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ARGENTINA
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Interdisciplinary work in neuroscience

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The goal of our research is to shed light on the **dynamical mechanisms** involved in the **perception** and the **generation** of **complex sounds** and to study the brain and the peripheral system in this process.
Lecture 1
Introduction to nonlinear dynamics and excitable systems

Lecture 2
Dynamical models for single neurons. Comparison with experimental data.

Lecture 3
The neuroethology perspective in neuroscience.
Case of study: models of vocal production in birds.
Lecture 1
Introduction to nonlinear dynamics and excitable systems
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**Definition**: set of variables that describe state of the system and a law that describes the evolution of the state variables with time.

Example:

The Hodgkin-Huxley model (4-dimensional dynamical system) its state is uniquely determined by the membrane potential, $V$, and the "gating variables" $n$, $m$, and $h$ for persistent $K^+$ and transient $Na^+$ currents. The evolution law is given by a 4-dimensional system of ordinary differential equations.

$$
\begin{align*}
C \dot{V} &= I - \left( \frac{I_K}{g_K n^4(V - E_K)} \right) - \left( \frac{I_{Na}}{g_{Na} m^3 h(V - E_{Na})} \right) - \left( \frac{I_L}{g_L(V - E_L)} \right) \\
\dot{n} &= \alpha_n(V)(1 - n) - \beta_n(V)n \\
\dot{m} &= \alpha_m(V)(1 - m) - \beta_m(V)m \\
\dot{h} &= \alpha_h(V)(1 - h) - \beta_h(V)h,
\end{align*}
$$

Is this dynamical system nonlinear?
Nonlinear Dynamics

Mechanisms responsible for governing the temporal evolution of a system

Nonlinear rules

Let’s see...

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

\[ \dot{n} = \alpha_n(V) (1 - n) - \beta_n(V) n \]

\[ \dot{m} = \alpha_m(V) (1 - m) - \beta_m(V) m \]

\[ \dot{h} = \alpha_h(V) (1 - h) - \beta_h(V) h \]

\[ \alpha_n(V) = 0.01 \frac{10 - V}{\exp\left(\frac{10 - V}{10}\right) - 1} , \]

\[ \beta_n(V) = 0.125 \exp\left(\frac{-V}{80}\right) , \]

\[ \alpha_m(V) = 0.1 \frac{25 - V}{\exp\left(\frac{25 - V}{10}\right) - 1} , \]

\[ \beta_m(V) = 4 \exp\left(\frac{-V}{18}\right) , \]

\[ \alpha_h(V) = 0.07 \exp\left(\frac{-V}{20}\right) , \]

\[ \beta_h(V) = \frac{1}{\exp\left(\frac{30 - V}{10}\right) + 1} . \]
Dynamical Systems

Types of dynamical systems:

Differential equations

\[
\begin{align*}
C \frac{dV}{dt} &= I - I_K g_K n^4 V - I_N a m^3 h V - I_L (V - E_L) \\
\dot{n} &= \alpha_n(V)(1 - n) - \beta_n(V)n \\
\dot{m} &= \alpha_m(V)(1 - m) - \beta_m(V)m \\
\dot{h} &= \alpha_h(V)(1 - h) - \beta_h(V)h,
\end{align*}
\]

Maps

Logistic map

\[x_{n+1} = rx_n(1 - x_n)\]

where \(x_n\) is a number between 0 and 1, which represents the ratio of existing population to the maximum possible population.

Chaos!
The power of the dynamical systems approach to neuroscience (and to many other sciences) is that we can tell many things about a system without knowing all the details that govern the system evolution.
Isn’t it amazing that we can reach such a conclusion without knowing the equations that describe the neuron’s dynamics?

We do not even know the number of variables needed to describe the neuron.
Phase portraits

Quiescent neuron whose membrane potential is resting

(a) resting

membrane potential, $V(t)$

stimulus

PSP

time, $t$

Neuron in an excitable mode

(b) excitable

membrane potential, $V$

PSP

stimuli

Small perturbations (A) result in small excursions from the equilibrium (PSP, postsynaptic potential).

