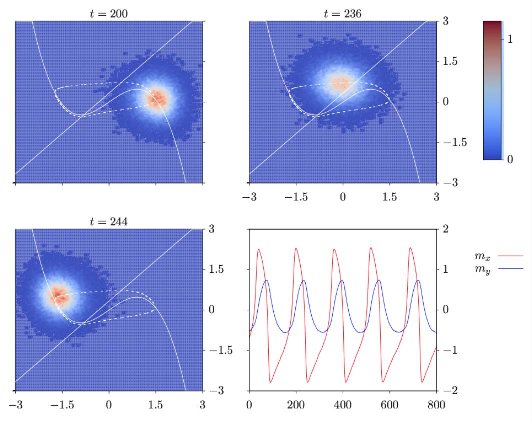


Activity patterns in visual cortex [Bressloff-etal:03]



McKean-Vlasov [Lucon-etal:18]

$$\mathrm{d}X_t = \left(\delta F\left(X_t\right) - K\left(X_t - \mathbb{E}\left[X_t\right]\right)\right)\mathrm{d}t + \sqrt{2}\sigma \mathrm{d}B_t, t \geqslant 0$$



$$V_t = V_0 + \int_0^t b\left(V_u\right) du + J \int_0^t \mathbb{E} f\left(V_u\right) du - \int_0^t \int_{\mathbb{R}_+} V_{u-} 1_{\left\{z \leq f\left(V_{u-}\right)\right\}} \mathbf{N}(du, dz)$$

Outline

http://romainveltz.pythonanywhere.com/teaching/

A few notions concerning the biology of the brain

Towards the Hodgkin-Huxley model

Simplified models of spiking neuron

Introduction to dynamical systems

Invariant sets

- Stable/Unstable manifolds

A few notions concerning the biology of the brain

Different scales

$\sim 10^{11}$ neurons, connected by $\sim 10^{15}$ synapses. Glial cell number more controversial

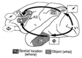
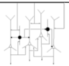
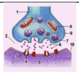
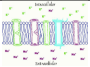
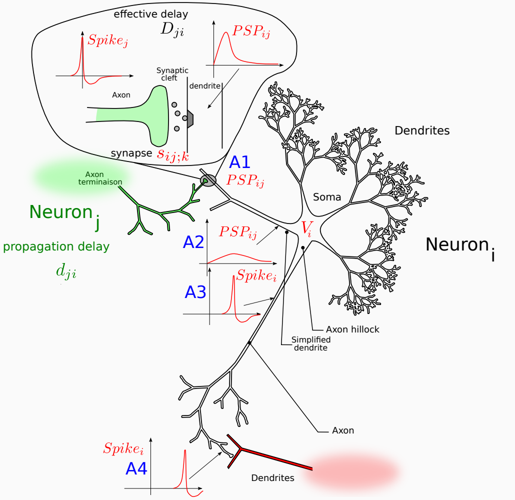
~10cm	Whole brain	
~1cm	Brain structure/cortical areas	
100μm- 1mm	Local network/'column'/'module'	
10μm- 1mm	Neuron	
100nm- 1μm	Sub-cellular compartments	
~10nm	Channel, receptor, intracellular protein	

Figure 1: Picture by N.Brunel

A cartoon neuron



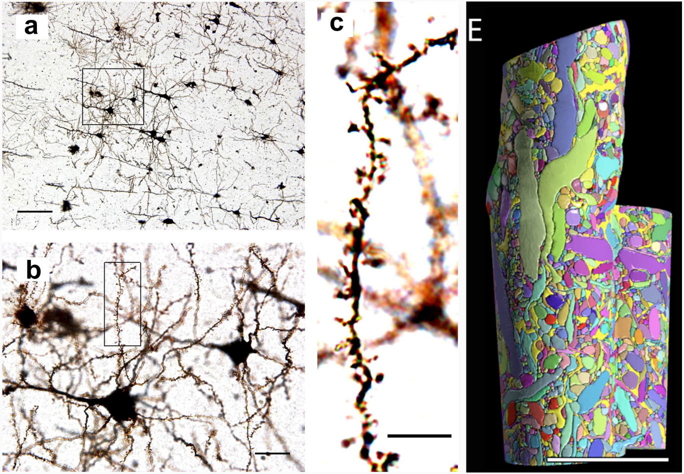


Figure 2: **Left:** Photomicrographs of Golgi-stained mouse cortical neurons from slices. (a) Scale = 50 μm. (b) Scale = 10 μm. (c) Scale = 5 μm. **Right:** Kasthuri et al. 2015 Video

