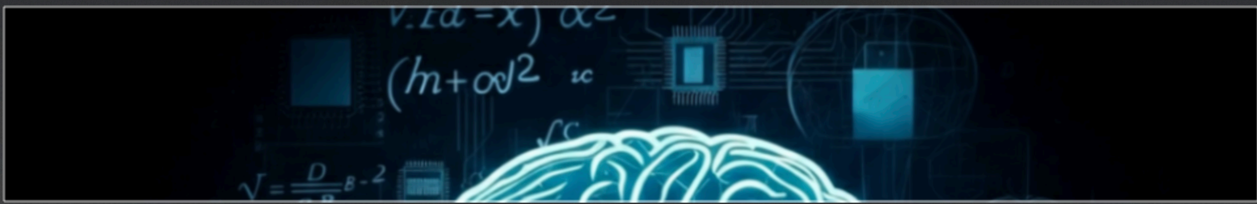
MODELLING NEURAL SYSTEMS



COMPUTATIONAL MODELLING OF NEURONS AND MICROCIRCUITS

Prof. Ing. Michele GIU**G**LIANO, PhD

Simplified models of excitability

Plan for the day

- Simplification of AP generation: the Integrate-&-Fire model
- The Frequency-Current formula for the Integrate-&-Fire
- Electrodiffusion and ionic concentrations
- The Integrate-&-Fire with spike-frequency adaptation
- Assignment (optional, not compulsory!)
- How good is this model? Families of Integrate-and-Fire…

So far: adding biological **realism** and grounding mathematical descriptions into biophysics

Now: **simplify** the detailed models of neurons into reduced descriptions

Stripping down a complex model to its bare essential may provide an **explanatory model** (easier to *understand*)

Ultimate goal of studying emergence of non-intuitive phenomena in **large networks of neurons** where simpler neurons are *easier/faster* to simulate

where to stop???!

The data available.
it might (not) be possible to **constraint all parameters** of a complex model

The desired type of analysis.
one might want to investigate and analyse **collective properties** and not single-neuron phenomena

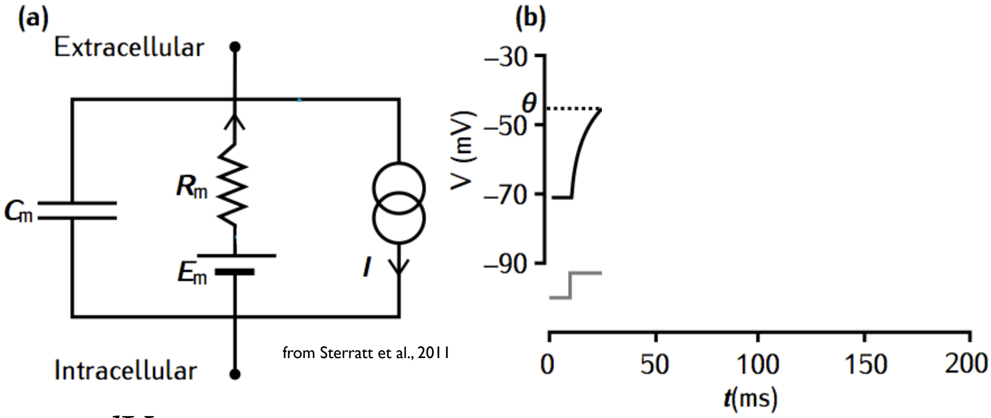
Computational resources.
Simpler models are **faster to simulate** than complex ones.

The level of explanation.
Correspondence between model parameters and physical elements (e.g. models of the appropriate types of ion channels are needed in order to predict what happens to a neuron when a particular neuromodulator is released or a particular type of channel is blocked).

from Sterratt et al., 2011

Integrate-and-Fire model(s)

G = 1 / R



$$C \frac{dV}{dt} = G \ (E - V) + I_{ext} \qquad if \ \ V < \theta$$

$$t^* spike, \quad V(t^*) \leftarrow H \qquad V(t) \ fixed \ at \ H, \ t \in \ [t^*; t^* + \tau_{arp})$$

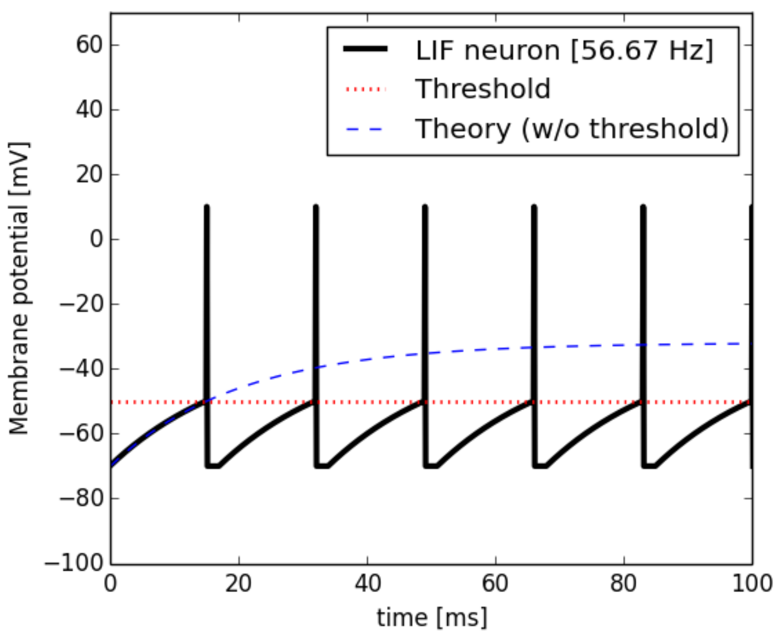
Integrate-and-Fire model(s)

- there is a (fixed) explicit threshold (θ)
- a spike *is said* to occur when there is a threshold crossing
- after a spike, the membrane potential is clamped to H a (hyperpolarized) level, for a time interval τ_{arp}

