Maths pre-requisites for data analysis in neuroscience

2/ Differential equations

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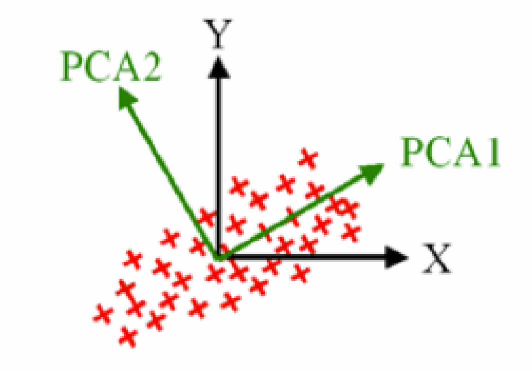
12/04/2019 - Workshop “computational neuroscience”, pre-requisite course

Ultimate goal: understand and develop tools for the analysis of neural data

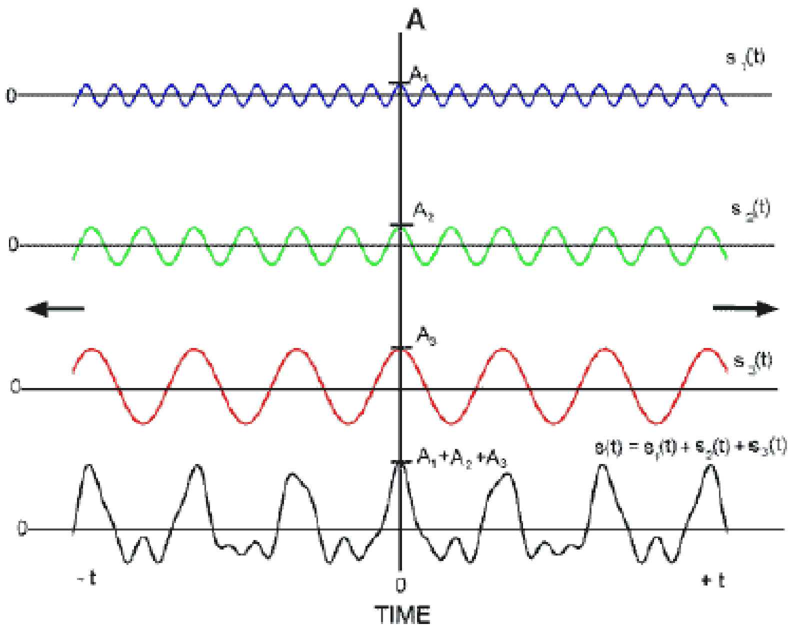
$$C_m \frac{dV}{dt} = -g_L(V - E_L) + g_L \Delta_T e^{\frac{V-V_T}{\Delta_T}} - u + I$$

$$\tau_w \frac{du}{dt} = a(V - E_L) - u$$

differential equations and modeling



dimensionality reduction



Fourier transforms, convolutions, and filtering out noise

"What is an eigenvector?"

"What exactly is PCA doing?"

"What *really* is a Fourier transform?"

Many slides from Lane McIntosh & Kiah Hardcastle

(NBIO course, Stanford Univ, https://web.stanford.edu/class/nbio228-01/info.html)

Differential equations

- Derivatives and integrals
- Define differential equations (DE)
- When and why are differential equation useful?
- Illustrative examples with neurons
- Graphic interpretation
- Numerical resolution
- Analytical resolution

Differential equations

A/ Derivatives and integrals

- Derivatives: definition and basic properties
- Derivatives of elementary function
- Intergrals: definition and basic properties
- Primitives of elementary function

B/ Differential equations

- General definition of DE
- Why DE in biology
- Illustrative example 1: The “integrate-and-fire” neuron
- Illustrative example 2: Two interacting neuronal populations
- A graphic interpretation (first order DE)
- Numerical resolution (first order DE)
- Analytical resolution (first order linear DE)

A1- Definition and basic properties of derivatives

Given the function f:

$$y = f(x)$$

The derivative of f is:

$$f'(x) = \lim_{h \to 0} \frac{f(x+h) - f(x)}{h}$$

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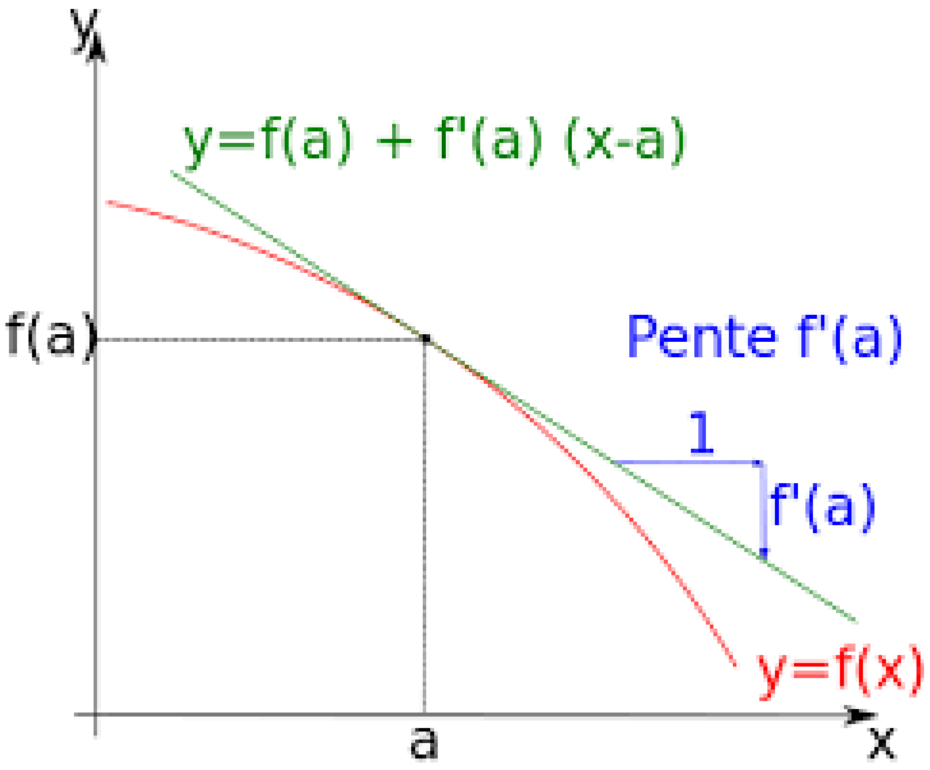