Neuropil

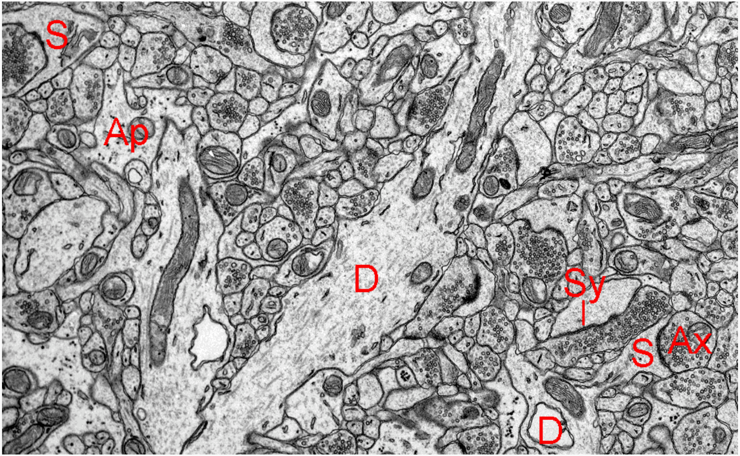
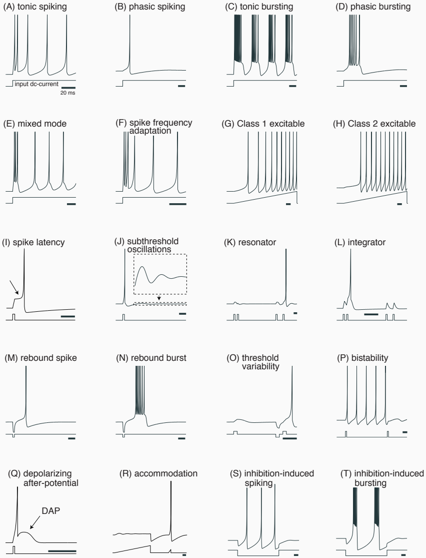


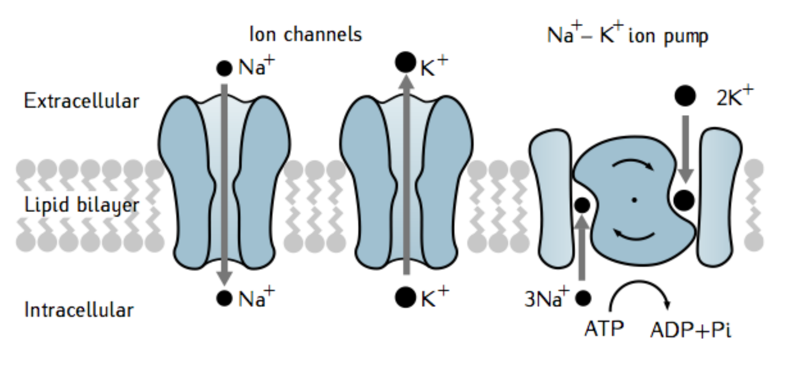
Figure 3: *axons (Ax) synaptic contacts (Sy) dendritic shafts (D) spines (S) astrocytes (Ap). Fine Structure of the Nervous System: Neurons and Their Supporting Cells*

Towards the Hodgkin-Huxley model

Outline

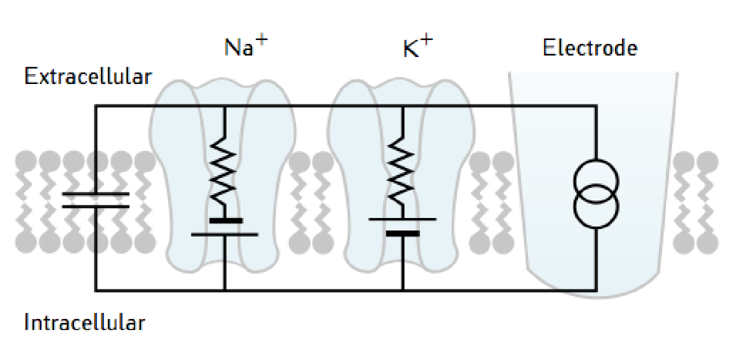
Towards the Hodgkin-Huxley model





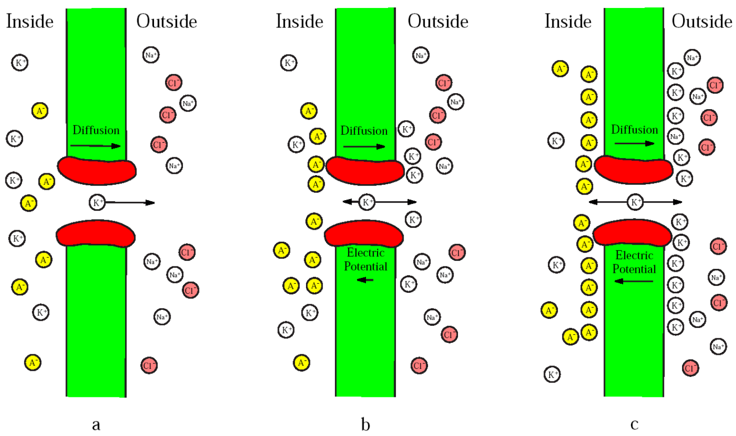
The channels are ion selective. More K^+ inside, more Na^+outside

