Mathematical Models and Numerical Methods of Computational Neuroscience
計算神経科学の数学モデルと数値手法

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Agenda

- Brief introduction of Differential Equations
- Neuronal Models
- Numerical Method to Simulate Neuronal Models
- How the Network can be trained

Ordinary Differential Equations

- A fundamental tool in theoretical Science (Not only in Physics or Computational Neuroscience)
- The differential equation gives the dependence of derivatives

$$\boxed{F\left[\frac{d^n x(t)}{dt^n}, \ldots, \frac{dx(t)}{dt}, C\right] = 0}$$

Interpretation of Differential Equations

- The first differential equation I have ever seen is the definition of velocity:

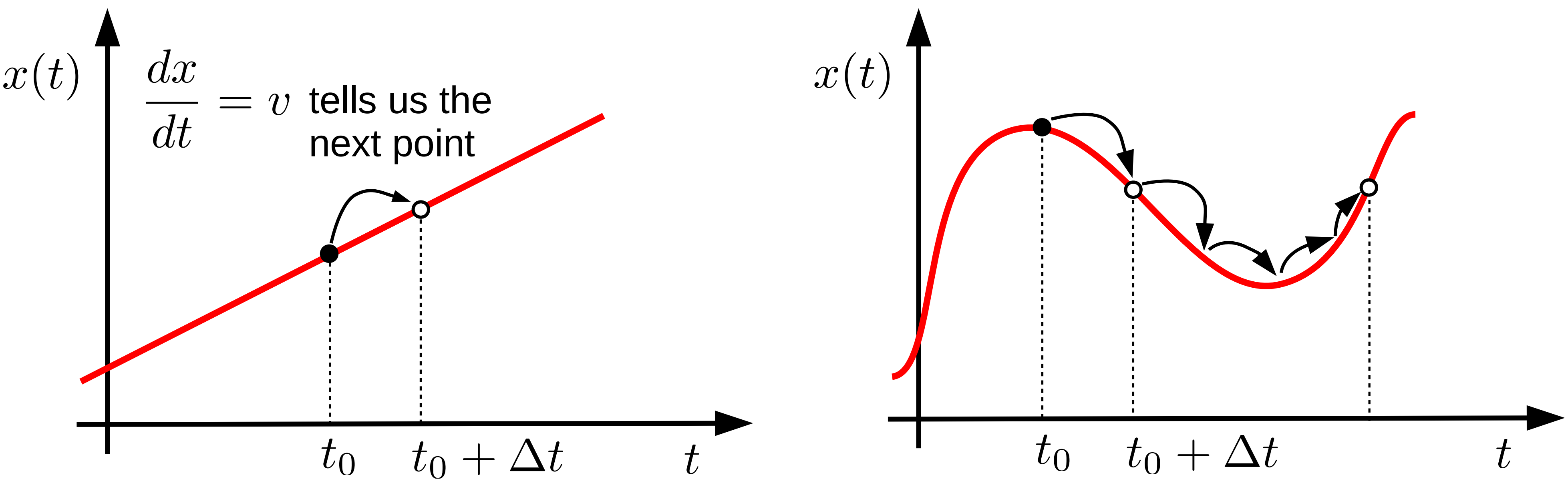
$$\boxed{\frac{dx(t)}{dt} = v}$$

- By definition,

$$\boxed{\frac{dx(t)}{dt} = \lim_{\Delta t \to 0} \frac{\Delta x}{\Delta t} \approx \frac{\Delta x}{\Delta t}}$$

Interpretation of Differential Equations

- By knowing the slopes, one may trace the whole curve!



Examples of Models and Theories

- Simple Harmonic Oscillator

Acceleration

$$\frac{d^2x(t)}{dt^2} + \omega^2 x(t) = 0$$

Returning Force

- Heat Equation

Rate of Heat

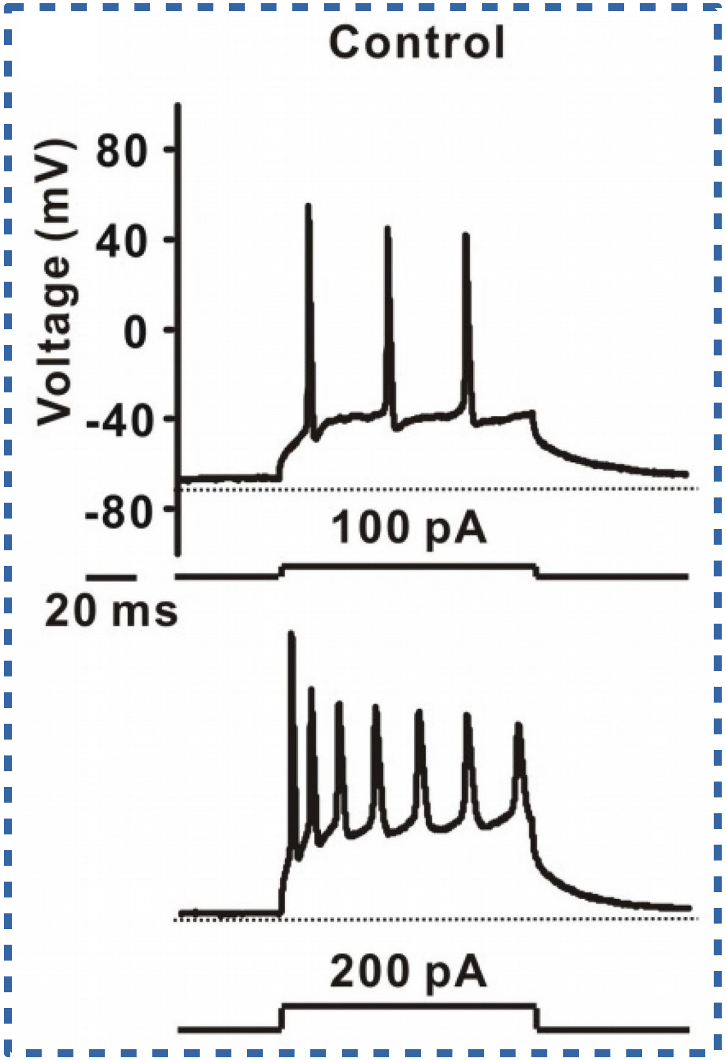
$$\frac{\partial u(x,t)}{\partial t} = \alpha \frac{\partial^2 u(x,t)}{\partial x^2}$$

Influx of Heat (by Divergence Theorem)

To Model a Neuron …

- Neurons can be excited by current injection
- If the <u>membrane potential</u> is larger than some thresholds, an action potential will be triggered

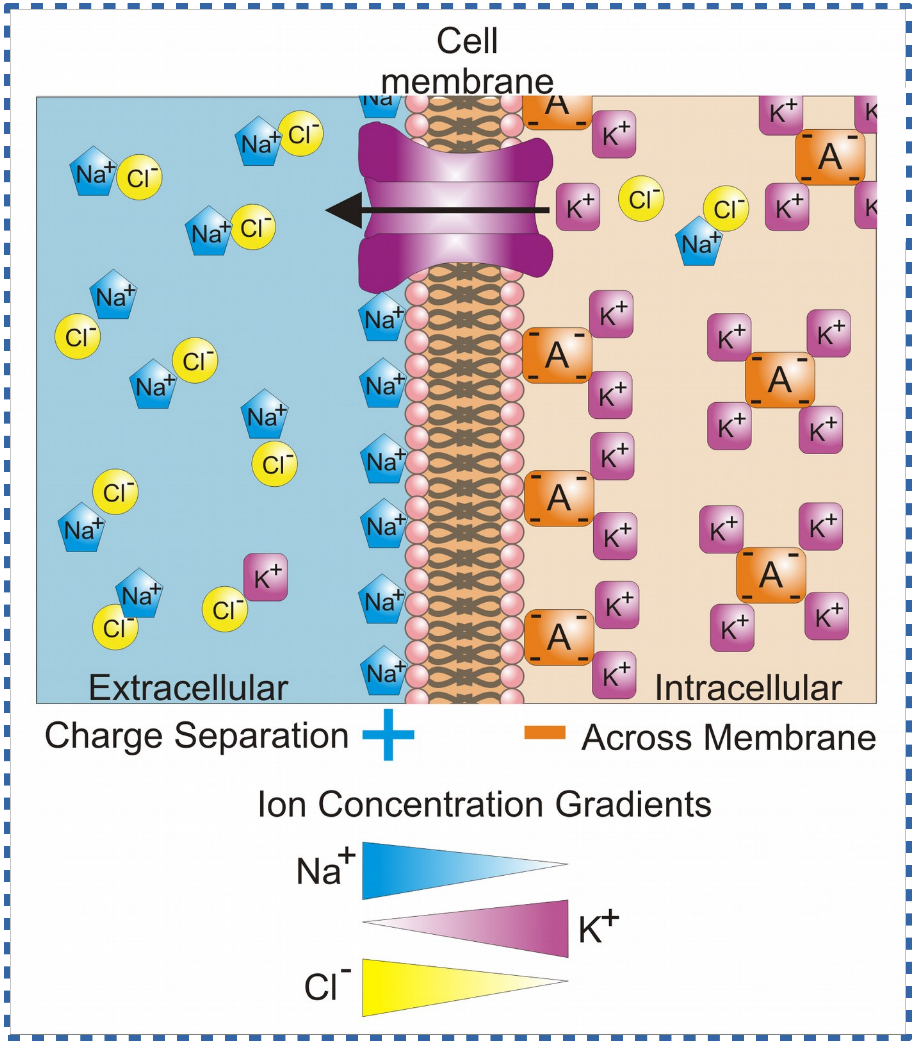
A. D. Reyes, Nature (2019)