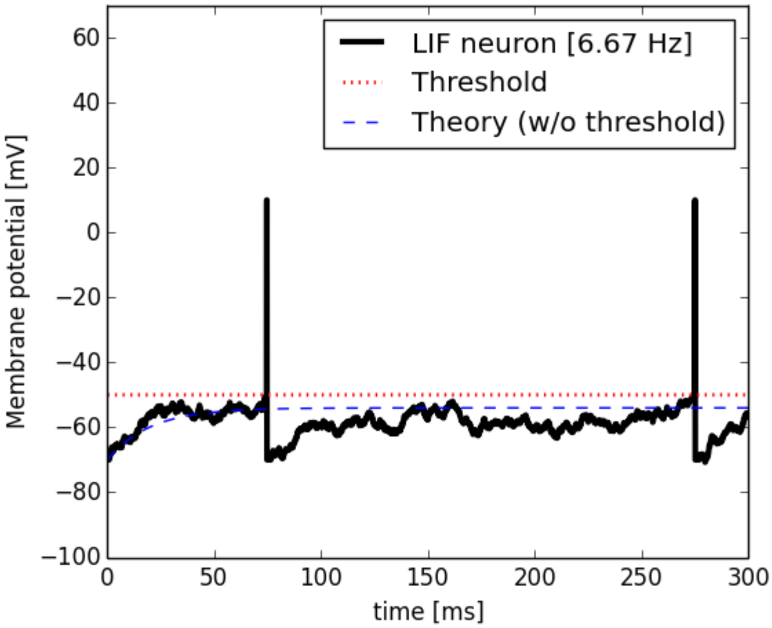
```
if V >= theta
 V  = H
 to = t
elseif t < (to+Tarp)
 V = H
else
 V = V + dt*G/C * (E - V) + dt/C *I
end
```

Demo

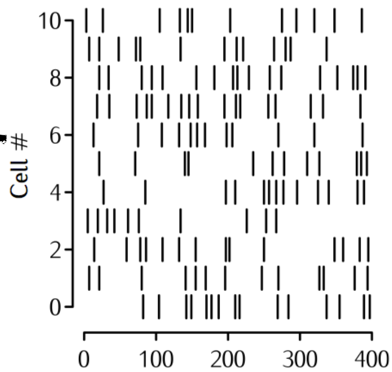
Leaky Integrate-and-Fire model



Leaky Integrate-and-Fire model

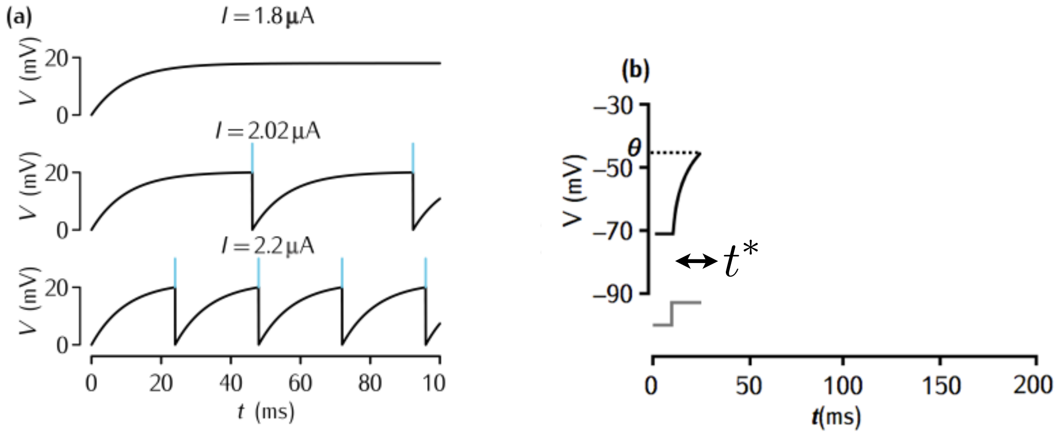


A network of **non-interacting** (**identical**) *Leaky* Integrate-and-Fire neurons




```
for i=1:10
 if V[i] >= theta
  V[i]  = H
  to[i] = t
 elseif t < (to[i]+Tarp)
  V[i] = H
 else
  V[i] = V[i] + dt/(R*C) * (E - V[i]) + dt/C *I[i]
 end
end
```

Frequency vs (DC) current curve for a *Leaky* I&F model



from Sterratt et al., 2011

Frequency vs (DC) current curve for a *Leaky* I&F model

G = 1 / R

$$C \frac{dV}{dt} = G \ (E - \ V) \ + \ I_{ext}$$

$$V(t) \ = \ E \ + \ I_0/G \ \left(1 \ - \ e^{-G/C \ t}\right)$$

$$V(t^*) \ = \ V_{th}$$

$$t^* \ = \ \frac{C}{G} \ log \left(\frac{I_0}{G(E - V_{th}) + I_0} \right)$$

$$f(I) = \frac{1}{\tau_{arp} + t^*}$$

Frequency vs (DC) current curve for a *Leaky* I&F model

- there is a minimal current (*rheobase*) for spikes to be fired (i.e. for the threshold to be crossed)

$$C \frac{dV}{dt} = G \ (E - \ V) \ + \ I_{ext}$$

...at the steady-state $\quad V = E + I_{ext}/G$

$$I_{rhe} = G \ (V_{th} - E)$$

(or if you like math, then look at where ln(x) is defined...)

Frequency vs (DC) current curve for a *Leaky* I&F model

- if we neglect the refractoriness, for very large currents (i.e. far away the rheobase, where you have a non-linearity)...

$$f(I) \approx \frac{1}{t^*} \qquad t^* = -\frac{C}{G} \ log\left(1 + \frac{G(E - V_{th})}{I_0}\right)$$

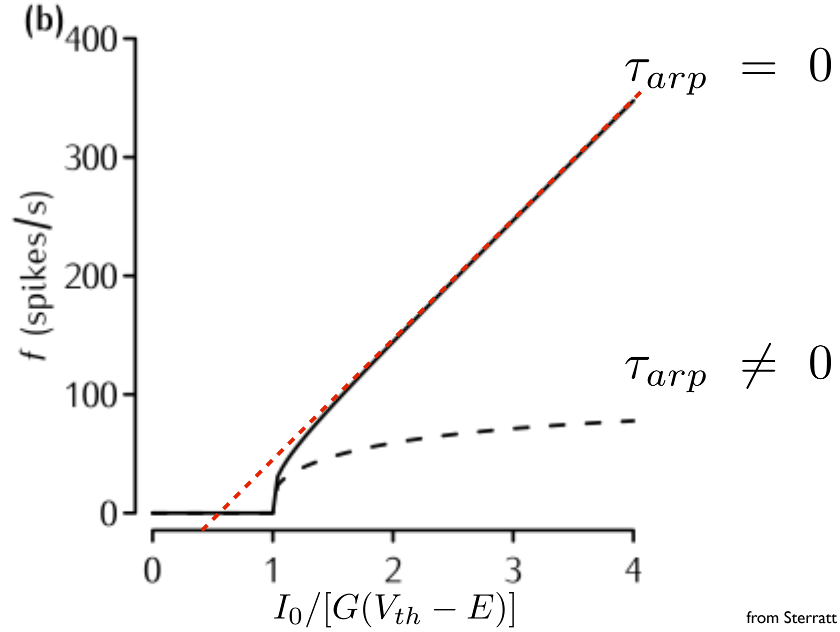
$$ln(1 \ + \ x) \ \approx \ x$$

$$t^* \ \approx \ -C \ \frac{(E - V_{th})}{I_0}$$

$$f(I) \ \approx \ \frac{I_0}{C(V_{th} - E)}$$

Then, the f-I curve is threshold-linear.