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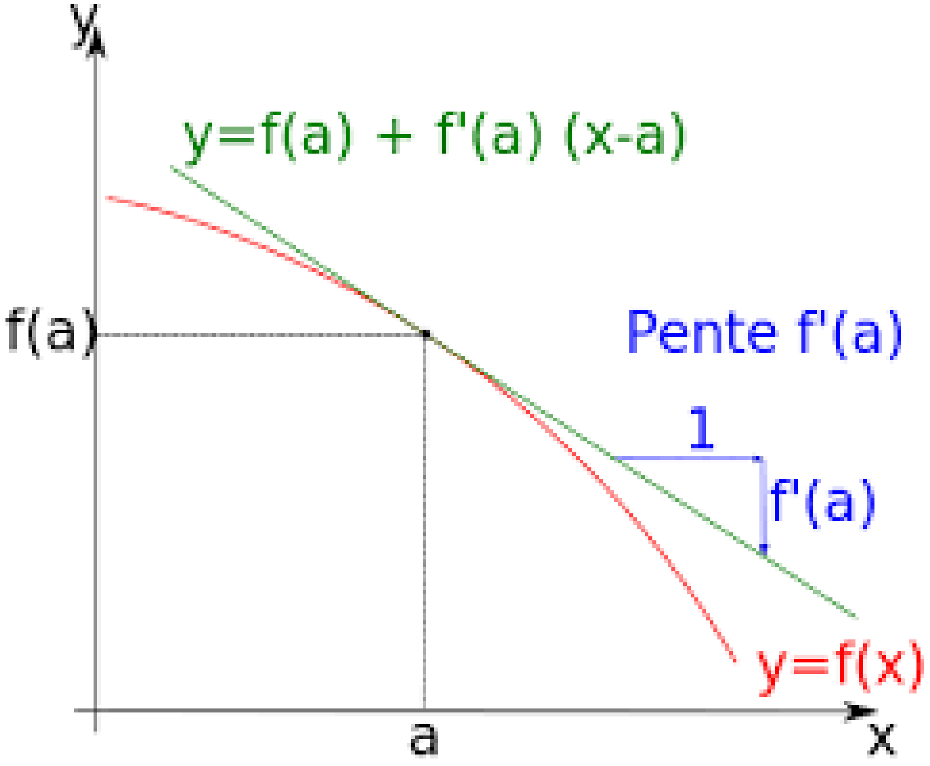
Equivalent notations: $f' = \dfrac{df}{dx} = f_x$



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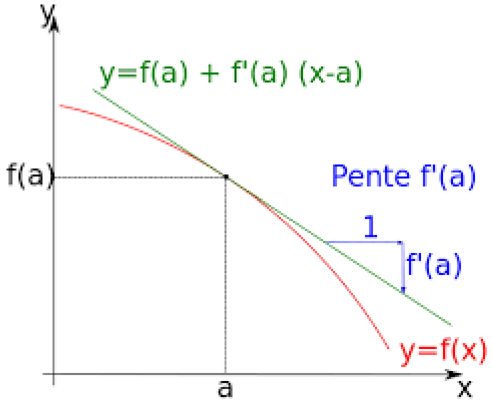

Basic properties:

$$(f+g)' = f' + g'$$

$$(f-g)' = f' - g'$$

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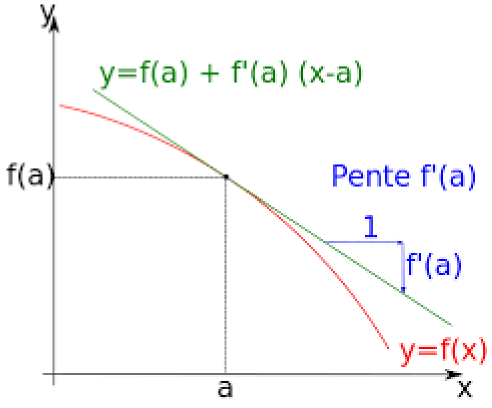

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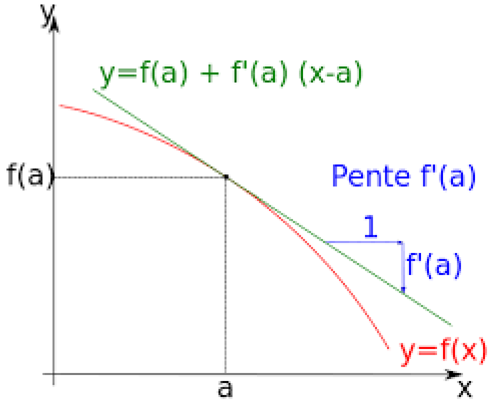

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$$\big(f(g(x))\big)' = f'(g(x)) \cdot g'(x)$$

A2- Derivatives of elementary functions

$$\frac{d}{dx}x^p = px^{p-1}$$

$$(\sin x)' = \cos x, \quad (\cos x)' = -\sin x$$

$$(e^x)' = e^x$$

$$(\ln x)' = \frac{1}{x}$$

A3- Definition and basic properties of integrals

Given the function f:

$$y = f(x)$$

The integral of f between a and b is:

$$\int_a^b f(x)dx = \lim_{h\to 0}\sum_{n=1}^{N} f(a+(n-1)h)\cdot h$$

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$$F(x) = \int_a^x f(s)ds + c$$