Z. Lin et al, Front. Pharmacol. (2019)

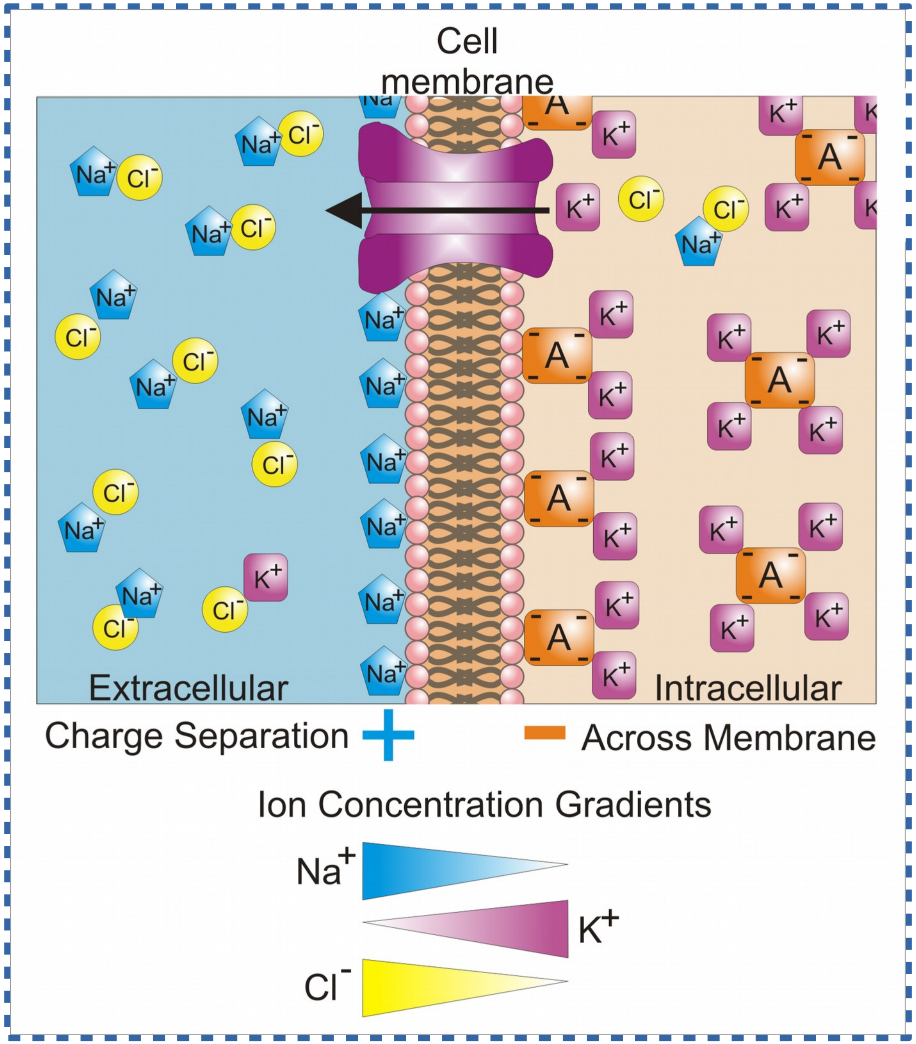
Membrane Potential

- The voltage mentioned in the previous slide is the membrane potential
- Membrane potential means the potential difference across the neuron membrane



Membrane Potential

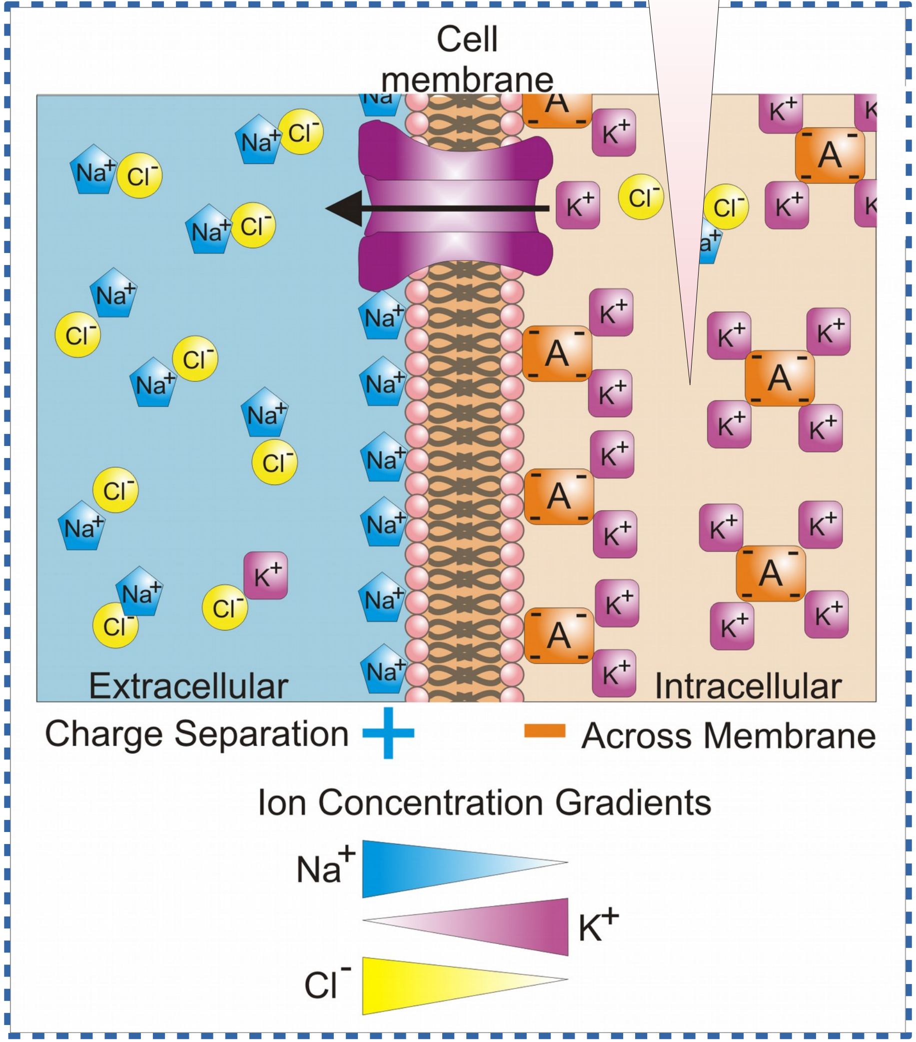
- The membrane potential can be controlled by concentrations of ions
- Living cells actively maintain the potential difference by their ion bumps
- The typical resting potential difference is -65 mV



Membrane Potential

Current Injection

- By injecting current, the membrane potential can be changed
- As the membrane potential large than the threshold, the neuron gives a spike



For More Knowledge about Membrane Potential

Membrane potential

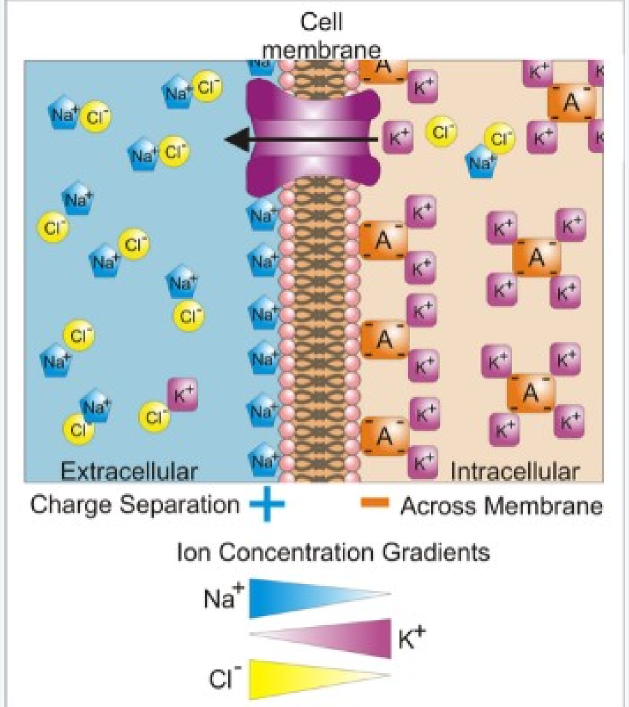
From Wikipedia, the free encyclopedia

Membrane potential (also **transmembrane potential** or **membrane voltage**) is the difference in electric potential between the interior and the exterior of a biological cell. With respect to the exterior of the cell, typical values of membrane potential, normally given in units of millivolts and denoted as mV, ranges from –40 mV to –80 mV.

All animal cells are surrounded by a membrane composed of a lipid bilayer with proteins embedded in it. The membrane serves as both an insulator and a diffusion barrier to the movement of ions. Transmembrane proteins, also known as ion transporter or ion pump proteins, actively push ions across the membrane and establish concentration gradients across the membrane, and ion channels allow ions to move across the membrane down those concentration gradients. Ion pumps and ion channels are electrically equivalent to a set of batteries and resistors inserted in the membrane, and therefore create a voltage between the two sides of the membrane.