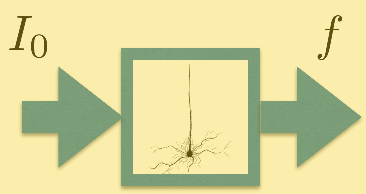
Frequency vs (DC) current curve for a I&F model



from Sterratt et al., 2011

Very rough (functional) approximation

$$t^* = -\frac{C}{G} \, log\left(1 + \frac{G(E - V_{th})}{I_0}\right)$$

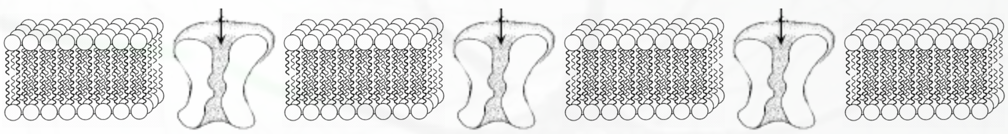


$$f(I) \approx \frac{I_0}{C(V_{th} - E)}$$

*A neuron is a device that converts input current (**amplitudes**) into a train of action potential with a certain **frequency**.*

Electrodiffusion and ionic concentrations

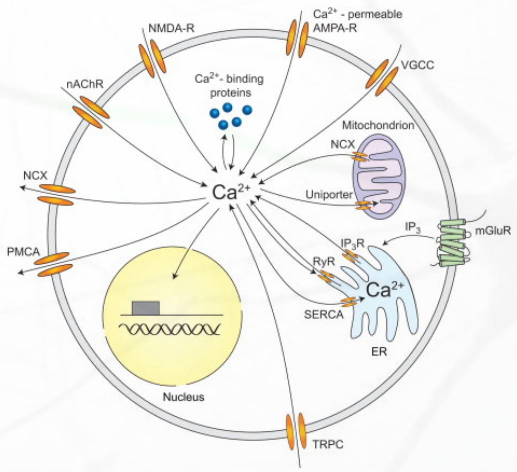
Given the existing concentration gradients, then the individual ionic membrane permeabilities determine V

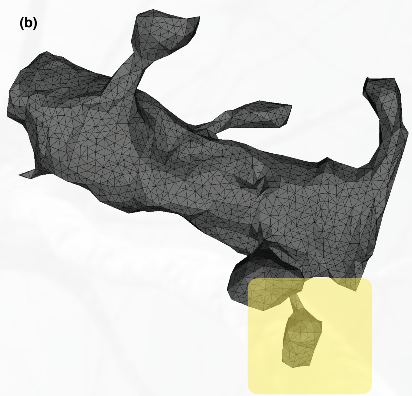


$$i_{tot} = G_1 \ (V - E_1) + G_2 \ (V - E_2) + G_3 \ (V - E_3) + ... + G_N \ (V - E_N)$$

$$E_{Nernst} \ = \ V_{in} \ - \ V_{out} \ = \ \frac{R \ T}{z \ F} \ ln \left(\frac{c_{out}}{c_{in}} \right)$$

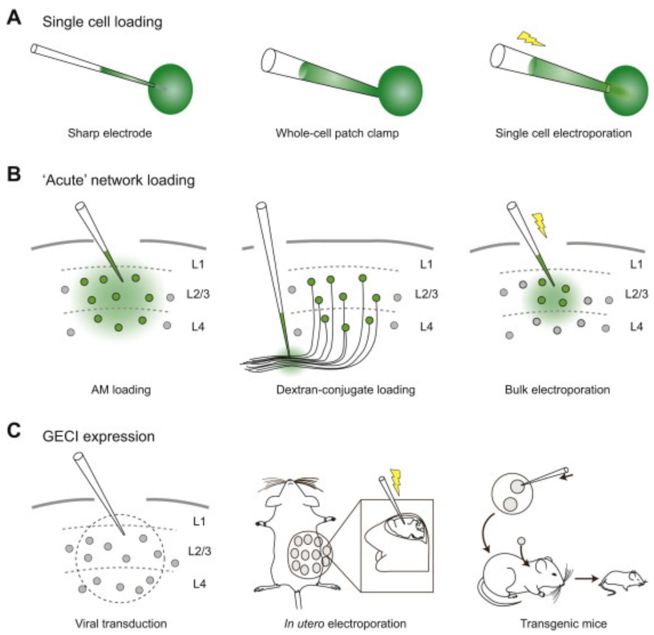
Ion currents through the membrane may
alter local ionic concentrations, thus alter Nernst potentials!

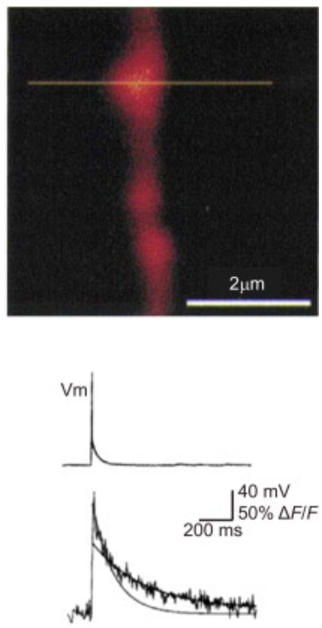




(Intracellular) ions often act as second-*messengers*!
Membrane potential may locally alter ionic concentrations

Fluorophores and fluorescence-imaging of [Ca++]

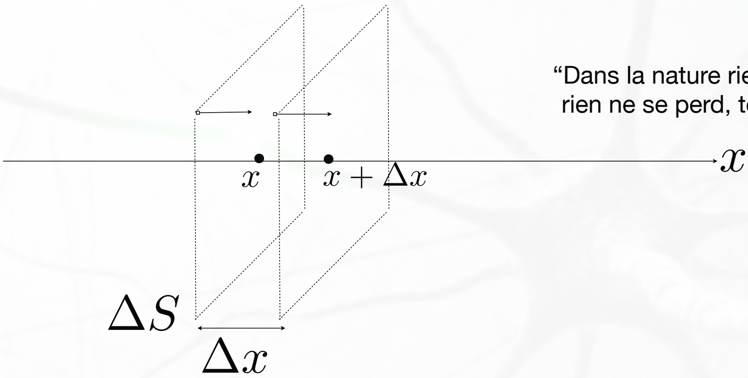




Grienberger & Konnerth (2012)

Electro-diffusion equation

invoking conservation of mass for charged particles in aq. solution



"Dans la nature rien ne se crée, rien ne se perd, tout change."