Larger perturbations (B), are amplified by the neuron’s intrinsic dynamics and result in the spike response.

Stable equilibrium

$K^+$ activation gate, $n$

$V$

Equilibrium

Excitable system
Phase portraits

**Quiescent neuron whose membrane potential is resting**
(a) resting

**Neuron in an excitable mode**
(b) excitable

**Pacemaker neuron**
(c) periodic spiking

Stable equilibrium

**Phase portrait**

\[ V(t) \]

stimulus

PSP

time, \( t \)

\[ n \]

K⁺ activation gate, \( n \)

membrane potential, \( V \)

\[ V(t) \]

PSP

A

B

stimuli

spike

periodic orbit
Equilibria and limit cycles can coexist, so a neuron can be switched from one mode to another by a transient input.
What is a bifurcation?
Quiescent neuron whose membrane potential is resting

Neuron in an excitable mode

(a) resting
(b) excitable

PSP
stimulus
time, t

membrane potential, \( V(t) \)

Stable equilibrium

\( \text{K}^+ \) activation gate, \( n \)

membrane potential, \( V \)

Phase portrait

If the dynamical system goes from (a) to (b), is it going through a bifurcation?

No bifurcation!

This dynamical system contains (a)

The differences between (A) and (B) are the initial conditions.

There is not a qualitative change
If the dynamical system goes from (b) to (c), is it going through a bifurcation?

Let’s see…
(b) : stable fix point
(c) : unstable fix point and a limit cycle.

There is a qualitative change

Bifurcation!
As the magnitude of the injected current slowly increases, the neurons bifurcate from resting (equilibrium) mode to tonic spiking (limit cycle) mode.
Equilibrium state leading to the transition from **resting** to **periodic spiking** behavior in neurons. (codimension-1, i.e., 1 control parameter)

Depending on the initial conditions, the neuron may spike (or decay to the stable resting position) or burst.

**Saddle-node bifurcation**

Bifurcation point

The saddle and node colapse and annihilate each other. Only the limit cycle survives.
Bifurcations

Equilibrium state leading to the transition from **resting** to **periodic spiking** behavior in neurons. (codimension-1, i.e., 1 control parameter)

![Diagram of bifurcations](image)

**Saddle-node bifurcation**

**Saddle-node on invariant circle bifurcation**
**Bifurcations**

**Saddle-node bifurcation**

- Spiking limit cycle
- Saddle-node bifurcation

**Saddle-node on invariant circle bifurcation**

- Invariant circle
- Saddle-node bifurcation

**Saddle-node ghost**

- Time plots
  - $x$ vs. $t$
  - $P_{sub}$ vs. $x$
Equilibrium state leading to the transition from **resting** to **periodic spiking** behavior in neurons. (codimension-1, i.e., 1 control parameter)

(c) A small unstable limit cycle shrinks to a stable equilibrium and makes it lose stability

The only stable state is the limit cycle

(d) The stable equilibrium loses stability and gives birth to a small-amplitude limit cycle attractor

As the magnitude of the injected current increases, the amplitude of the limit cycle increases, and it becomes a full-size spiking limit cycle
Equilibrium state leading to the transition from **resting** to **periodic spiking** behavior in neurons. (codimension-1, i.e., 1 control parameter)

### Bi-stable

- **Subcritical Andronov-Hopf bifurcation**
  - A small unstable limit cycle shrinks to a stable equilibrium and makes it lose stability.

### Mono-stable

- **Supercritical Andronov-Hopf bifurcation**
  - The stable equilibrium loses stability and gives birth to a small-amplitude limit cycle attractor.
Bifurcations

Coexistence of resting and spiking states

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>(bistable)</td>
<td>(monostable)</td>
</tr>
<tr>
<td>saddle-node</td>
<td>saddle-node on</td>
</tr>
<tr>
<td></td>
<td>invariant circle</td>
</tr>
<tr>
<td>subcritical</td>
<td>supercritical</td>
</tr>
<tr>
<td>Andronov-Hopf</td>
<td>Andronov-Hopf</td>
</tr>
</tbody>
</table>

Subthreshold oscillations

YES (resonator) NO (integrator)
Bifurcations

(a) Spiking limit cycle

(b) Invariant circle

(c) Spiking limit cycle adjunction

(d) Supercritical Andronov-Hopf bifurcation

Saddle-node bifurcation

Saddle-node on invariant circle (SNIC) bifurcation

Subcritical Andronov-Hopf bifurcation

Unstable
Building models

First of all: you need neural recordings!
(from your own experiments or from a collaborator)

To make a model of a neuron: put the right kind of currents together and tune the parameters so that the model can fire spikes like the ones recorded.