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$$\int_a^b f(s)ds = F(b) - F(a)$$

$$\begin{aligned}
\frac{d}{dx}\int_a^x f(s)ds &= \lim_{h\to 0} \frac{\int_a^{x+h} f(s)ds - \int_a^x f(s)ds}{h} \\
&= \lim_{h\to 0} \frac{\int_x^{x+h} f(s)ds}{h} \\
&= \lim_{h\to 0} \frac{hf(x)}{h} \\
&= f(x).
\end{aligned}$$

$$F'(x) = f(x)$$

A3- Definition and basic properties of integrals

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The integral of f between a and b is:

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$$\int_a^b f(s)ds = F(b) - F(a)$$

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$$F'(x) = f(x)$$

Basic properties:

$$\int (f(x)+g(x))dx = \int f(x)dx + \int g(x)dx$$

$$\int Af(x)dx = A\int f(x)dx$$

A4- Primitives of elementary functions

$$\int x^n dx = \frac{x^{n+1}}{n+1} + c \qquad n \neq -1$$

$$\int \frac{1}{x} dx = \ln x + c$$

$$\begin{aligned}\int f'(g(x))g'(x)dx &= \int f'(y)dy \\ &= f(y) + c \\ &= f(g(x)) + c\end{aligned}$$

Differential equations

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B1/ General definition of differential equations

Definition of a differential equation

$$F(x, y(x), y'(x), \ldots, y^{(n)}) = 0$$

First order differential equation:

$$\begin{aligned} y'(x) &= f(x, y(x)) \\ y(x_0) &= y_0 \ , \end{aligned}$$

Second order differential equation:

$$\begin{aligned} y''(x) &= f(x, y(x), y'(x)) \\ y(x_0) &= y_0, \ y'(x_0) = y_1, \end{aligned}$$

B1/ General definition of differential equations

Multi-dimensional first order differential equation:

$$\frac{d}{dt}\mathbf{x} = \mathbf{f}(\mathbf{x}); \;\; \mathbf{x} \in \mathbb{R}^n, \quad \mathbf{x}(0) = \mathbf{x}_0$$

$$\mathbf{f}(\mathbf{x}) = \begin{pmatrix} f_1(x_1, \ldots, x_n) \\ \vdots \\ f_n(x_1, \ldots x_n) \end{pmatrix}, \;\; \mathbf{x} = \begin{pmatrix} x_1 \\ \vdots \\ x_n \end{pmatrix}$$

B2- Why DE in biology?

Growth process (population *N(t)*, fecondity *f* and death rate *d* over a period *h*):

$$N(t+h) \;=\; N(t) + (f-d)\,N(t)h$$

$$(f-d)\,N(t)h \;=\; N(t+h) - N(t)$$

$$(f-d)\,N(t) \;=\; \frac{1}{h}(N(t+h) - N(t))$$

$h \to 0$

$$\frac{dN}{dt} = (f-d)\,N$$

B2- Why DE in biology?

A simple chemical reaction

production and degradation of a molecule A from B and C

$$B + C \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A$$

k_1: production rate; k_2: degradation rate

B2- Why DE in biology?

A simple chemical reaction

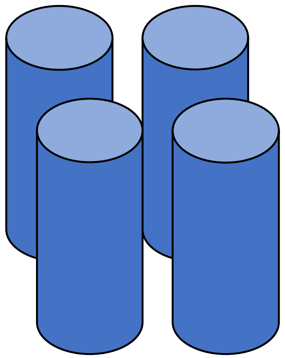
production and degradation of a molecule A

$$B + C \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A \qquad \frac{d[A]}{dt} = k_1[B][C] - k_2[A]$$

k_1: production rate; k_2: degradation rate

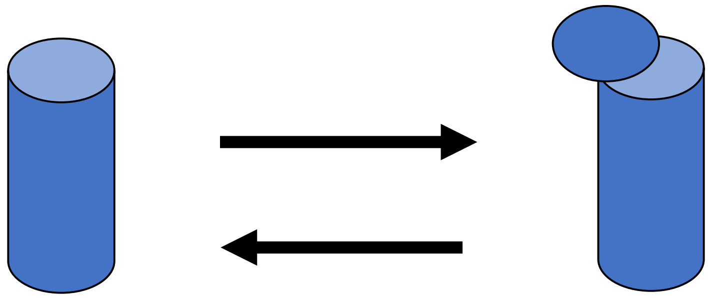
B2- Why DE in biology?

The potassium channel



- 4 similar sub-units

- Each unit can be « open » or « closed »

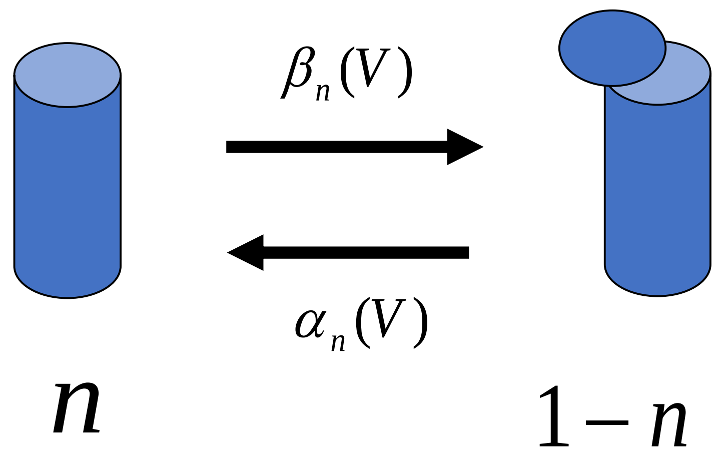


- The channel is « open » if and only if the units are « open »

B2- Why DE in biology?