The Brain: an electro-chemical machine



Passive ion channel

$\Rightarrow$ Interplay between diffusion and $\vec{E}$



The Nernst equation- Reversal / resting membrane potential

⇒ Case of a single ion specie

We start with the Nernst-Planck equation which describes the ionic flux accross the membrane

$$J = J_{diff} + J_{drift} = -D\nabla[X] - \mu z[X]\nabla V$$

- z ion valence

Improved by Goldman-Hodgkin-Katz equation which takes into account all ions

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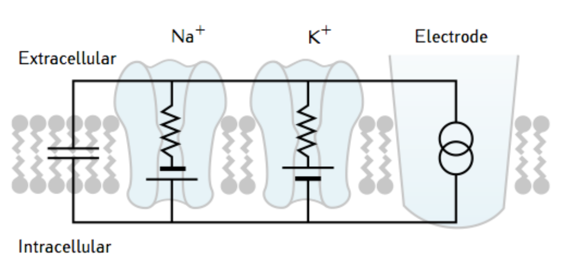
Nernst equation:

- flux across a 1d membrane $I = -D\left(\nabla[X] + \frac{zF}{RT}[X]\nabla V\right)$
- $I = 0$ gives:

$$E_X \equiv V_{in} - V_{out} = -\frac{RT}{zF}\ln\frac{[X]_{in}}{[X]_{out}}$$

Improved by Goldman-Hodgkin-Katz equation which takes into account all ions

Equivalent Model



$$I_x = g_X(V) \cdot (V - E_X)$$

- More ion types of the Nernst-Planck equation $\rightarrow$ Goldman–Hodgkin–Katz current
- Linearize GHK current

$$C\frac{dV}{dt} = -I_L - I_{Na} - I_K$$

Active channels

Properties

- affected by membrane potential V
- affected by intracellular molecules/ions (Calcium)
- affected by extracellular molecules (Glu, GABA...)
- channels can be open / closed
- channels can be activated / inactivated

- Patch clamp: Fix V by adjusting I: gives $I - V$ curve

$$I_X = \bar{g}_X m^a h^b (V - E_X)$$

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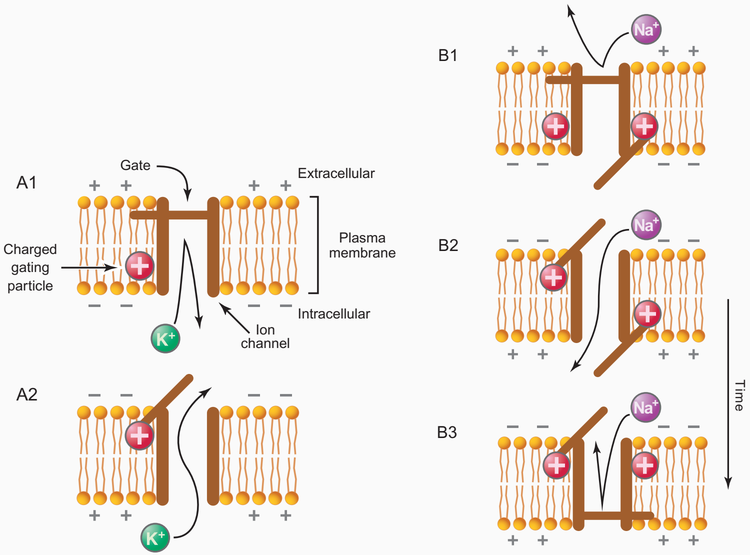
- Patch clamp: Fix V by adjusting I: gives $I - V$ curve
- Ion substitution: select some I_X (Hodgkin-Huxley 1952)
- Toxin to block some channel, to select some I_X
  - tetrodotoxin (fugu) for Na^+ channel
  - tetraethylammonium for K^+ channel

$$I_X = \bar{g}_X m^a h^b (V - E_X)$$


A1
Gate
Extracellular
Charged
gating
particle
Plasma
membrane
Intracellular
Ion
channel
K+
A2
K+
B1
Na+
B2
Na+
B3
Na+
Time