Almost all plasma membranes have an electrical potential across them, with the inside usually negative with respect to the outside.[1] The membrane potential has two basic functions. First, it allows a cell to function as a battery, providing power to operate a variety of "molecular devices" embedded in the membrane. Second, in electrically **excitable cells** such as neurons and muscle cells, it is used for transmitting signals between different parts of a cell. Signals are generated by opening or closing of ion channels at one point in the membrane, producing a local change in the membrane potential. This change in the electric field can be quickly affected by either adjacent or more distant ion channels in the membrane. Those ion channels can then open or close as a result of the potential change, reproducing the signal.

In non-excitable cells, and in excitable cells in their baseline states, the membrane potential is held at a



Differences in the concentrations of ions on opposite sides of a cellular membrane lead to a voltage called the **membrane potential**. Typical values of membrane potential are in the range –40 mV to –70 mV. Many ions have a

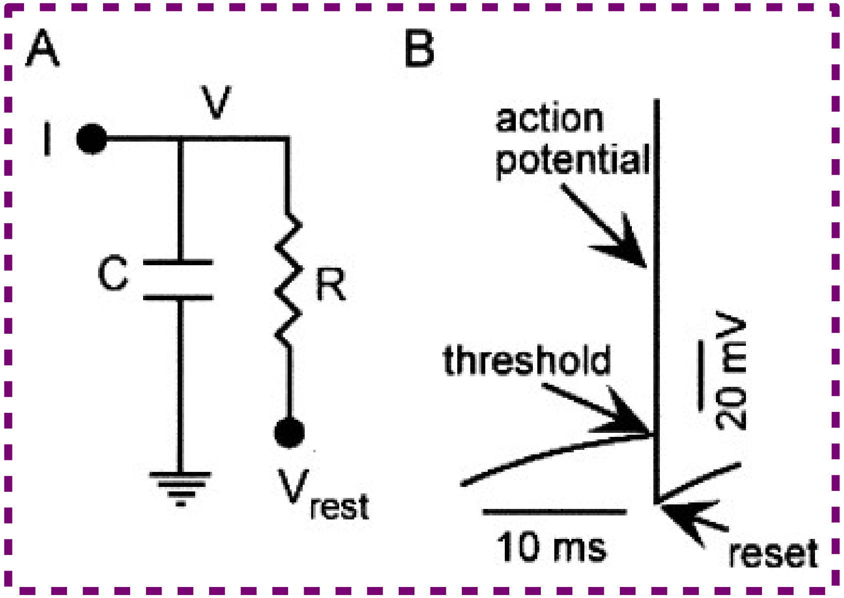
Membrane Works Like ...

- By injecting current, the potential across membrane changes
- As the potential across the threshold, the neuron fires
- It works like <u>a capacitor</u> with a leaky current

Leaky Integrate-and-Fire (LIF) Model

- In 1907, Lapicque proposed a simple model for neurons

$$I(t) - \frac{V_{\mathrm{m}}(t) - V_{\mathrm{rest}}}{R_{\mathrm{m}}} = C_{\mathrm{m}} \frac{dV_{\mathrm{m}}(t)}{dt}$$

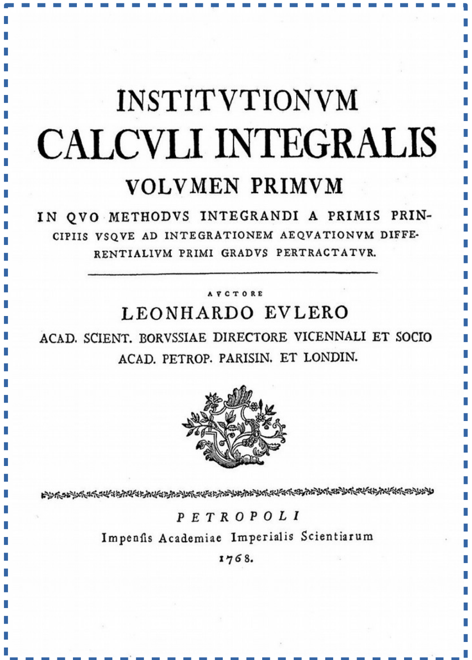


L. F. Abbott, Brain Research Bulletin (1999)

Euler Method

- Demonstrated by Euler in 1768
- Easy to understand, but the error could be big

$$\frac{dy(x)}{dx} = x$$



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IN QVO METHODVS INTEGRANDI A PRIMIS PRINCIPIIS VSQVE AD INTEGRATIONEM AEQVATIONVM DIFFERENTIALIVM PRIMI GRADVS PERTRACTATVR.
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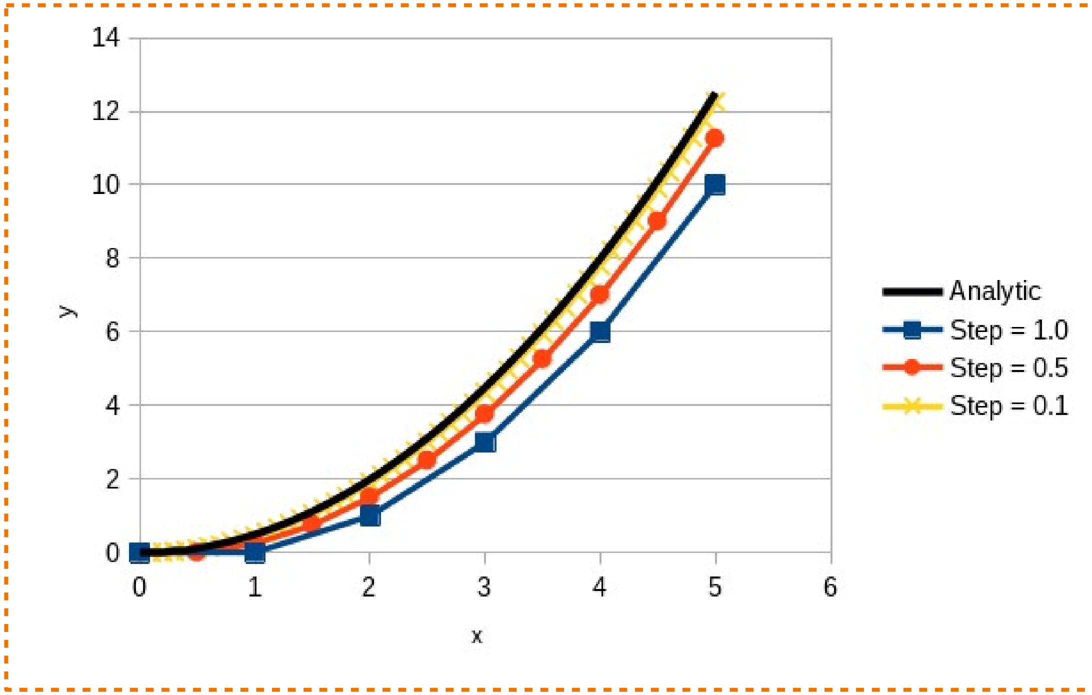
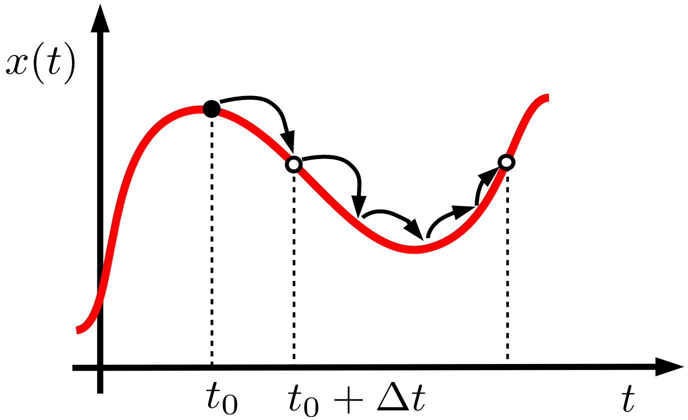
Impenſis Academiae Imperialis Scientiarum
1768.