The potassium channel

Kinetics of K^+ channel sub-units:



$$n(t+\Delta t) = n(t) - \beta_n \,\Delta t\, n(t) + \alpha_n \,\Delta t\,(1-n(t))$$

$$\frac{n(t+\Delta t)-n(t)}{\Delta t} = \alpha_n\,(1-n(t)) - \beta_n\; n(t)$$

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n\, n$$

$$\frac{dn}{dt} = -(\alpha_n+\beta_n)\,n + \alpha_n$$

$$\left(\frac{1}{\alpha_n+\beta_n}\right)\frac{dn}{dt} = -n + \frac{\alpha_n}{\alpha_n+\beta_n}$$

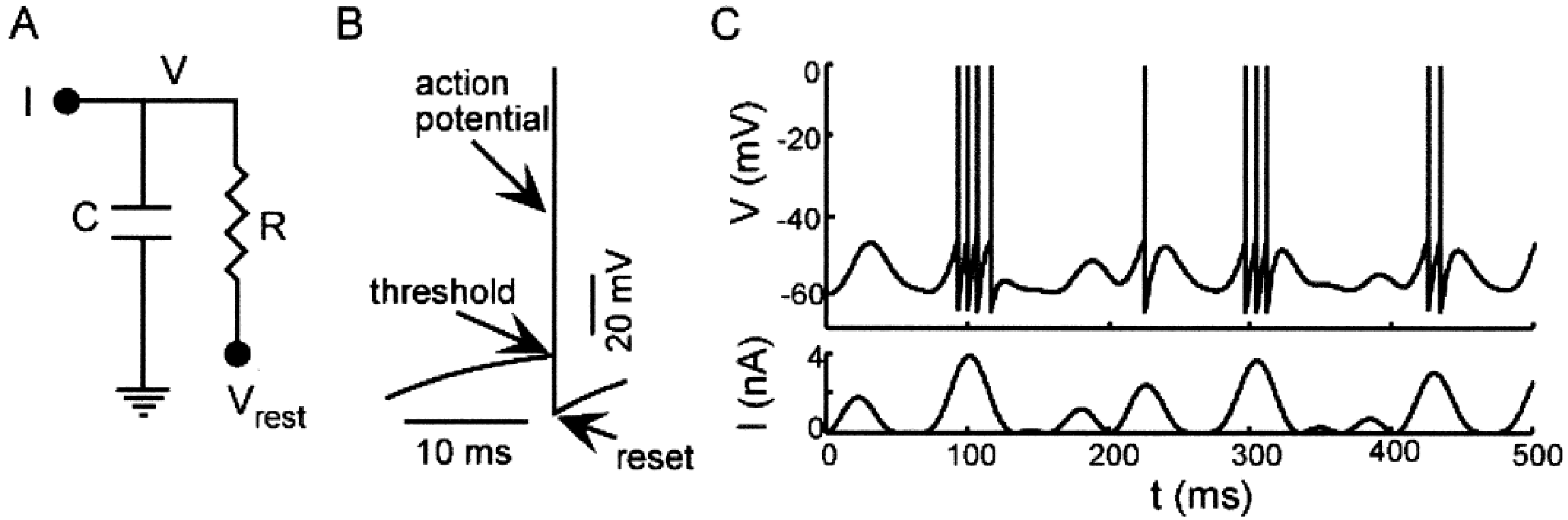
$$\tau_n\frac{dn}{dt} = -n + n_\infty \;\;,\;\; \tau_n = \frac{1}{\alpha_n+\beta_n},\;\; n_\infty = \frac{\alpha_n}{\alpha_n+\beta_n}$$

$$\frac{dn}{dt} \to 0 \Rightarrow n \to n_\infty, \text{rate of change } \propto \frac{1}{\tau_n}$$

B2- Why DE in biology?

Example 3: The leaky integrator neuron

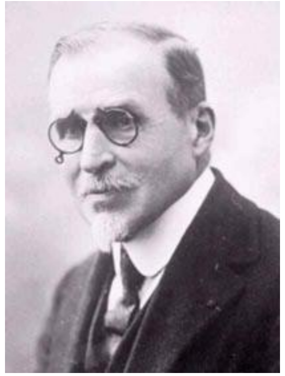
1907: Louis **Lapique** – « Integrate-and-fire » model



(Abbott, 1999)

B2- Why DE in biology?

Example 3: The leaky integrator neuron



« Integrate-and-fire » model (Louis **Lapique** 1907)

$$C\frac{dV}{dt} = G_{tot}(V_0 - V) + \tilde{I}_{ext}$$

$$\tau = \frac{C}{G_{tot}}$$

$$\boxed{\tau\frac{dV}{dt} = (V_0 - V) + \frac{\tilde{I}_{ext}}{G_{tot}}}$$

B3- Graphic interpretation

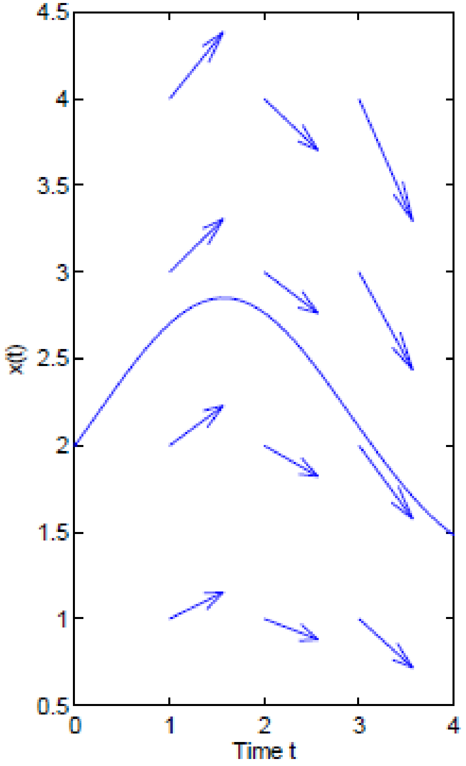
$$\dot{x} = f(x,t), \quad x(t_0) = x_0$$