Ion channels are stochastic

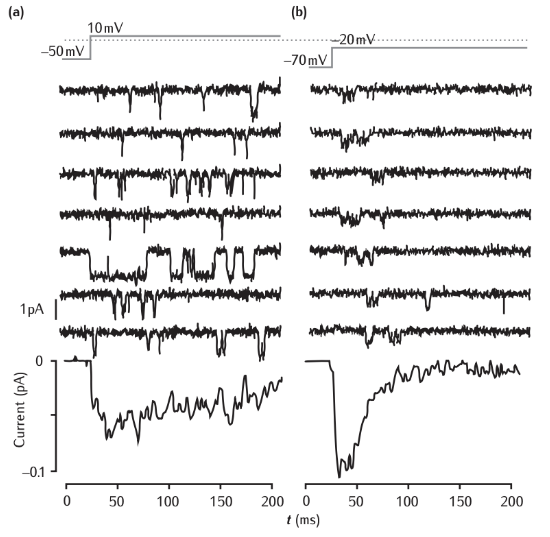
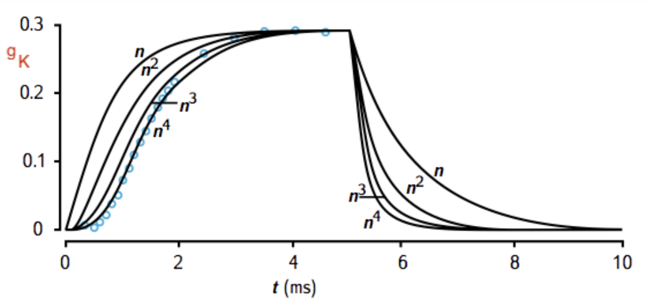


Figure 4: VGCC a) L-type b) T-type, from Sterratt.

The Potassium current $g_K = \bar{g}_K n^4$, $E_K \approx -72mV$



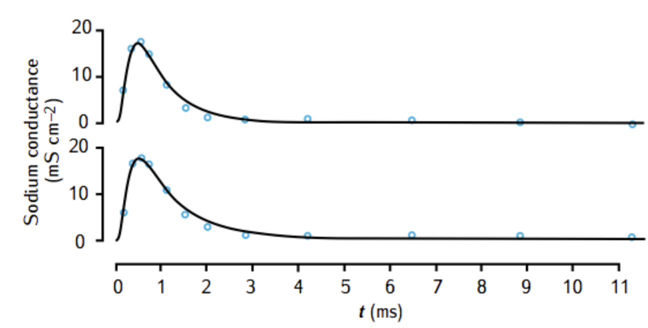
(From Sterratt)

$$C \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} O \text{ or } \frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n n$$

- Voltage clamp gives $n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}$
- Rising time: $\tau_n = \frac{1}{\alpha_n + \beta_n}$
- $\alpha_n = 0.01 \frac{V+55}{1-exp(-(V+55)/10)}$
- $\beta_n = 0.125exp(-(V+65)/80)$

The sodium current $g_{Na} = \bar{g}_{NA} m^3 h,\ E_{Na} \approx 55mV$

We compute $g_K(t)$ with previous equation



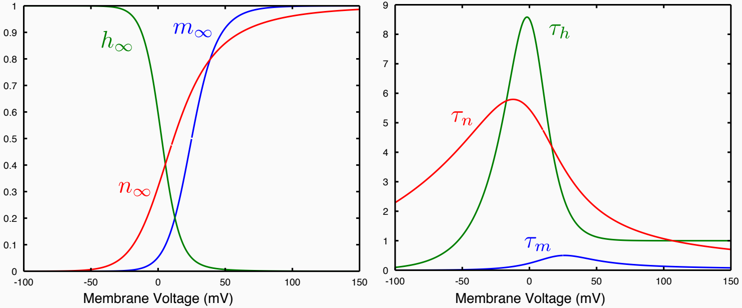
a) $V_{rest} \rightarrow V_{rest} + 76mV$ b) $V_{rest} \rightarrow V_{rest} + 88mV$ (From Sterratt)

Introduction of the state *not inactivated* h independent of the state m.
It is called the inactivation gate.

- $\alpha_m = 0.1 \frac{V+40}{1-exp(-(V+40)/10)}$
- $\beta_m = 4exp(-(V+65)/18)$
- $\alpha_h = 0.07exp(-(V+65)/20)$
- $\beta_n = \frac{1}{exp(-(V+35)/10)+1}$

Their work earned them a Nobel prize in 1963.

$$C\dot{V} = I - \bar{g}_K n^4 (V - E_K) - \bar{g}_{Na} m^3 h (V - E_{Na}) - \bar{g}_L (V - E_L)$$

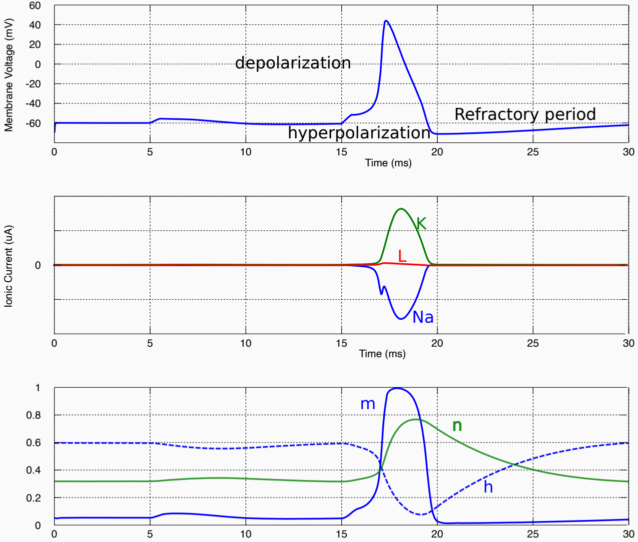


Summary 2/2

Their work earned them a Nobel prize in 1963.