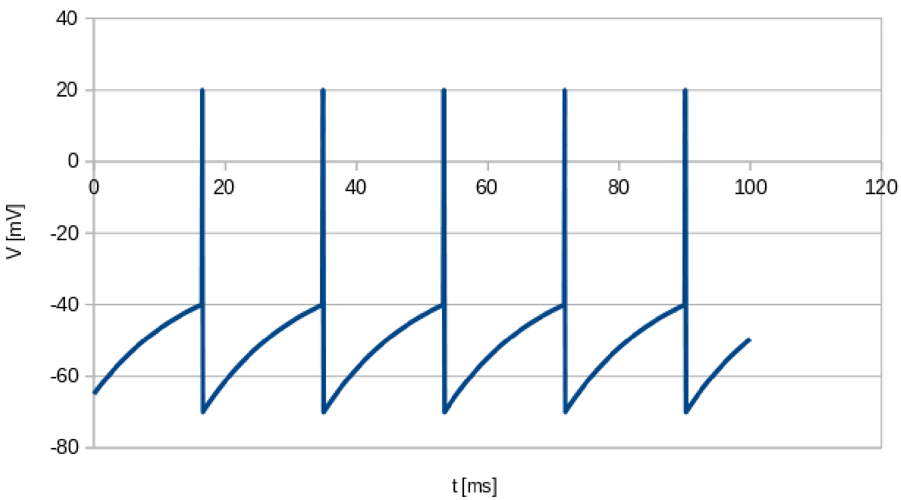
First Simulation (Numerically Solve the Differential Equation)

- By calculating derivatives at t_0, one can estimate the voltage at $t_0+\Delta t$



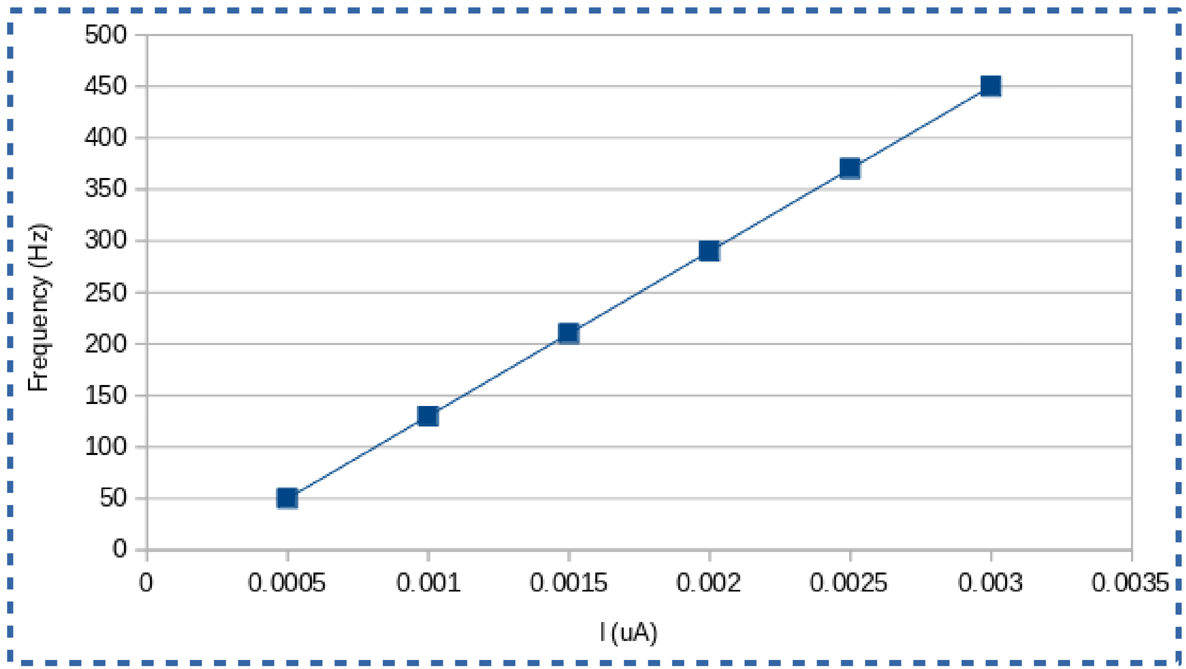
G3 =(C8-(F3-C2))/C9

	A	B	C	D	E	F	G
1					t	V	dVdt
2		V_rest (mV)	-65		0	-65	2.5
3		V_thre (mV)	-40		0.1	-64.75	2.483333333
4		V_reset (mV)	-70		0.2	-64.5016667	2.466777778
5		C (uF)	0.0002		0.3	-64.2549889	2.450332593
6		R (k-ohm)	75000		0.4	-64.0099556	2.433997042
7		I (uA)	0.0005		0.5	-63.7665559	2.417770395
8		I*R	37.5		0.6	-63.5247789	2.401651926
9		R*C	15		0.7	-63.2846137	2.385640913
10					0.8	-63.0460496	2.36973664
11					0.9	-62.8090759	2.353938396
12					1	-62.5736821	2.338245473
13					1.1	-62.3398576	2.32265717
14					1.2	-62.1075918	2.307172789
15					1.3	-61.8768746	2.291791637
16					1.4	-61.6476954	2.276513026
17					1.5	-61.4200441	2.261336273
18					1.6	-61.1939105	2.246260697
19					1.7	-60.9692844	2.231285626
20					1.8	-60.7461558	2.216410389
21					1.9	-60.5245148	2.201634319



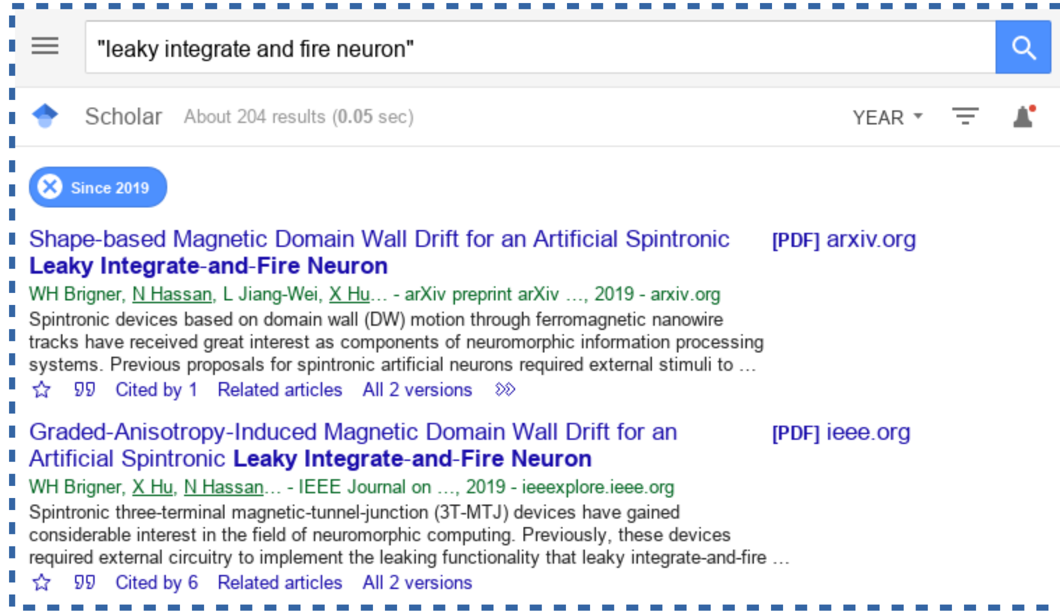
How Spiking Frequency Depends on Input Current

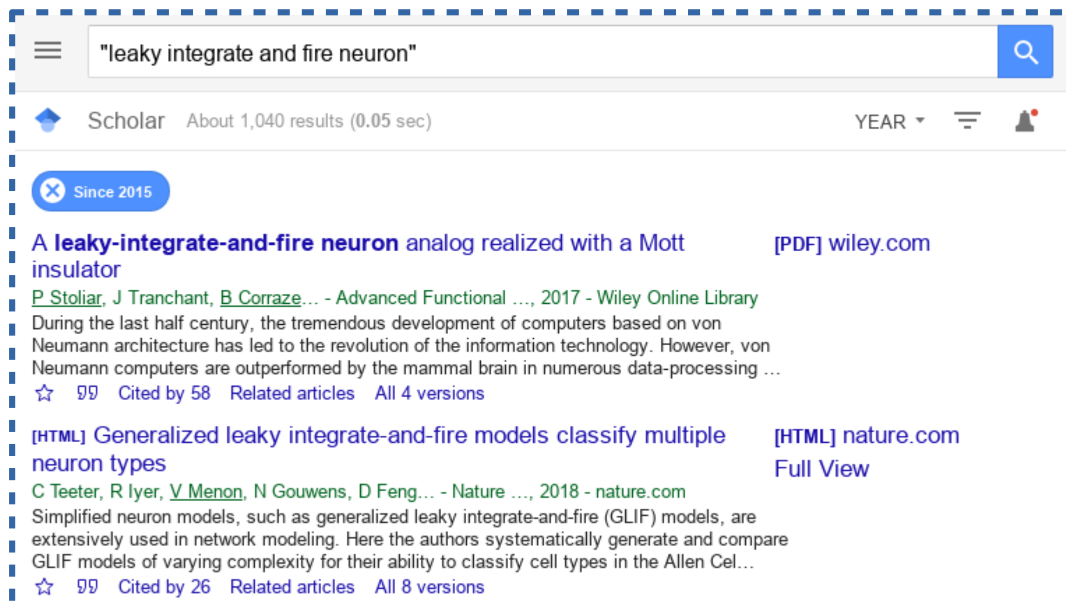
- The LIF neuron fired more frequently as the input current increases
- Gaston will tell you how to do it in Nest



Studies Involving LIF Model

- Last 10 Months, 204 papers
- Last 4.83 Years, 1040 papers
- There are ~200 paper talking about “leaky integrate and fire neuron” every year





Other Neuronal Models

- Hodgkin–Huxley model
  - Proposed by Hodgkin and Huxley in 1952
    - They received the 1963 Nobel Prize in Physiology or Medicine for this work
  - The input current charges up the membrane capacitor
  - But there are other types of current influenced by the change in membrane potential