 Δt

A. Lavoisier

$$c(x, t + \Delta t)\ (\Delta S\ \Delta x) =$$
$$c(x,t)\ (\Delta S\ \Delta x) + J(x,t)\ \Delta t\ \Delta S - J(x+\Delta x, t)\ \Delta t\ \Delta S$$

Electro-diffusion equation

$$c(x, t + \Delta t)\ (\cancel{\Delta S}\ \Delta x) = c(x,t)\ (\cancel{\Delta S}\ \Delta x) + J(x,t)\ \Delta t\ \cancel{\Delta S} - J(x+\Delta x, t)\ \Delta t\ \cancel{\Delta S}$$

$$\frac{c(x, t + \Delta t) - c(x,t)}{\Delta t} = -\frac{J(x + \Delta x, t) - J(x,t)}{\Delta x}$$

$$\Big\downarrow \begin{array}{l} \Delta x \to 0 \\ \Delta t \to 0 \end{array}$$

$$\boxed{\frac{\partial c(x,t)}{\partial t} = -\frac{\partial J(x,t)}{\partial x}}$$

$$J = J_{diff} + J_{drift} \qquad J = -D\frac{dc}{dx} - u\ c\ z\ F\ \frac{dV}{dx}$$

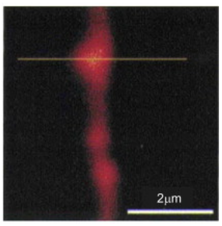
$$J_k \approx \frac{1}{z_k\ F}\ G_k\ (E_{Nernst,\ k} - V_m)$$

$$\frac{\partial c(x,t)}{\partial t} = - \frac{\partial J(x,t)}{\partial x}$$

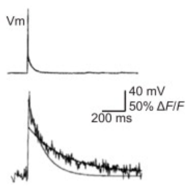
$$\downarrow$$

$$\frac{dc}{dt} = \frac{J_k}{vol} + \ \ldots .$$

$$\boxed{\frac{dc}{dt} = \frac{J_k}{vol} - \beta\ (c - c_{min})}$$



$$\boxed{\frac{dc}{dt} = \frac{J_k}{vol} - \beta\ (c - c_{min})}$$



Grienberger & Konnerth (2012)

$$\frac{dc}{dt} \approx -\beta\ (c\ \ - c_{min})$$

$$c \to c + \Delta$$

Blackboard:
prove that on average,
"c" (e.g. [Ca++]i) is proportional to ~f

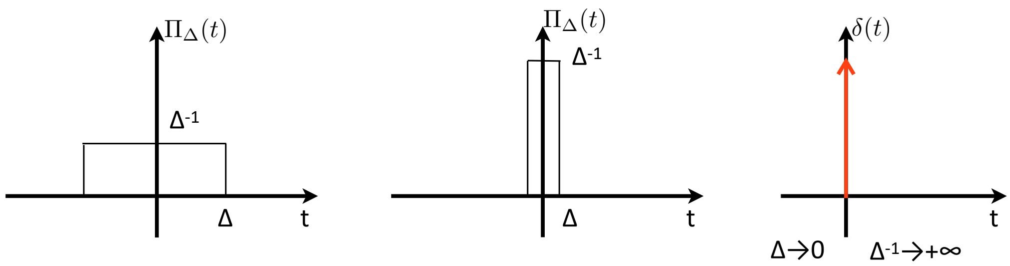
(MG's "bank account")

Module 1: Mathematical preliminaries on the Dirac's Delta function $\delta(t)$

- It is **not** a *conventional* function
- It is defined through the "effect" on a test function $g(t)$

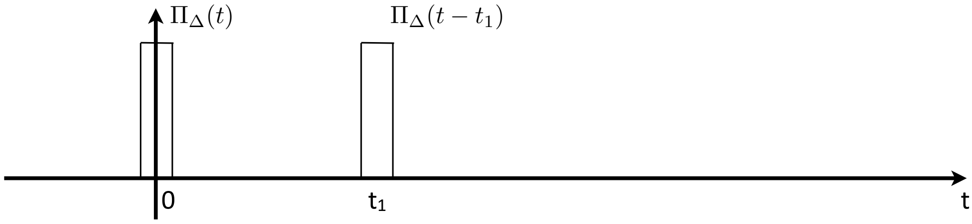
$$\int_{-\infty}^{+\infty} g(t)\delta(t)\ dt \;=\; g(0)$$

...it *extracts* the value in t = 0 of the test function

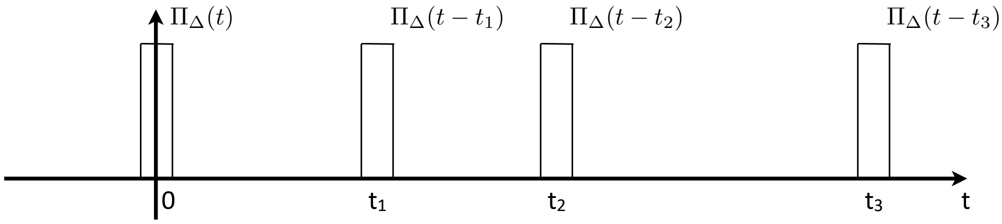


Module 1: Mathematical preliminaries on the Dirac's Delta function $\delta(t)$

- Remember how to "*translate a function through time*" ?



- and how to sum two functions (graphically) ?



Module 1: Mathematical preliminaries on the Dirac's Delta function $\delta(t)$

(it is like having a "train" of pulses... overlapping)

$$f(t) = \Pi_\Delta(t) + \Pi_\Delta(t-t_1) + \Pi_\Delta(t-t_2) + \Pi_\Delta(t-t_3)$$

- Dirac's Deltas as the "input" to a first-order o.d.e.