2/ Differential equations

$$\dot{x} = f(x,t), \quad x(t_0) = x_0$$

Graphical interpretation: vector fields

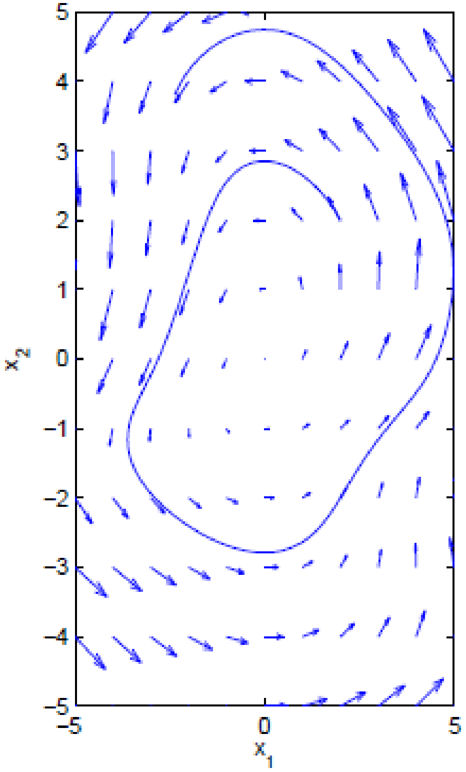
One dimension



Fix point

Stability

Two dimensions: $x=(x_1\ x_2)$



B3- Graphic interpretation

$$\dot{x} = f(x,t), \quad x(t_0) = x_0$$

Numerical resolution: Euler method

$$x_{n+1} = x_n + \Delta t\, f(x_n, t_n)$$

$$t_n = t_0 + n\Delta t$$

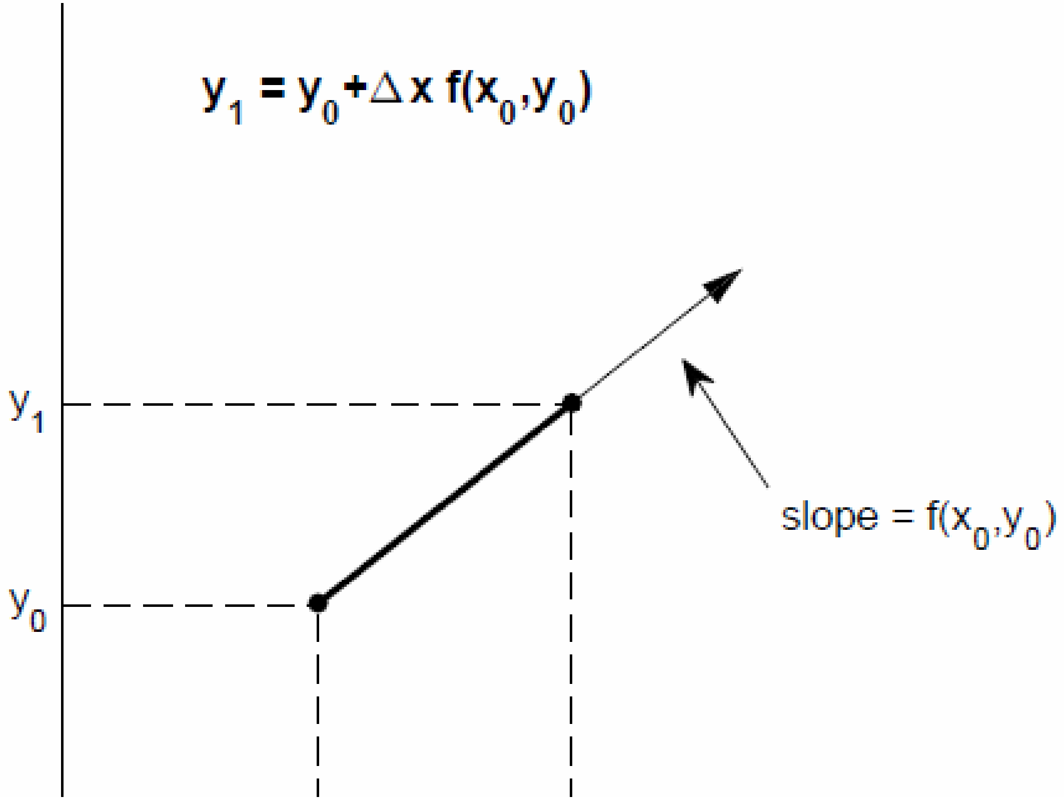


Figure 2.1: *The differential equation $dy/dx = f(x,y)$, $y(x_0) = y_0$, is in*
using the Euler method $y_1 = y_0 + \Delta x f(x_0, y_0)$, with $\Delta x = x_1 - x_0$.

2/ Differential equations

Fix point, stability, limit cycle

2/ Differential equations

Numerical resolution

$$\dot{x} = f(x,t), \quad x(t_0) = x_0$$

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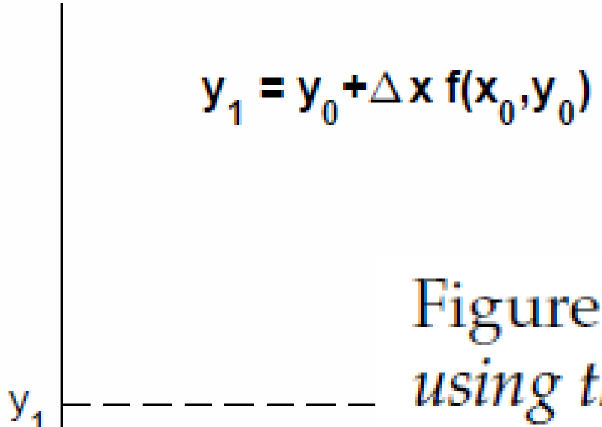