- Model of membrane patch. Can be used for dendrites, axons...
- Derived for the squid at $T \sim 10^o C$. Extended to mammals at $36^o C$ by **[Traub-Mile:91]**
- Detailed compartmental model NEURON simulator, HBP project.
- Ions channels modeled by Markov Chains, PSICS simulator
- Finite size effects
- Ion channel regulation (E. Marder, T. O'Leary...)

Action potential, $E_{Na} \approx 55mV, E_K \approx -72mV$



"Relatively" straightforward, but see next...

Simplified models of spiking neuron

Outline

A variety of models

On the blackboard...

Morris-Lecar model

Simple 2d excitable model with two channels.

Equations:

$$\begin{cases} C\dot{V} = I - g_L(V - V_L) - g_{Ca} m_\infty(V) \cdot (V - V_{Ca}) - g_K n \cdot (V - V_K) \\ \dot{n} = \lambda(V)(n_\infty(V) - n) \end{cases}$$

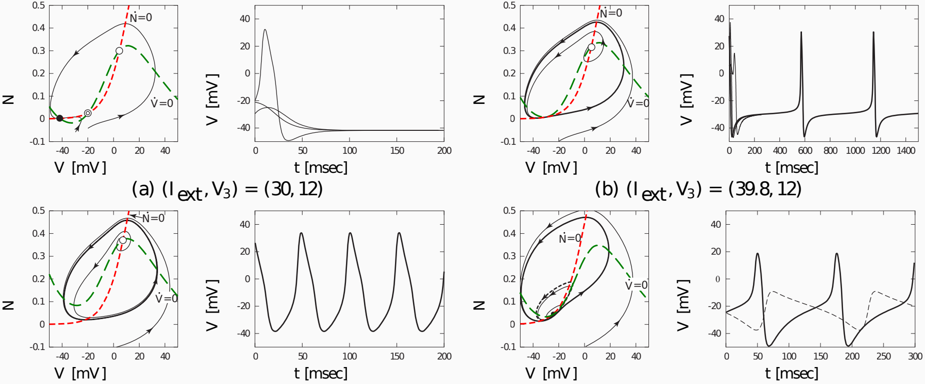
where

$$m_\infty(V) = \frac{1}{2}\left(1 + \tanh\left[\frac{V - V_1}{V_2}\right]\right), n_\infty(V) = \frac{1}{2}\left(1 + \tanh\left[\frac{V - V_3}{V_4}\right]\right),$$

$$\lambda(V) = \bar{\lambda} \cosh\left[\frac{V - V_3}{2V_4}\right]$$

- can generate AP
- there is a threshold for firing → see *Lecture 3.*
- possible oscillatory behavior

Morris-Lecar: Phase diagrams



(a) $(I_{ext}, V_3) = (30, 12)$

(b) $(I_{ext}, V_3) = (39.8, 12)$

(c) $(I_{ext}, V_3) = (70, 12)$

(d) $(I_{ext}, V_3) = (50.5, 2)$

Observation

- $\tau_m(V)$ is much smaller than $\tau_h(V)$,$\tau_n(V)$
- (n, h) almost lies on a line $n = b - rh$

This gives:

- $m(V) \approx m_\infty(V)$
- a system in the variables (V, n)

It shows that the V-nullcline has a cubic shape. It gives:

$$C\dot{V} = I - \bar{g}_K n^4 (V - E_K) - \frac{\bar{g}_{Na}}{r} m_\infty(V)^2 (b - n)(V - E_{Na}) - g_L(V - E_L)$$

$\Rightarrow$ Reduction not trivial, use of singular perturbations and slow/fast dynamics.

Simplified model to capture the essence of the cubic nature of the V-nullcline

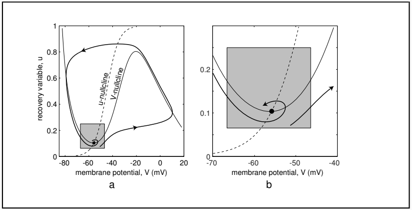
Equations:

$$\begin{cases} C\dot{V} = V(V-a)(1-V) - w + I \\ \dot{w} = \epsilon(V - \gamma w) \end{cases}$$

- It has been used to model nerve conduction, heart...
- ϵ is small so the recovery variable is much slower than voltage