$$\tau \frac{dx}{dt} = -x(t) + a\ \delta(t)$$

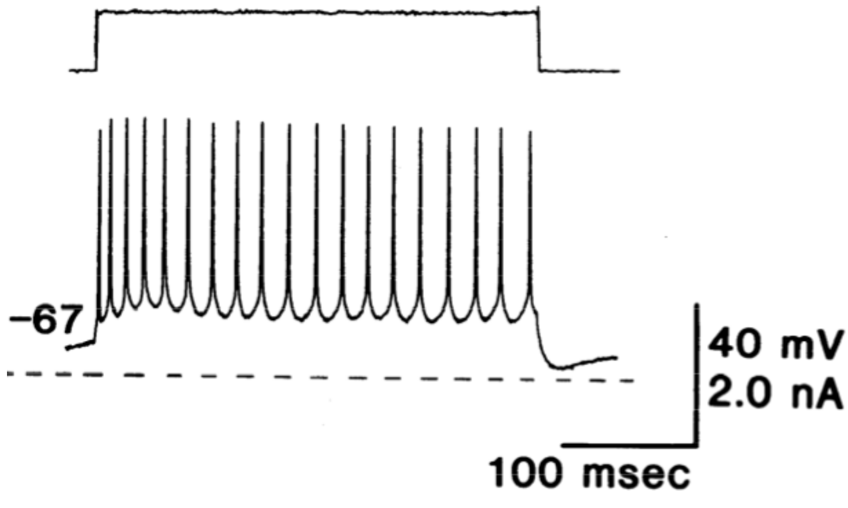
$$\int_{0^-}^{0^+} \tau \frac{dx(t)}{dt} dt =$$

$$\tau \frac{dx}{dt} = -x(t) \quad t \neq 0$$

$$\int_{0^-}^{0^+} -x(t)dt + \int_{0^-}^{0^+} a\ \delta(t)dt$$

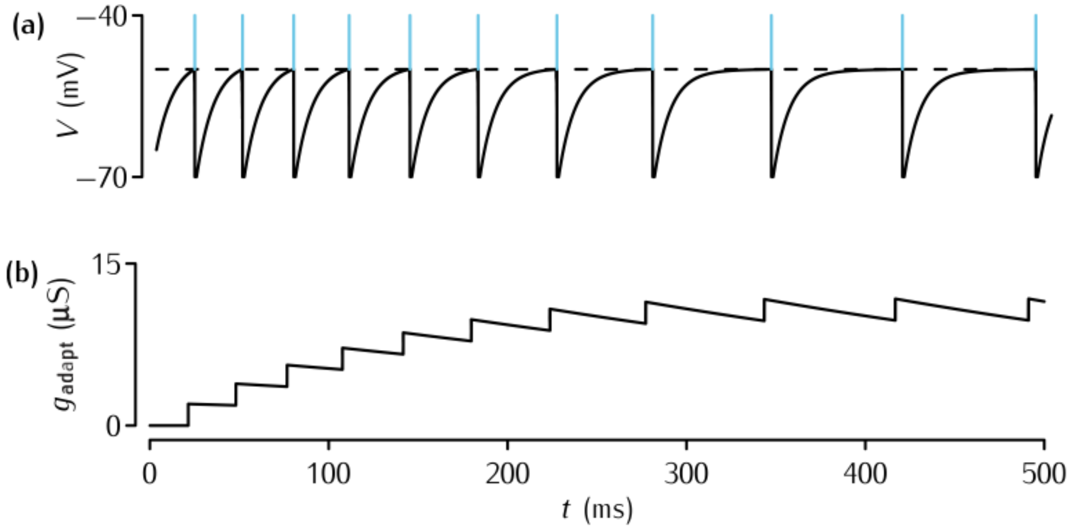
Spike-frequency *adaptation / accommodation*

But… cortical pyramidal neurons do display spike-frequency adaptation!



from McCormick et al., 1985

Integrate-&-Fire with extra "adaptation mechanism" (i.e. spike-frequency adaptation *current*)



from Sterratt et al., 2011

Integrate-&-Fire with extra "adaptation mechanism" (i.e. spike-frequency adaptation *current*)

$$I_{adapt} = \bar{g}_{adapt}\ x\ (E - V)$$

$$\frac{dx}{dt} = -\frac{x}{\tau_{adapt}}$$ below threshold, $if \quad V < \theta$

$$x \rightarrow x + \Delta_{adapt}$$ during a "spike"

$\boxed{I_{adapt} \approx -\bar{g}_{adapt}\ x \quad \text{approx. equivalent}}$

Exercise:
implement, simulate, and
explore the I&F model

(extensive narrative) text/
discussion/comments
+
code and figure(s)

as a Google Colab Notebook

Exercise:
implement, simulate, and
explore the following points

- Simulate the IF model to plot its F-I curve
- Test whether the analytical formula for F(I) is accurate
- Discuss possible differences between theory and simulation
- Simulate the IF model + adaptation and plot its F-I curve
- Discuss the effects of the adaptation near the rheobase
- Discuss the effects of the adaptation far from the rheobase

Exercise:
implement, simulate, and
explore the following points

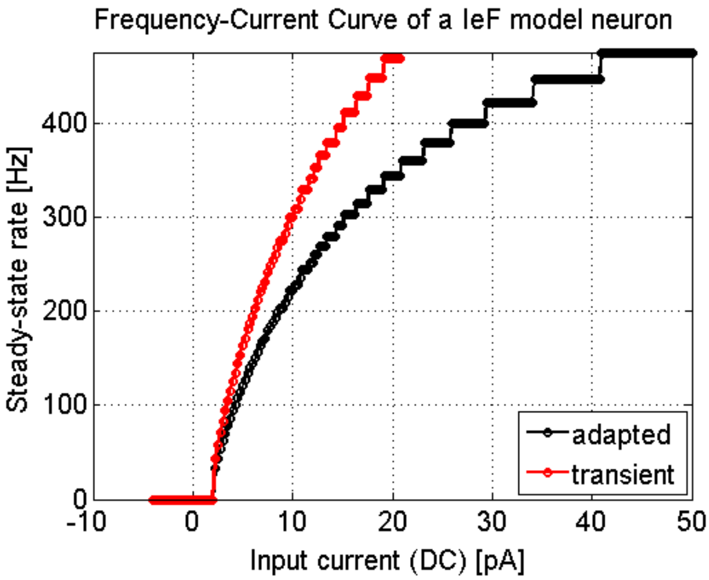
Parameters - given

$$1/G_m = R_m = 10\ k\Omega$$
$$C_m = 1\ \mu F$$
$$\theta = -50mV$$
$$E = -70\ mV$$
$$\tau_{arp} = 1\ ms$$