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Maltus law

$$\frac{dx}{dt} = kx$$
$$x(0) = x_o$$

$$\frac{dx}{x} = kdt$$

$$\begin{aligned} \int \frac{dx}{x} &= \int kdt \\ \ln \frac{x(t)}{x(0)} &= k\,t \\ \ln x(t) &= \ln x(0) + k\,t \end{aligned}$$

$$x(t) = x_o e^{kt}$$

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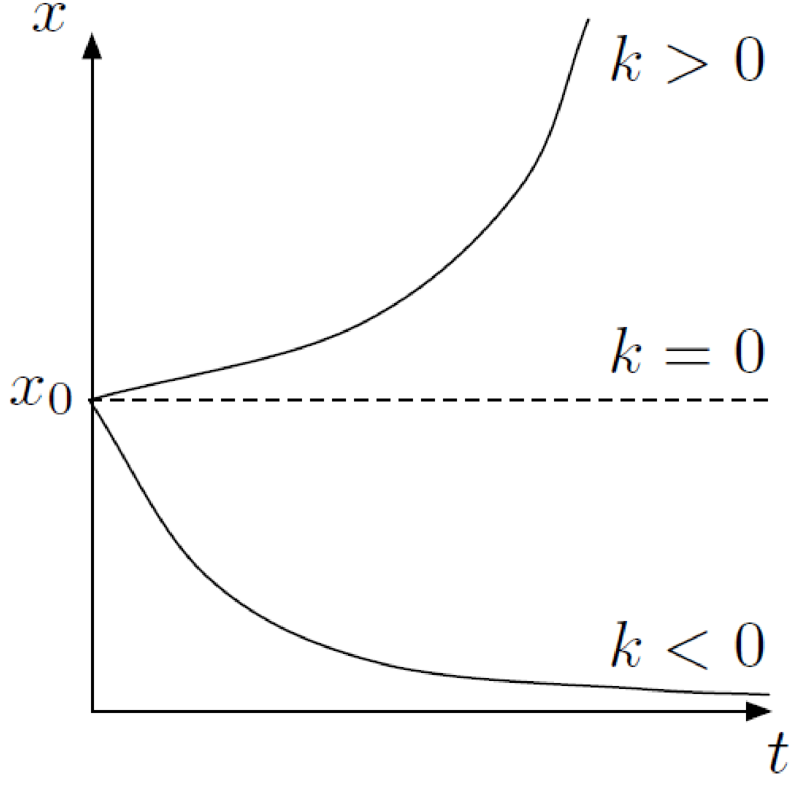
1. $k > 0$ exponential growth

2. $k < 0$ exponential decay



B Single neuron models: Integrate-and-fire

$$\tau \frac{dV}{dt} = (V_0 - V) + \frac{\tilde{I}_{ext}}{G_{tot}}$$

- V_0 : resting potential
- τ : membrane time constant
- I : external current (synaptic)
- G_{tot} : total conductance

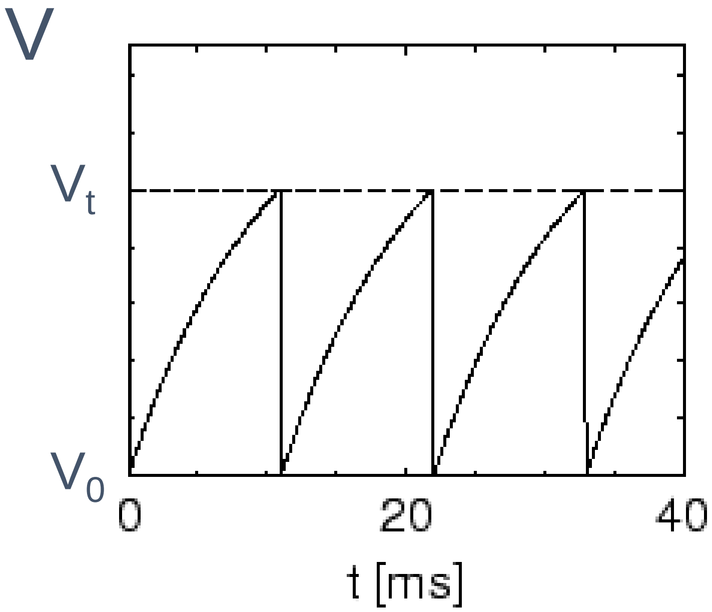
$$V = V_0 + \frac{I_0}{G_{tot}}(1 - e^{-\frac{t-t0}{\tau}})$$

If V=Vt (threshold), neuron spikes and $V \longrightarrow V_0$

B Single neuron models: Integrate-and-fire

Voltage as a function of time

$$V_t - V_0 = \frac{I_0}{G_{tot}}(1 - e^{-\frac{T}{\tau}})$$



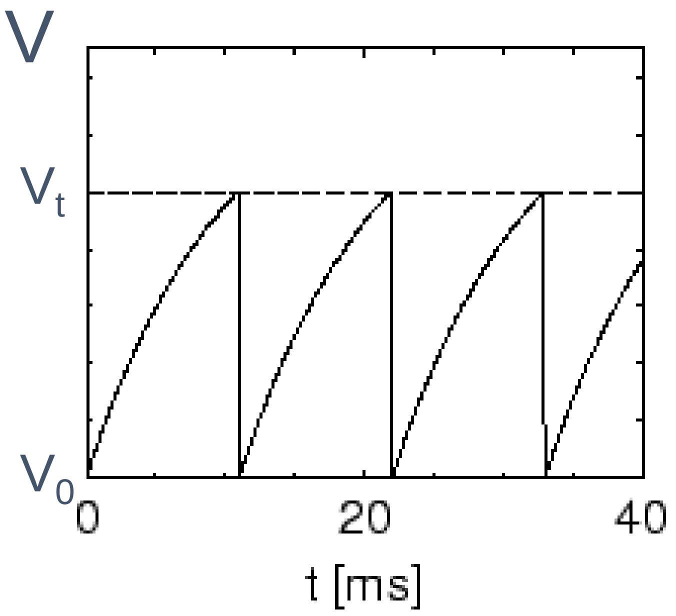
$$T = \tau \ln\left(\frac{I_0}{I_0 - G_{tot}(V_t - V_0)}\right)$$