Nonlinear integrate and fire

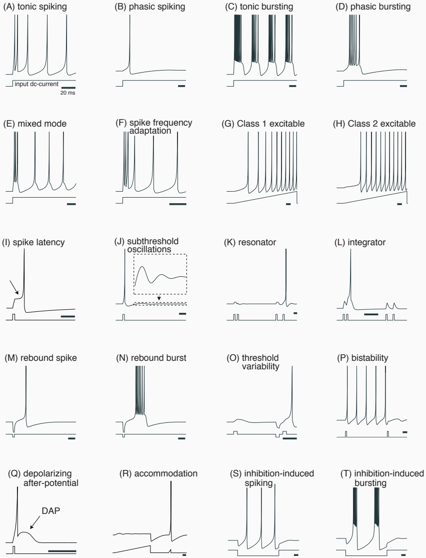
- Neglect the spike generation mechanism
- Previous models can be reduced to 2d models with:
    - fast membrane potential V: *N-shaped nullcline*
    - slow recovery variable (K activation, Na inactivation...): *sigmoid-shaped nullcline*



$$\begin{cases} C\dot{V} = F(V) - w + I \\ \dot{w} = a(bV - w) \end{cases}$$

- Spike emitted at $t = t^*$ when V reaches a cutoff value θ or when it blows up.
- Reset $V^* \to c$ and $w^* \to w^* + d$

Spiking regimes from simplified models



Introduction to dynamical systems

Outline

Definition

A dynamical system is a triplet (T, X, ϕ^t) where $T \subset \mathbb{R}$ ou $\mathbb{Z}$, X is the state space and $\phi^t : X \to X$ is a family of operators such that:
- $\phi^0 = Id$
- $\phi^{t+s} = \phi^t \circ \phi^s$

- The system maps an initial state x_0 to a state $x(t) = \phi^t(x_0)$ at time t
- If T contains negative values, the system is said *invertible*
- The state $\phi^t(x_0)$ may be defined only locally in time. The *orbit* of x_0 is the family $\phi^t(x_0)$ when it is defined.

$\Rightarrow$ Think about the solutions of ordinary differential equations or sequences...

$\Rightarrow$ For us, X will be a Banach space.

$$\dot{x} = F(t, x)$$

- $F : I \times \Omega \to X$ where Ω open set in X, Banach space.
- F is continuous, locally lipschitz in the second variable

Theorem

For all $\tau \in I$ and $u_0 \in \Omega$, there are $\delta > 0, \alpha > 0$ such that the system

$$\begin{cases} \dot{x} = F(t, x) \\ x(t_0) = x_0 \end{cases} \tag{E}$$

has a unique solution defined on $]t_0 - \alpha, t_0 + \alpha[$ for all $x_0 \in B(u_0, \delta), t_0 \in\,]\tau - \delta, \tau + \delta[$.

About the maximal solution:

Fact

Let J be the union of all time intervals containing t_0 for which (E) has a solution. Then, there is a solution x defined on J. All other solutions are restriction of x.

Invariants sets

$\Rightarrow$ Very important to understand the dynamics globally

Definition

An invariant set of a dynamical system (T, X, ϕ^t) is a subset $S \subset X$ such that $x_0 \in S$ implies $\phi^t(x_0) \in S$ for all $t \in T$.

Example

An **equilibrium** is a point x_0 such that $\forall t\ \phi^t(x_0) = x_0$ when ϕ^t is defined

Example

A **limit cycle** is a periodic orbit

Example

A **2-torus**. For example when the flow can be written $\phi^t(x_0) = u(t, \alpha t)$ with $u : [0, T]^2 \to X$ periodic wrt the 2 variables.

Stability of invariant sets 1/2

Definition

An invariant set S_0 is **stable** if for any sufficiently small neighborhood U of S_0, there exists a neighborhood $V \subset U$ such that $\phi^t(V) \subset U$ for all $t > 0$.

Definition

An invariant set S_0 is **unstable** if it is not stable.

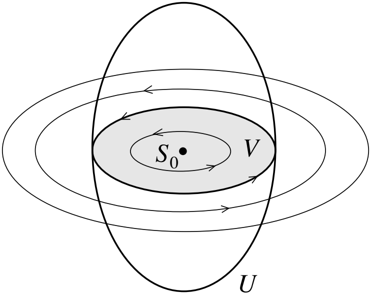


Figure 5: Note: S_0 is not asymptotically stable

Definition

An invariant set S_0 is **asymptotically stable** if it is stable and there is neighborhood U of S_0 such that $d(\phi^t(x_0), S_0) \to 0$ as $t \to \infty$ for all $x_0 \in U$.

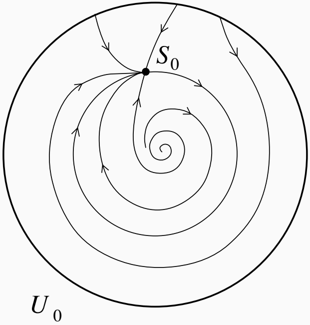


Figure 6: Note: S_0 is not asymptotically stable

Theorem

Let $x \to F(x)$, $x \in \mathbb{R}^n$, F differentiable at x^f and x^f a fixed point of F: $x^f = F(x^f)$. Then x^f is asymptotically stable if all the eigenvalues λ of $dF(x^f)$ satisfy $|\lambda| < 1$.