Hodgkin–Huxley model

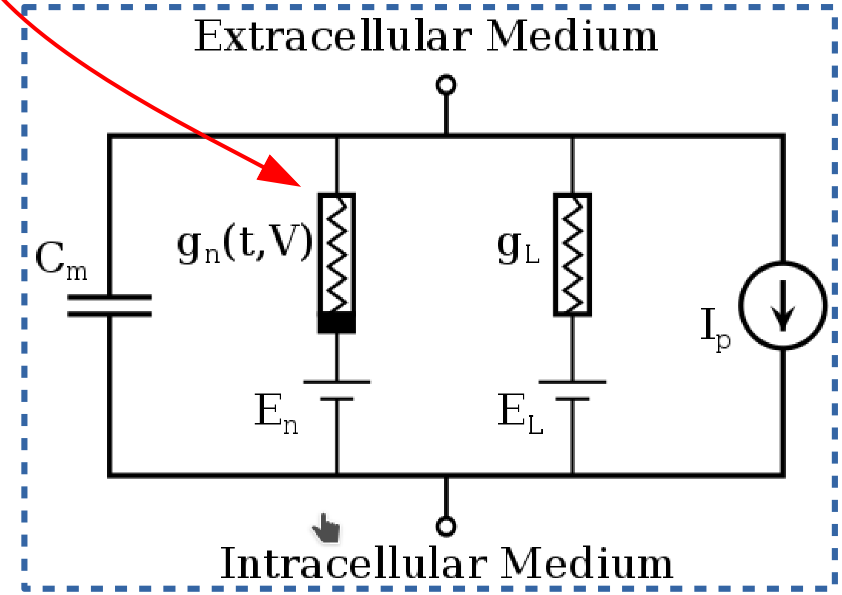
$$I = C_m \frac{dV_m}{dt} + g_l \left(V_m - V_l\right) + g_{\mathrm{K}} n^4 \left(V_m - V_{\mathrm{K}}\right) + g_{\mathrm{Na}} m^3 h \left(V_m - V_{\mathrm{Na}}\right)$$

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

$$\frac{dm}{dt} = \alpha_m \left(V_m\right)\left(1 - m\right) - \beta_m \left(V_m\right) m$$

$$\frac{dh}{dt} = \alpha_h \left(V_m\right)\left(1 - h\right) - \beta_h \left(V_m\right) h$$

- There are other equations omitted here
- This model considers also ion currents involving potassium ion and calcium ion induced by the potential difference

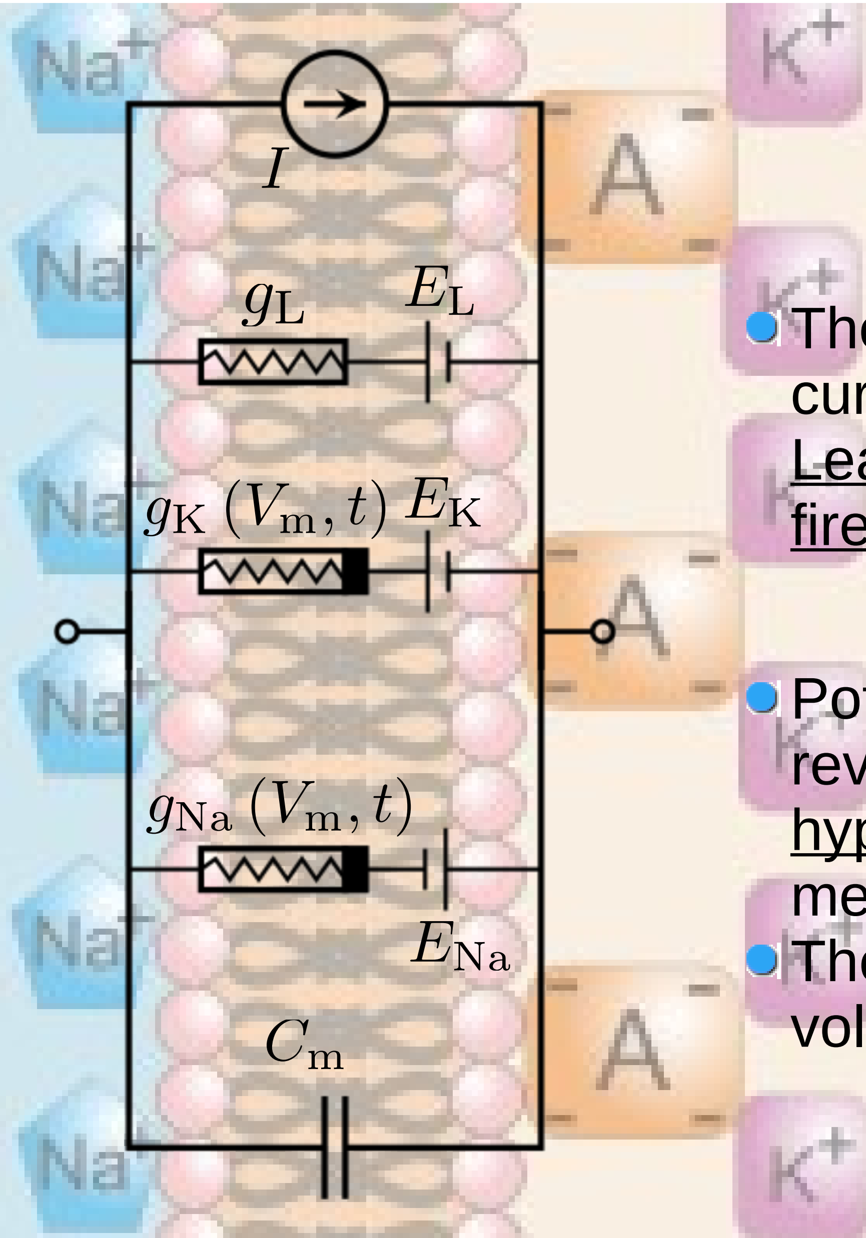


Wikipeida

Additional Ion Currents in the HH Model

- Sodium ion has a reversal potential <u>depolarizing</u> the membrane
- The conductivity is also voltage-gated

Extracellular Medium

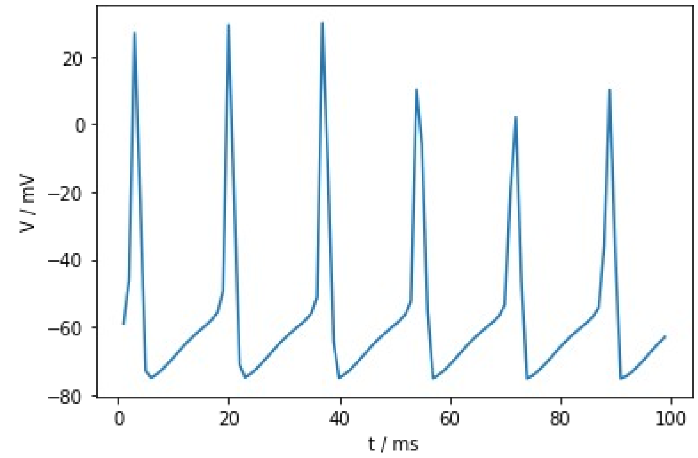


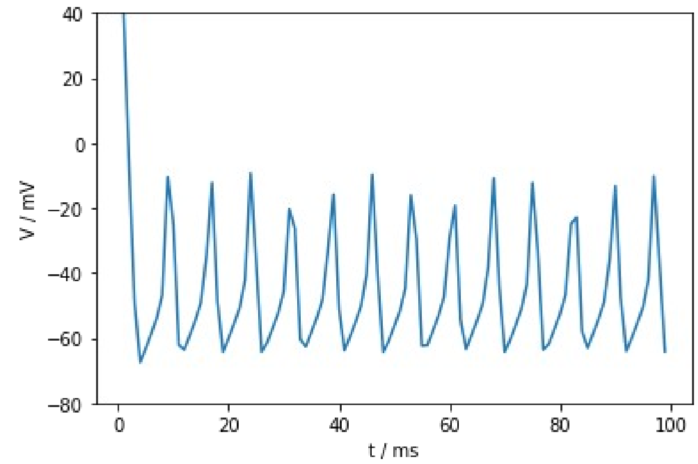
Intracellular Medium

- The same leaky current used in <u>Leaky-integrate-and-fire</u> model
- Potassium ion has a reversal potential <u>hyper-polarizing</u> the membrane
- The conductivity is voltage-gated

Simulating HH Neuron

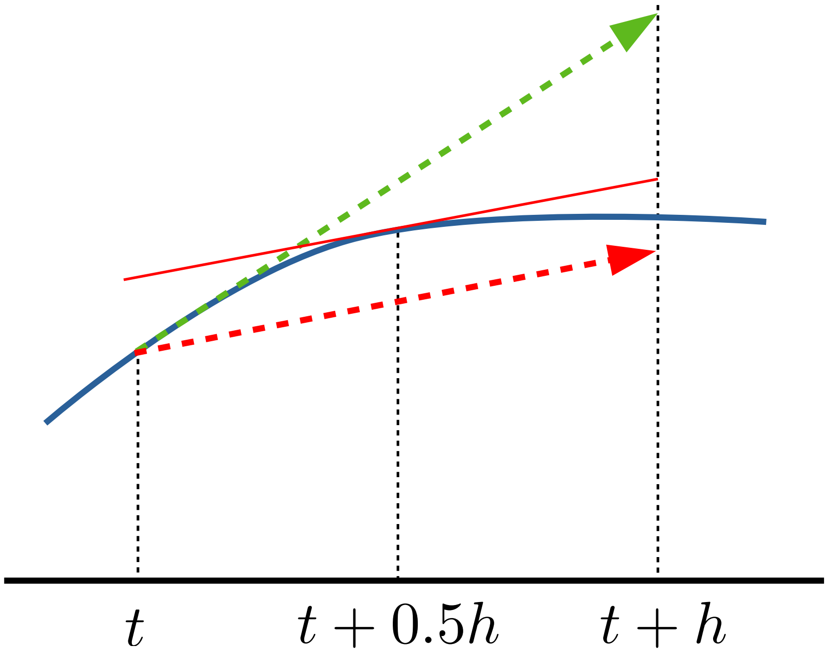
- HH Neurons show more biological behavior
- But more complicated
  - Very difficult to implement in Excel
  - But you can do it easily in Nest
- Computationally Expensive