With a refractory period, the firing rate is:

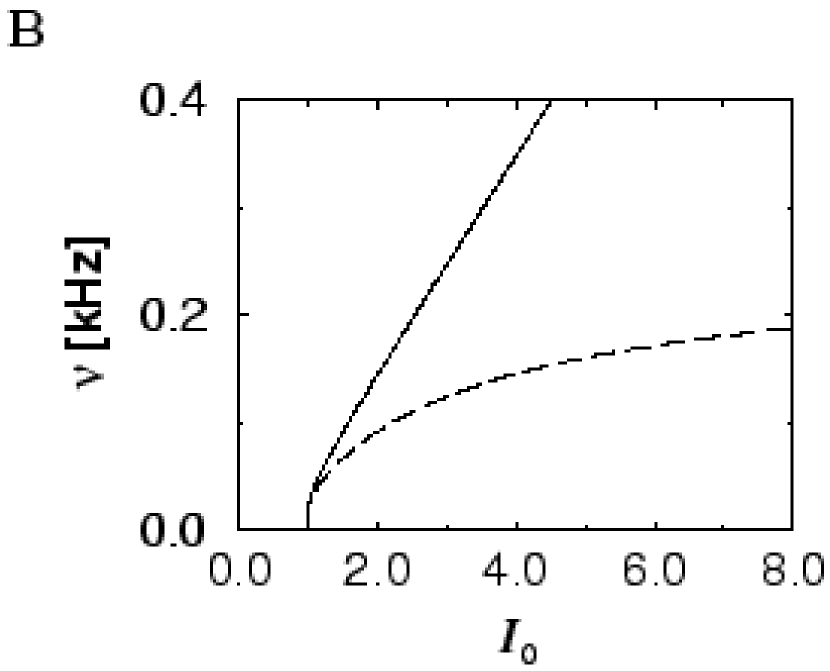
$$\nu = 1 \Big/ \left(D_{ref} + \tau \ln\left(\frac{I_0}{I_0 - G_{tot}(V_t - V_0)}\right)\right)$$

B Single neuron models: Integrate-and-fire

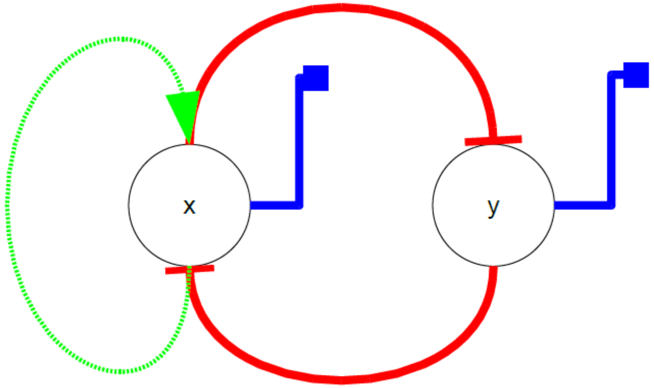
Voltage as a function of time



Frequency as a function of input



- Assumptions for ODEs:
  - Deterministic system
  - No uncertainity
  - Populational level of description
  - ***dynamics (***or time evolution***)of a system***
- Why ODEs:
  - Strong mathematical history and background
  - Historical relationships between ODEs and biology (bio)chemistry, enzymology, ecology, epidemiology
  - Well accepted formalism in biological communities
  - Software for *in silico* experiments for biologists



- Two biological species: *x* and *y*
- *x* repress *y*
- *y* repress *x*
- *x*,*y* : *degradation*
- *x* : *auto-activation*

- Fundamental idea:
  - We want the time evolution of *x* and *y*, that is $x(t)$
  - We don't know how to obtain a formula for $x(t)=???$
  - We know how to describe a small variation of the concentration of *x* and *y* during a small time interval *dt*
- Procedure (for each biological entity):
  - Identify each mechanism where *x* is involved
  - For each mechanism, give an equation describing a small variation of the concentration (*dx*) for a small time interval (*dt*)
  - Sum up to obtain $dx/dt = f(x,...)$

Newton's law, $F = ma$, results in the equation

$$m\frac{d^2x}{dt^2} = -mg,$$

where x is the height of the object above the ground, m is the mass of the object, and $g = 9.8$ meter/sec^2 is the constant gravitational acceleration. As Galileo suggested, the mass cancels from the equation, and

$$\frac{d^2x}{dt^2} = -g.$$

Here, the right-hand-side of the ode is a constant. The first integration, obtained by antidifferentiation, yields

$$\frac{dx}{dt} = A - gt,$$

with A the first constant of integration; and the second integration yields

$$x = B + At - \frac{1}{2}gt^2,$$

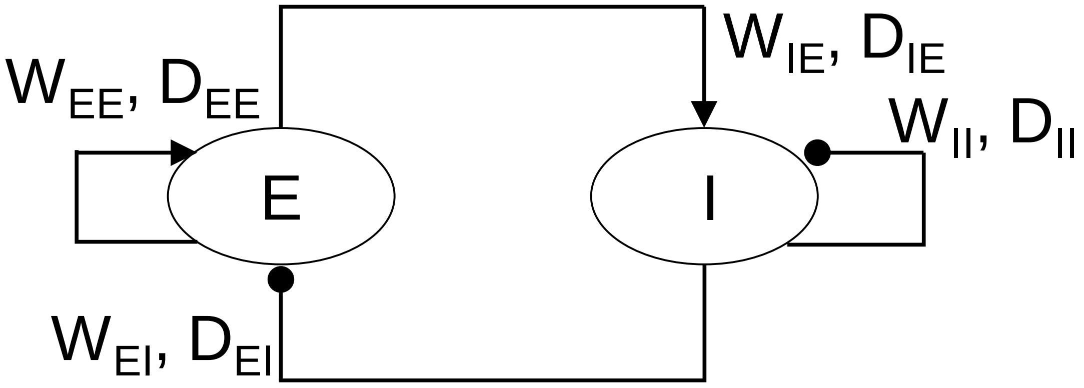
with B the second constant of integration. The two constants of integration A and B can then be determined from the initial conditions. If we know that the initial height of the mass is x_0, and the initial velocity is v_0, then the initial conditions are