Lemma

For $\mathbf{A} \in M_n(\mathbb{R})$, assume $\max_{\lambda \in \Sigma(\mathbf{A})} |\lambda| = r < \infty$, then, for all $\epsilon > 0$, there is an **equivalent** norm such that $|||\mathbf{A}||| \leq r + \epsilon$.

Theorem

Let $x \to F(x)$, $x \in \mathbb{R}^n$, F differentiable at x^f and x^f a fixed point of F: $x^f = F(x^f)$. If one eigenvalue λ of $dF(x^f)$ satisfies $|\lambda| > 1$, then x^f is not stable.

Exo: show this.

Stability of equilibria (ODE)

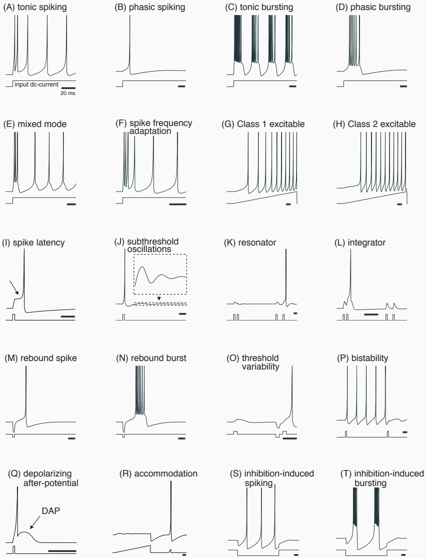
Theorem

Let $\dot{x} = F(x)$, $x \in \mathbb{R}^n$, F C^1 and x^f an equilibrium: $F(x^f) = 0$. Then x^f is asymptotically stable if all the eigenvalues λ of $dF(x^f)$ satisfy $\Re(\lambda) < 0$.

Theorem

Let $\dot{x} = F(x)$, $x \in \mathbb{R}^n$, F C^1 and x^f an equilibrium: $F(x^f) = 0$. If an eigenvalue λ of $dF(x^f)$ satisfies $\Re(\lambda) > 0$, then x^f is not stable.

Spiking behaviors



I as a parameter, see *Lecture 3.*

Quick reminder

- Asymptotic stability of equilibria for maps: $|\lambda| < 1$ (multipliers)
- Asymptotic stability of equilibria for ODE: $\Re\lambda < 0$
- Asymptotic stability of periodic orbits for ODE: $|\lambda| < 1$ where $\lambda \in \mathit{Spectrum}(\Pi^{\Sigma})$. (Floquet multipliers)
- Instability for maps (resp. ODEs) if there is λ such that $|\lambda| > 1$ (resp. $\Re\lambda > 0$)

Can we be more quantitative?

Two fundamental examples

1. The saddle-Node bifurcation
2. The Hopf bifurcation

Invariant sets

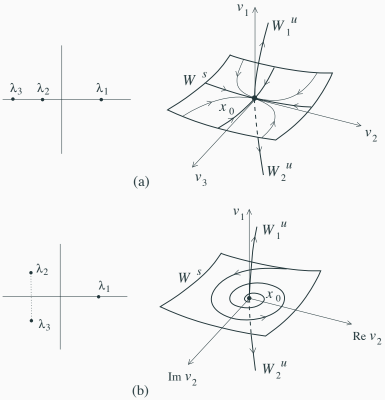


Figure 7: a) Saddle b) Saddle-Foci

Hyperbolic equilibria - Continuous DS

$$\dot{x} = \mathbf{F}(x),\ \mathbf{F} \text{ smooth with } \mathbf{F}(x_0) = 0$$

Let n_-, n_0, n_+ be the number of eigenvalues of $d\mathbf{F}(x_0)$ with *negative, null, positive* real part counted with multiplicity.

Definitions

An equilibrium is:

- *hyperbolic* if $n_0 = 0$
- a *hyperbolic saddle* if $n_- n_+ \neq 0$

Since a generic matrix has no eigenvalues on the imaginary axis, hyperbolicity is a typical property and an equilibrium in a generic system (i.e., one not satisfying certain special conditions) is hyperbolic.

Invariant sets: Local stable manifold - Continuous DS

Consider an equilibrium x_0, its stable and unstable sets are defined as subsets of

$$W^s_{loc} = \{x : t \to \phi^t(x) \in C^1_b(\mathbb{R}^+)\}$$

$$W^u_{loc} = \{x : t \to \phi^t(x) \in C^1_b(\mathbb{R}^-)\}$$

Exo: Check that the unstable manifold is not empty if the fixed point is unstable.

$$W^s_{loc} = \{x : t \to \phi^t(x) \in C^1_b(\mathbb{R}^+)\}$$

Define E^s(resp. E^u) as the **generalized eigenspace** corresponding to the eigenvalues of $d\mathbf{F}(x_0)$ of negative (resp. positive) real part.