Improve the Numerical Method

- Euler method has a relatively large error, are there alternatives?
- There are extensions of the Euler method
- The simplest one is the <u>mid-point method</u>



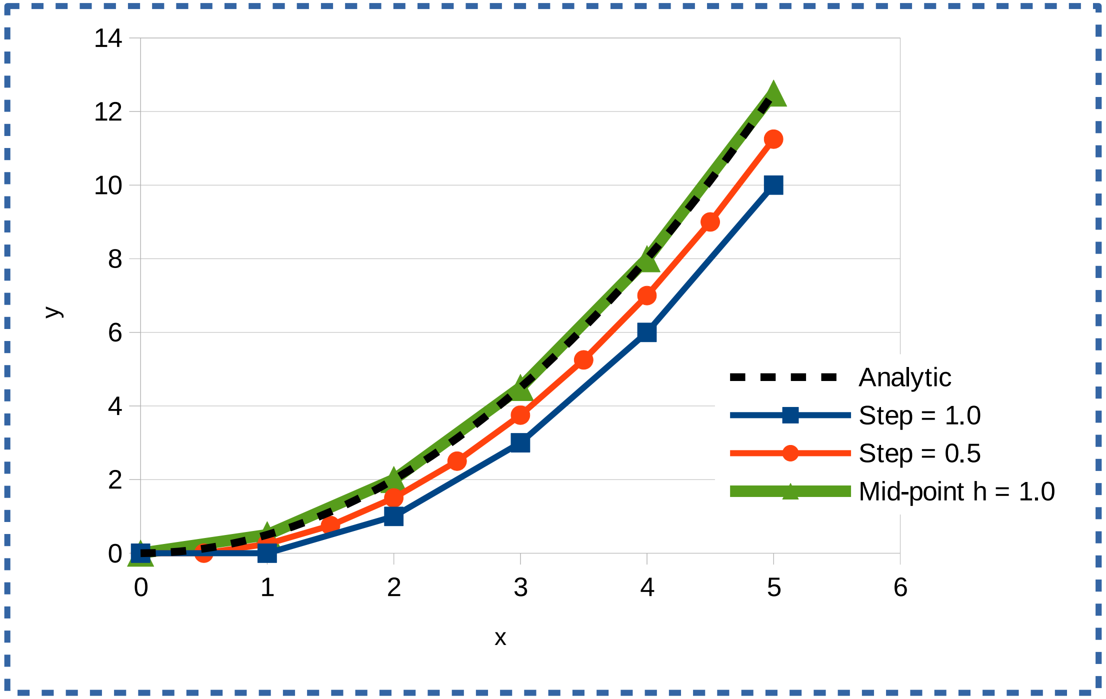
$$\frac{dx}{dt} = f(t, x)$$

$$x(t_{n+1}) = x(t_n) + hf\{t_n + \tfrac{1}{2}h, x(t_n) + \tfrac{1}{2}hf[t_n, x(t_n)]\}$$

Performance of Mid-point Method

- Can the Euler method with a smaller step beats mid-point method?
- The mid-point method is surprisingly good

$$\frac{dy(x)}{dx} = x$$



Runge–Kutta methods

- Runge–Kutta methods are a family of methods having the following form:

$$
\begin{aligned}
\frac{dx}{dt} &= f(t, x) \\
x_{n+1} &= x_n + h \sum_i^s b_i k_i \\
k_1 &= f(t_n, x_n) \\
k_2 &= f(t_n + c_2 h, x_n + h(a_{21} k_1)) \\
&\vdots \\
k_s &= f(t_n + c_s h, x_n + h(a_{s1} k_1 + a_{s2} k_2 + \cdots + a_{s,s-1} k_{s-1})
\end{aligned}
$$

No Worry. Use the Implementations Shipped with Libraries

Remarks of RK Methods

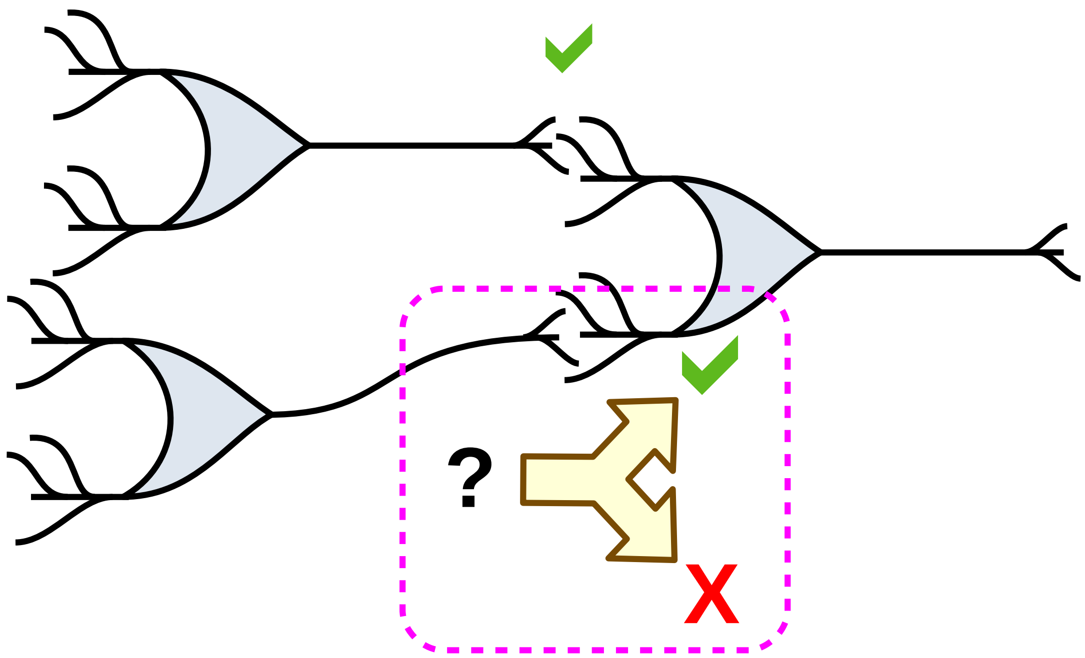
- Higher-order integration takes care of higher-order curves
- Some algorithms enable error control
- Implementation is tedious
  - Use libraries to avoid mistake
- RK methods are not perfect
  - In some scenario, implicit methods should be used (see Wikipedia)

Summary 1

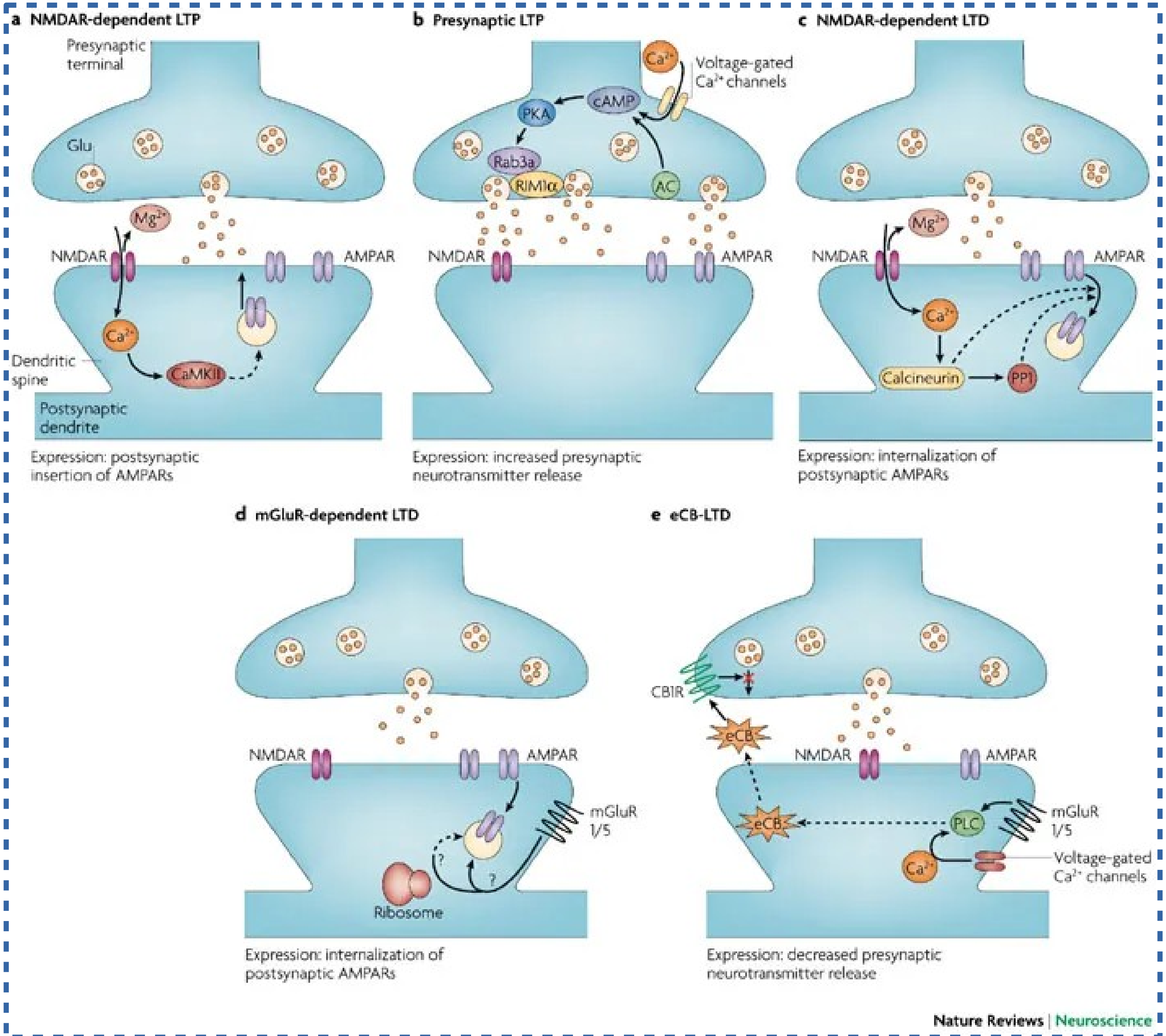
- Differential Equation
  - An important tool for Quantitative Science
- Numerical Method
  - Euler Method
  - Runge-Kutta Methods
- Neuronal Model
  - Leaky-Integrate-and-Fire Model
  - Hodgkin-Huxley model