$$x(0) = x_0, \quad \frac{dx}{dt}(0) = v_0.$$

$$x(t) = x_0 + v_0t - \frac{1}{2}gt^2$$

A.3 How to build the network model

Example 2: Excitatory and inhibitory populations interconnected



$$\tau_E \frac{dm_E}{dt}(t) = -m_E(t) + F_E\left(W_{EE} m_E(t - D_{EE}) - W_{EI} m_I(t - D_{EI}) + I_E - T_E\right)$$

$$\tau_I \frac{dm_I}{dt}(t) = -m_I(t) + F_I\left(-W_{II} m_I(t - D_{II}) + W_{IE} m_E(t - D_{IE}) + I_I - T_I\right)$$

A.3 How to build the network model

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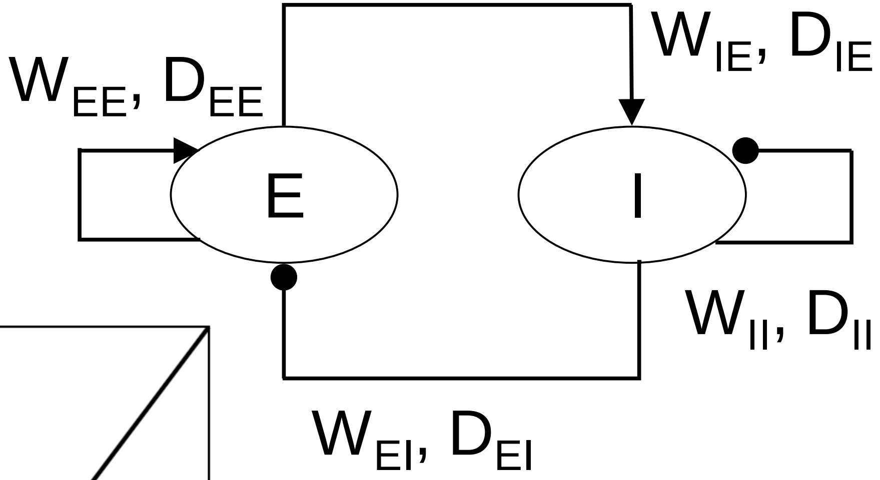

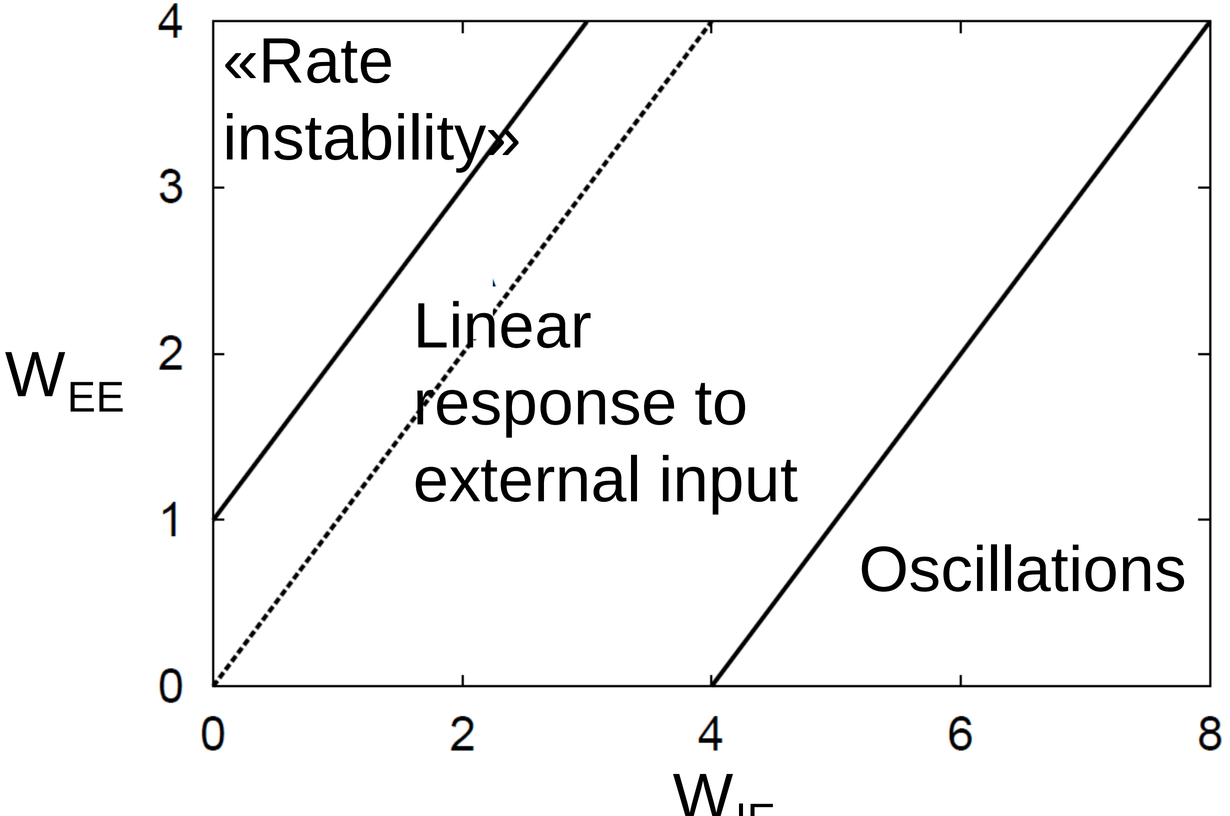

For:
$W_{EI} = 1$
$W_{II} = 0$
D = = 5ms
τ

Science is a differential equation. Religion is a boundary condition. *Alan Turing.*