Theorem

Let $x_0 \in \mathbb{R}^n$ be a **hyperbolic** equilibrium ($i.e.$, $n_0 = 0, n_- + n_+ = n$) for $\dot{x} = \mathbf{F}(x)$ with $\mathbf{F} \in C^1(U)$, U neighborhood of x_0 in $\mathbb{R}^n$. Then, there is a neighborhood $\mathcal{V}$ of x_0 in U such that W^s_{loc} and W^u_{loc} are manifolds tangent to E^s and E^u at $x = x_0$. More precisely:

- $W^s_{loc} \cap \mathcal{V} = \{x_0 + v + \Psi^s(v),\ v \in E^s \cap \mathcal{V}\}$ with $\Psi^s \in \mathcal{C}^1(E^s \cap V, E^u)$, $\Psi^s(0) = 0$ and $d\Psi^s(0) = 0$.
- $W^s_{loc} \cap \mathcal{V} = \{v \in \mathcal{V} \mid \lim_{t\to\infty} \phi^t(v) = x_0\}$.

The dynamics on the manifold read

$$\dot{v} = \Pi^s F(x_0 + v + \Psi(v))$$

where Π^s is the projector on E^s which commutes with $d\mathbf{F}(x_0)$.

We simplify assumptions to ease the formulation.

$$x \to \mathbf{F}(x),\ \mathbf{F} \text{ and } \mathbf{F}^{-1} \text{ smooth with } \mathbf{F}(x_0) = x_0,$$

Let n_-, n_0, n_+ be the number of eigenvalues of $d\mathbf{F}(x_0)$ with modulus $< 1, = 1, > 1$ counted with multiplicity.

Definitions

An equilibrium is:

- *hyperbolic* if $n_0 = 0$
- a *hyperbolic saddle* if $n_- n_+ \neq 0$

Local stable manifold in the discrete case

Definitions

Consider an equilibrium x_0, its stable (unstable) set is defined by

$$W^s(x_0) = \{x : \lim_{k\to\infty} \mathbf{F}^k(x) = x_0\}$$

$$W^u(x_0) = \{x : \lim_{k\to-\infty} \mathbf{F}^k(x) = x_0\}$$

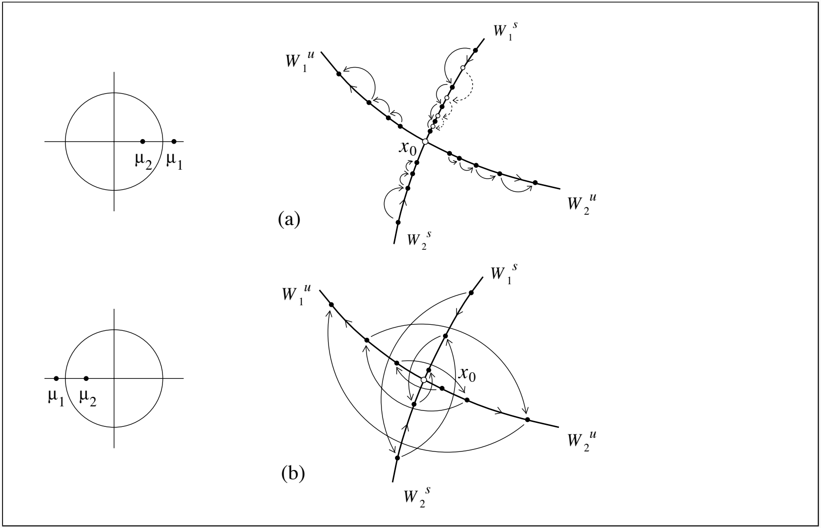
Theorem

Let $x_0 \in \mathbb{R}^n$ be a **hyperbolic** equilibrium ($n_0 = 0$). Then the intersections of $W^s(x_0)$ and $W^u(x_0)$ with a sufficiently small neighborhood of x_0 contain "smooth" **submanifolds** $W^s_{loc}(x_0)$ and $W^u_{loc}(x_0)$ of dimension n_- and n_+, respectively.

Moreover, $W^s_{loc}(x_0)$ (resp. $W^u_{loc}(x_0)$) is tangent to E^s(resp. E^u) at $x = x_0$ where E^s(resp. E^u) is the generalized eigenspace corresponding to the eigenvalues λ of $d\mathbf{F}(x_0)$ such that $|\lambda| < 1$ ($|\lambda| > 1$).

Proof analogous to continuous case if one substitutes ϕ^1 by $\mathbf{F}$.

Example with positive/negative multiplier



End of lecture 1.

Next time:

- Center Manifold
- Normal form theory