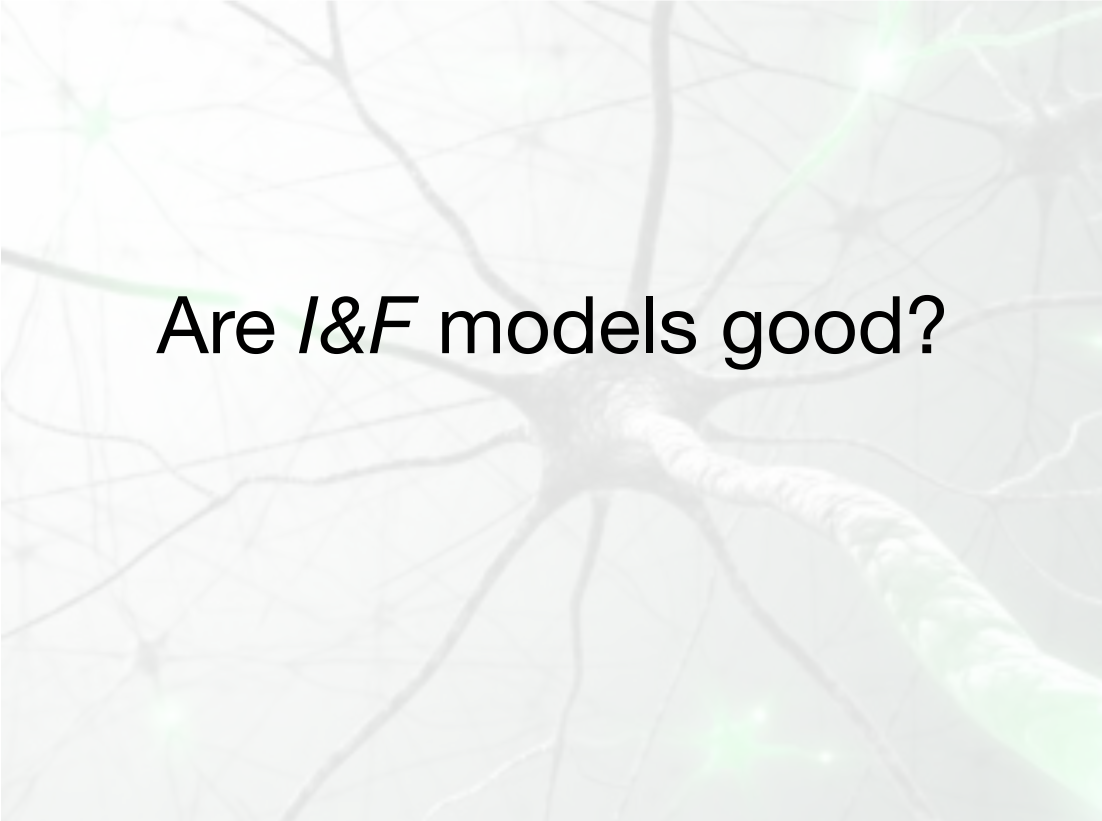
Parameters - to *explore*:

$$g_{adapt}, \Delta_{adapt}, \tau_{adapt}$$

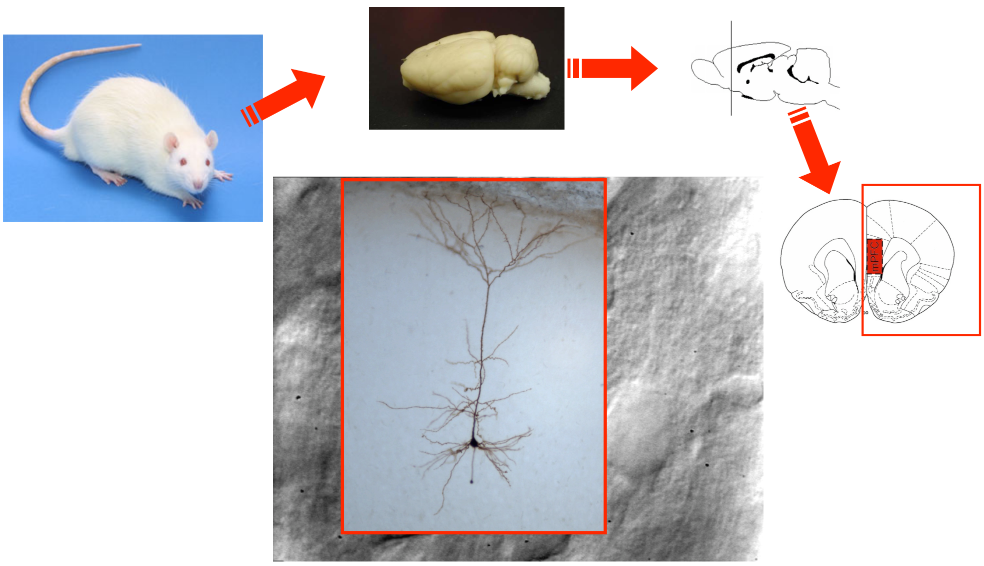
Leaky-Integrate-and-Fire model: f-I curve (with spike-frequency adaptation)



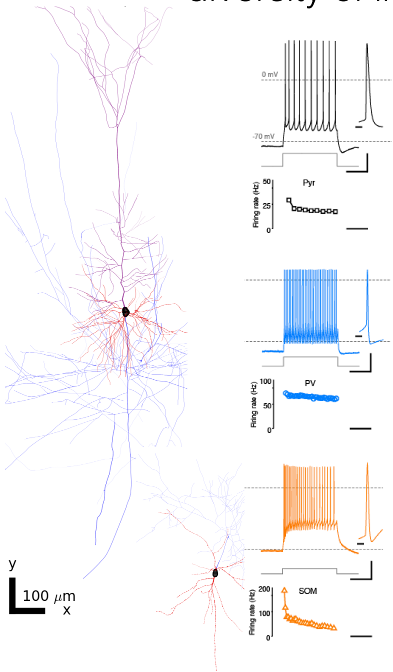
Are *I&F* models good?

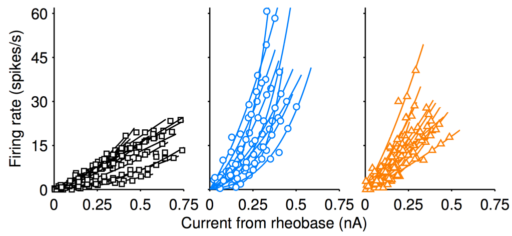


Frequency vs (DC) current curve for a real pyramidal neuron

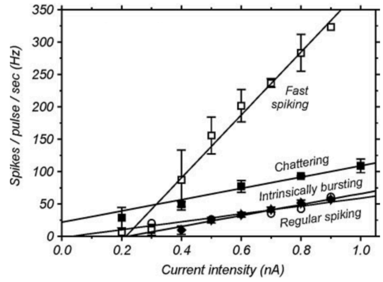


Cellular electrophysiology of neocortex
diversity of input-output transfer properties