Long-term Synaptic Plasticity

- In the previous talk, Fukai-sensei has introduced the spike-timing-dependent plasticity



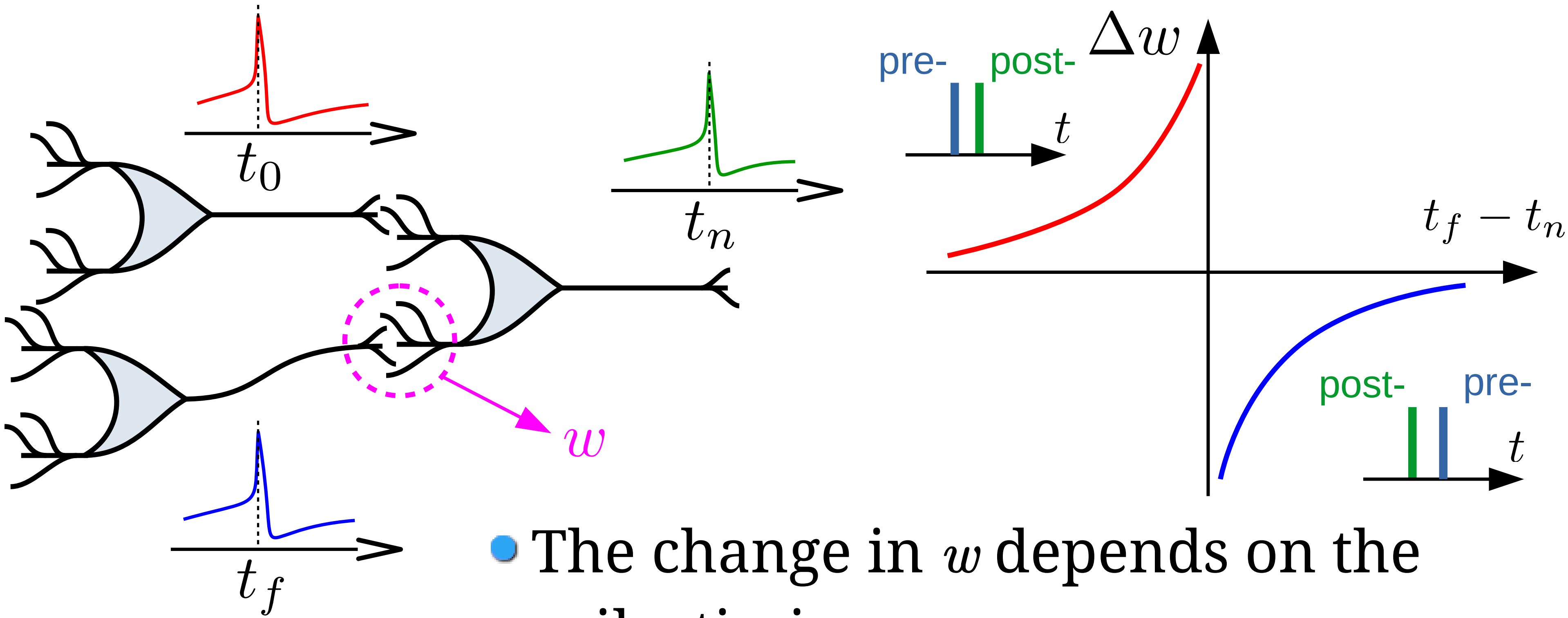
Highly Simplified Biology



Kauer & Malenka Nature Rev. (2007)

- There are various mechanisms able to modify to efficacy of chemical synapses
- Although there are different processes, for simplicity, we pay our attention on spiking timing rather than biological details

Spike-Timing-Dependent Plasticity (Classical)



- The change in w depends on the spike timings
- The change shown here is just a classical view

Online implementation of STDP models

- In order to perform STDP with differential equations, an online implementation of STDP is proposed

$$\left.\begin{aligned}\tau_{+}\frac{dx}{dt} &= -x + a_{+}(x)\sum_{t_f}\delta(t-t_f)\\ \tau_{-}\frac{dy}{dt} &= -y + a_{-}(y)\sum_{t_n}\delta(t-t_n)\end{aligned}\right\}$$

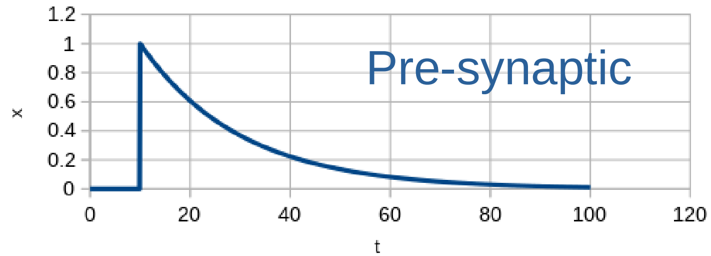
To be explained in the following

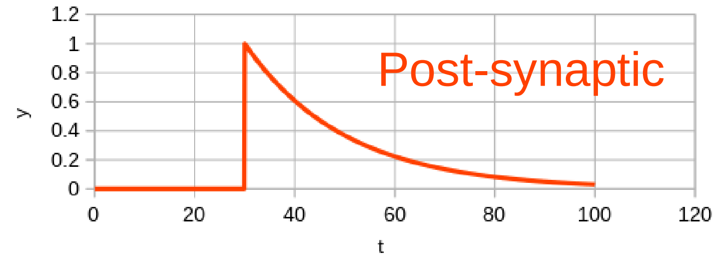
$$\frac{dw}{dt} = A_{+}(w)\,x(t)\sum_{t_n}\delta(t-t_n) - A_{-}(w)\,y(t)\sum_{t_f}\delta(t-t_f)$$

Simulation!

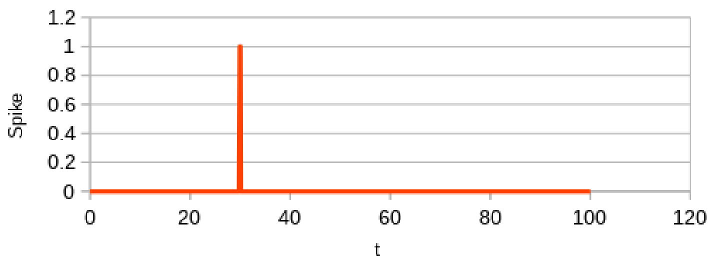
$$\tau_+ \frac{dx}{dt} = -x + a_+(x) \sum_{t_f} \delta(t - t_f)$$

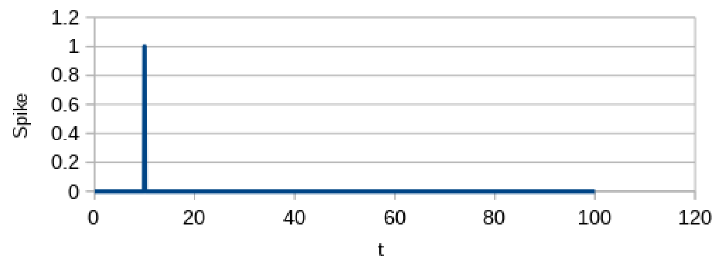
$$\tau_- \frac{dy}{dt} = -y + a_-(y) \sum_{t_n} \delta(t - t_n)$$