Another way is to determine what kind of bifurcations the neuron undergoes and how the bifurcations depend on neuromodulators and pharmacological blockers.

These approaches can be complementary.

Interdisciplinary work

Respect the different “ideologies”
Using **pioneering experimental techniques** of that time, Hodgkin and Huxley (1952) determined that the squid axon carries three major currents:

- **Voltage-gated persistent $K^+$ current** with four activation gates (resulting in the term $n^4$ in the equation below, where $n$ is the activation variable for $K^+$);
- **Voltage-gated transient $Na^+$ current** with three activation gates and one inactivation gate (the term $m^3h$ below)
- **Ohmic leak current**, $I_L$, which is carried mostly by $Cl^-$ ions.

\[
\begin{align*}
C \frac{dV}{dt} & = I - g_K n^4 (V - E_K) - g_{Na} m^3 h (V - E_{Na}) - g_L (V - E_L) \\
\dot{n} & = \alpha_n(V)(1 - n) - \beta_n(V)n \\
\dot{m} & = \alpha_m(V)(1 - m) - \beta_m(V)m \\
\dot{h} & = \alpha_h(V)(1 - h) - \beta_h(V)h ,
\end{align*}
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\[
\begin{align*}
\alpha_n(V) & = 0.01 \frac{10 - V}{\exp\left(\frac{10 - V}{10}\right) - 1} , \\
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\end{align*}
\]
The Hodgkin – Huxley model

Using **pioneering experimental techniques** of that time, Hodgkin and Huxley (1952) determined not only the equations but measured all the parameters values:

\[
C \frac{dV}{dt} = I - g_K n^4 (V - E_K) - g_{Na} m^3 h (V - E_{Na}) - g_L (V - E_L)
\]

\[
\dot{n} = \alpha_n(V)(1-n) - \beta_n(V)n
\]

\[
\dot{m} = \alpha_m(V)(1-m) - \beta_m(V)m
\]

\[
\dot{h} = \alpha_h(V)(1-h) - \beta_h(V)h
\]

Values of shifted Nernst equilibrium potentials (so that \(V_{rest} = 0\)):

\[E_K = -12 \text{ mV}, \quad E_{Na} = 120 \text{ mV}, \quad E_L = 10.6 \text{ mV};\]

Values of maximal conductances:

\[g_K = 36 \text{ mS/cm}^2, \quad g_{Na} = 120 \text{ mS/cm}^2, \quad g_L = 0.3 \text{ mS/cm}^2.\]

Value of membrane capacitance:

\[C = 1 \mu\text{F/cm}^2\]
The Hodgkin – Huxley model

The functions $\alpha(V)$ and $\beta(V)$ describe the transition rates between open and closed states of the channels. The notation presented before was used only for historical reasons. It is more convenient to use:

\[
\begin{align*}
\dot{n} &= (n_\infty(V) - n)/\tau_n(V), \\
\dot{m} &= (m_\infty(V) - m)/\tau_m(V), \\
\dot{h} &= (h_\infty(V) - h)/\tau_h(V),
\end{align*}
\]

where

\[
\begin{align*}
n_\infty &= \alpha_n/(\alpha_n + \beta_n), & \tau_n &= 1/(\alpha_n + \beta_n), \\
m_\infty &= \alpha_m/(\alpha_m + \beta_m), & \tau_m &= 1/(\alpha_m + \beta_m), \\
h_\infty &= \alpha_h/(\alpha_h + \beta_h), & \tau_h &= 1/(\alpha_h + \beta_h)
\end{align*}
\]
The Hodgkin – Huxley model
To be continued…