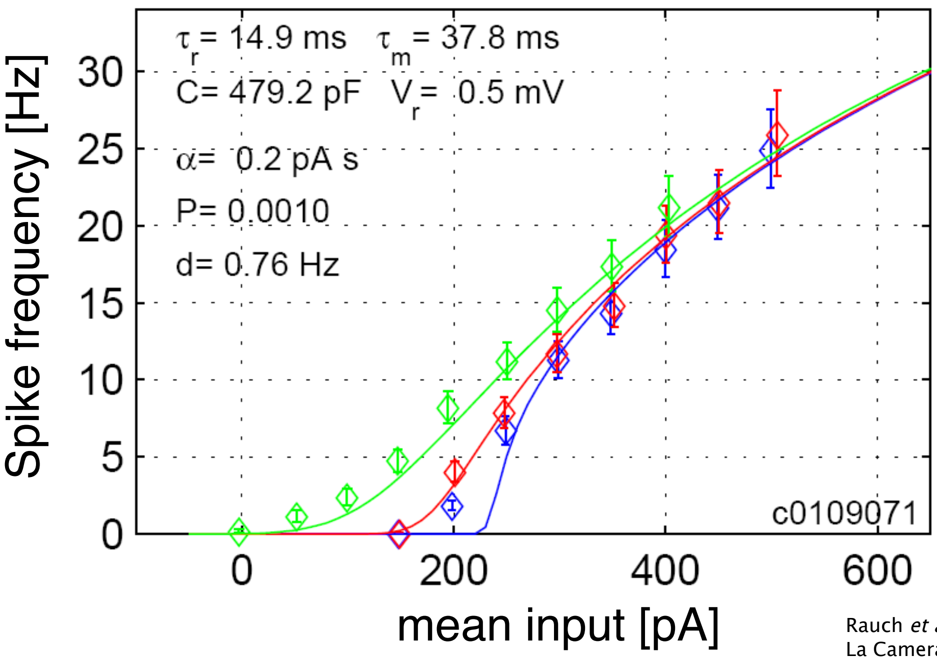


$$F = \Phi(i)$$



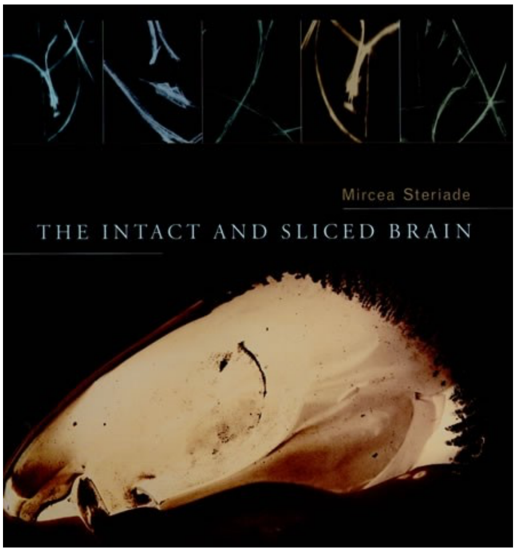
Linaro et al., in 2019
Nowak et al. (2003). J. Neurophysiol. 89(3), 1541-66
McCormick et al. (1985). J. Neurophysiol. 54(4), 782–806

Frequency vs current curve for a pyramidal neuron: I&F are accurate enough!!

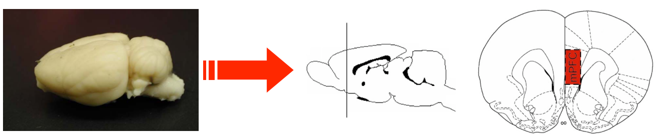


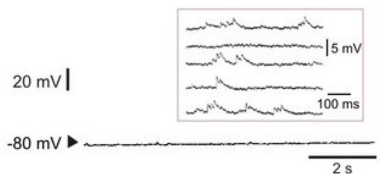
Rauch *et al.*, 2003
La Camera *et al.*, 2006

(Cortical) *in vitro* vs *in vivo* physiology



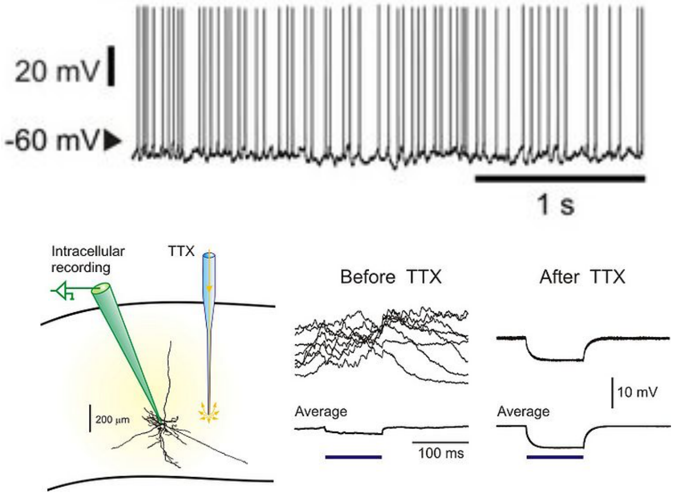
"Sliced" brain: acute brain tissue slices





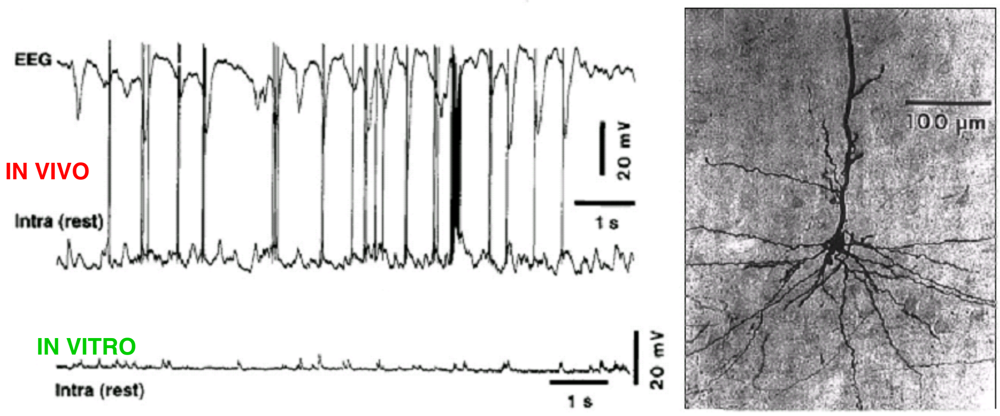
- Lack of any spontaneous firing
- The membrane potential "sits" at resting membrane potential
- Episodic, small synaptic potentials

Awake, *in vivo* cortical recordings

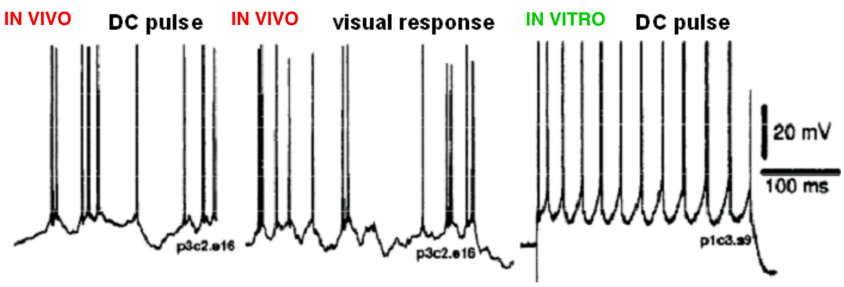


- Spontaneous irregular firing
- Random fluctuations of the membrane potential, subthreshold
- Reduction of the apparent "membrane input resistance"