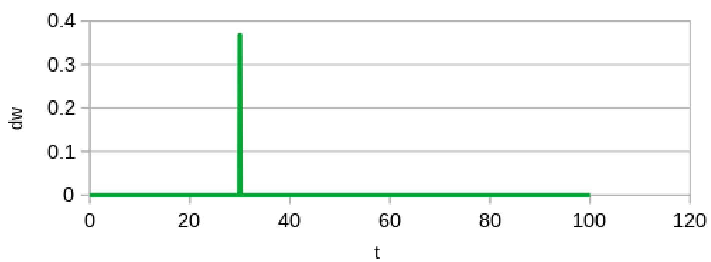


Both pre-synaptic spike and post-synaptic spike generate a decay curve in *x* and *y*





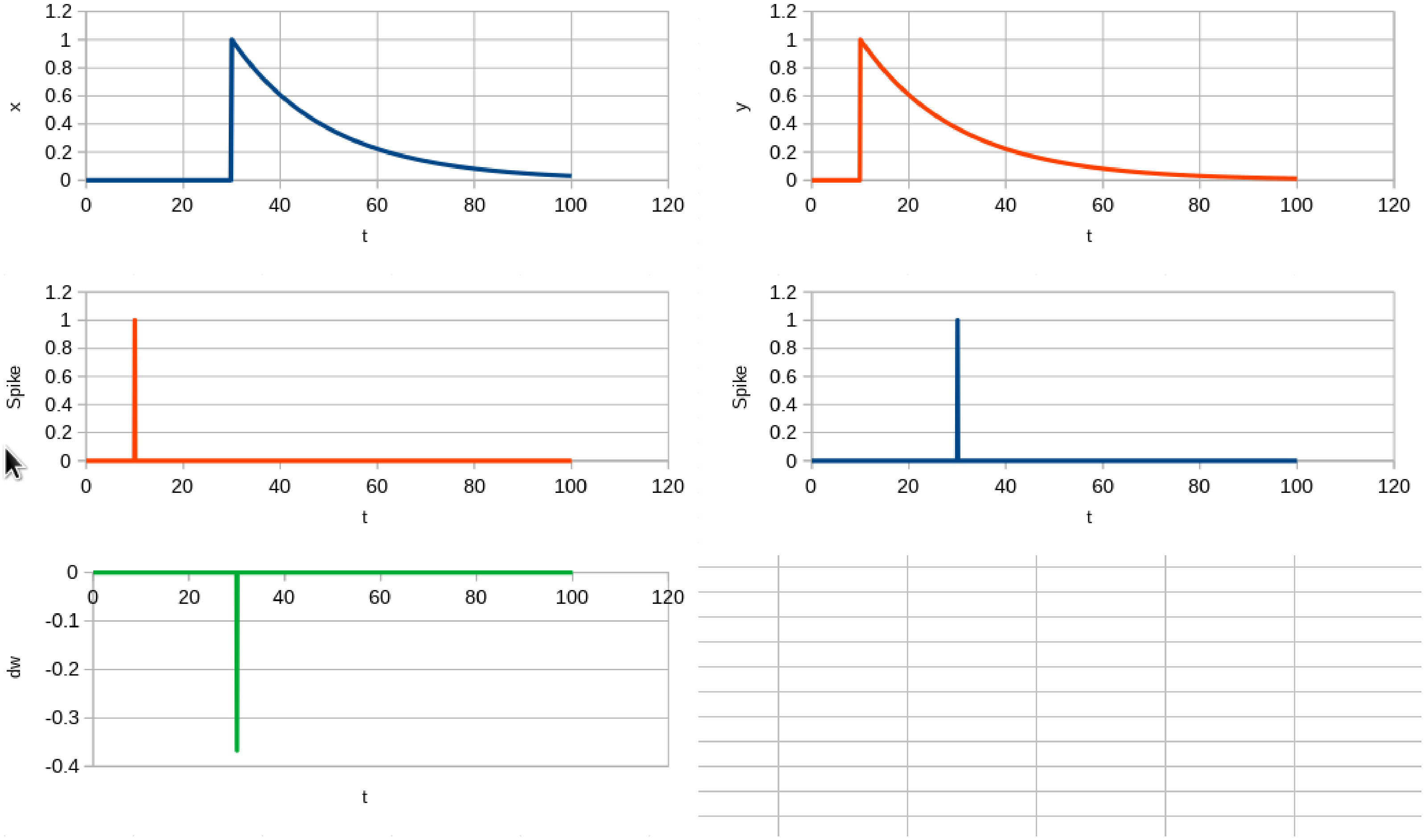
If x / y is compared with delta functions of corresponding to post-synaptic / pre-synaptic spike ...



$$\frac{dw}{dt} = A_+(w)\, x(t) \sum_{t_n} \delta(t - t_n) - A_-(w)\, y(t) \sum_{t_f} \delta(t - t_f)$$

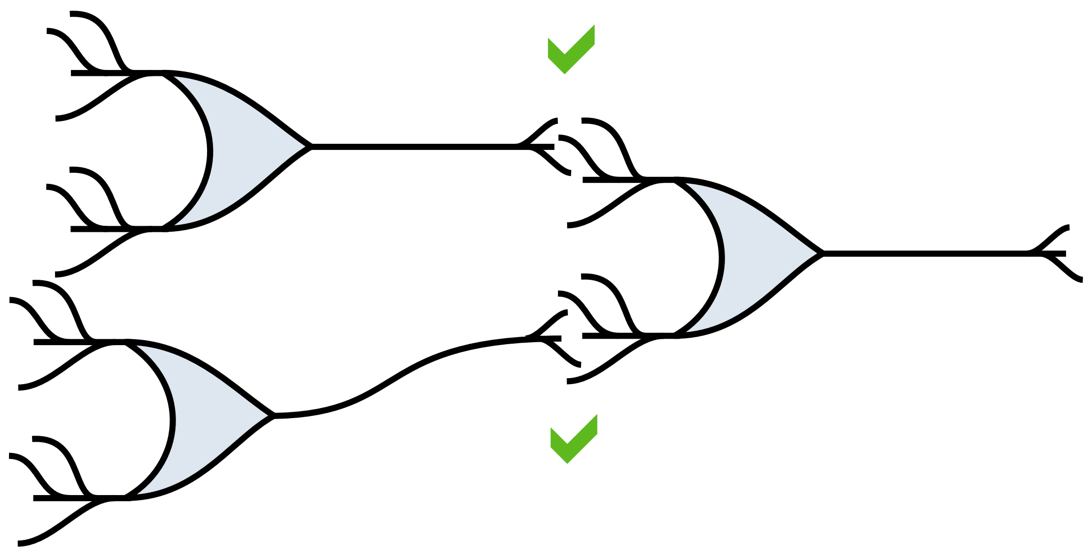
The change in w is then determined

If the Spike Order is Reversed, ...



Then, ...

- With an appropriate firing sequence, the network can be trained.



Summary 2

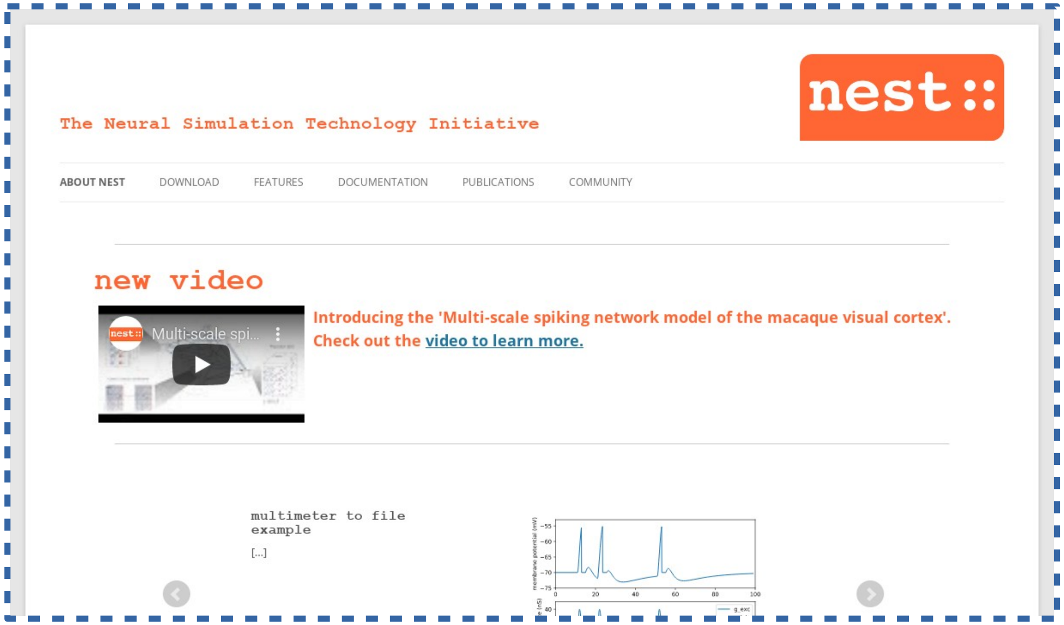
- Networks of neurons can perform more complicated computations
- The output of the computation can be trained
  - The output is determined by connections between neurons
- In real neuronal networks, one important process changing connections between neurons is STDP
- STDP can be implemented using a group of differential equations

Take-Home Message

- Some neuronal behaviors can be mathematically modeled
- Networks of neurons has the potential to do different computations
- Those networks can be trained

Caution

- Don’t really do scientific simulations in spreadsheet
- In the following, other lab members will tell you about the usage of nest simulator for neuronal computation



Thank you