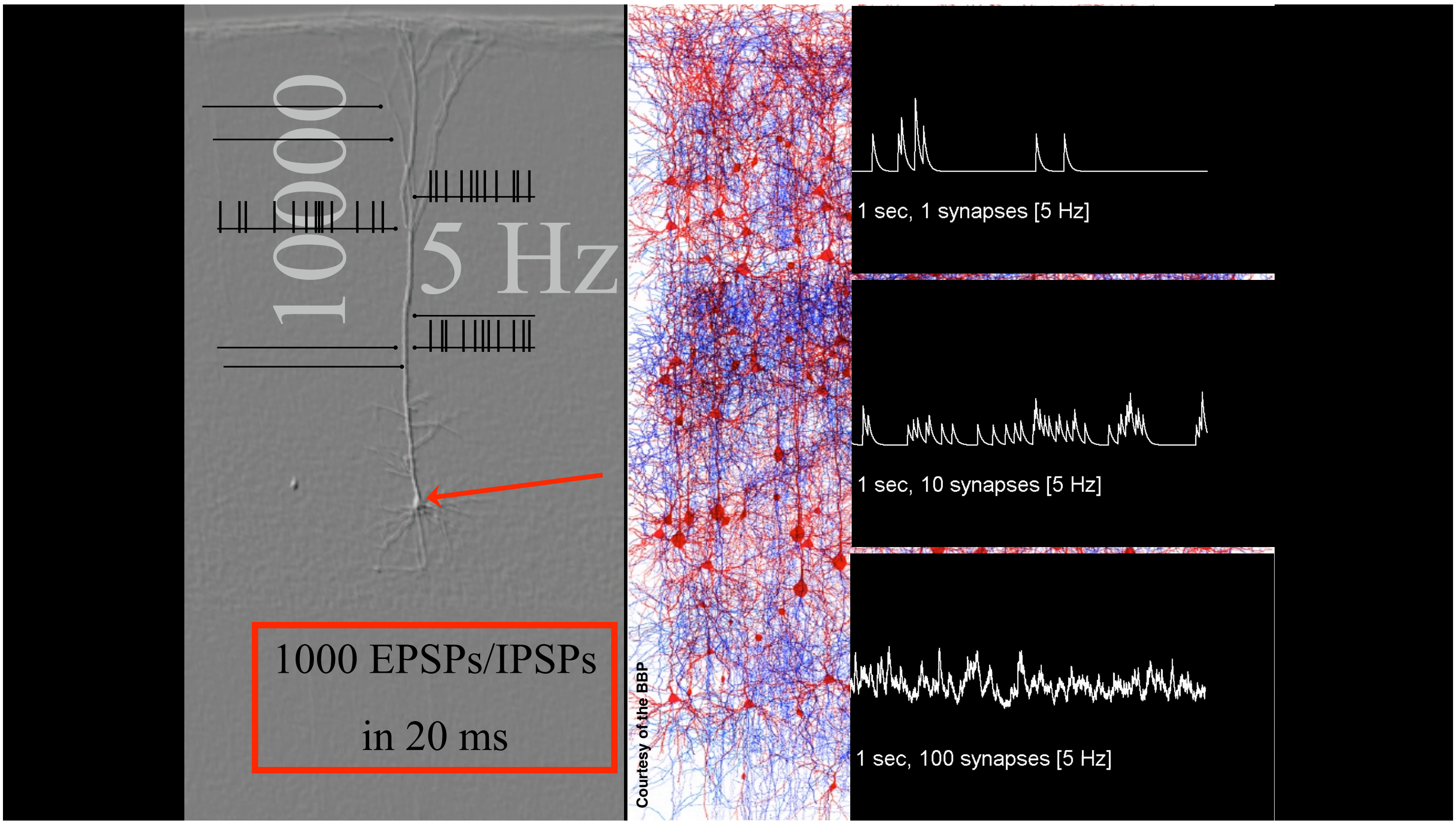
(Cortical) *in vitro versus in vivo physiology*

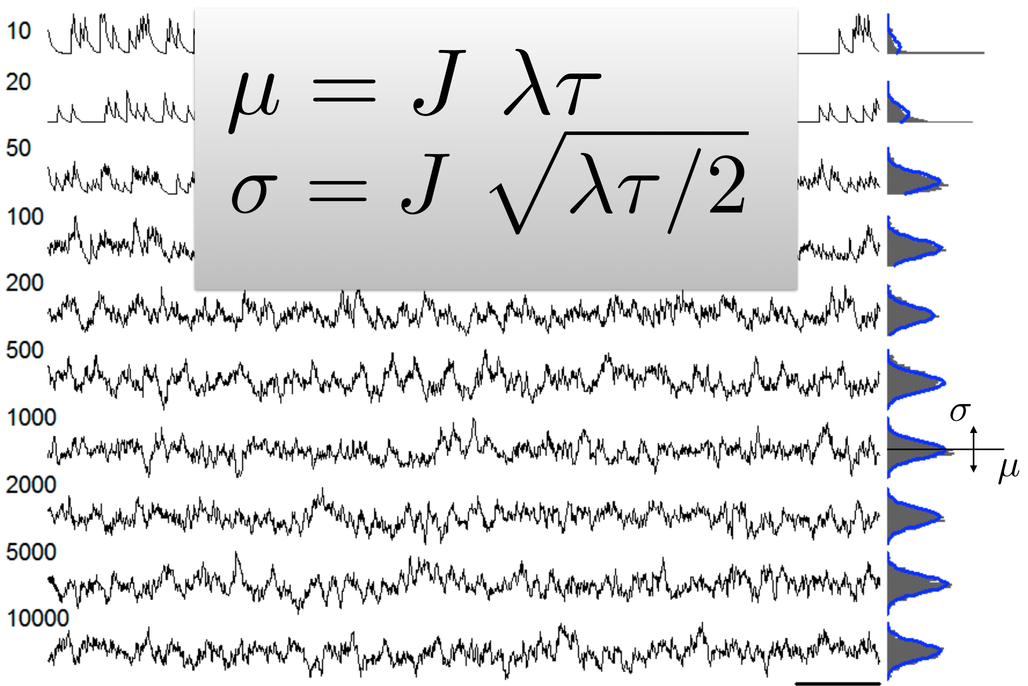


Steriade, J. Neurophysiol. 2001



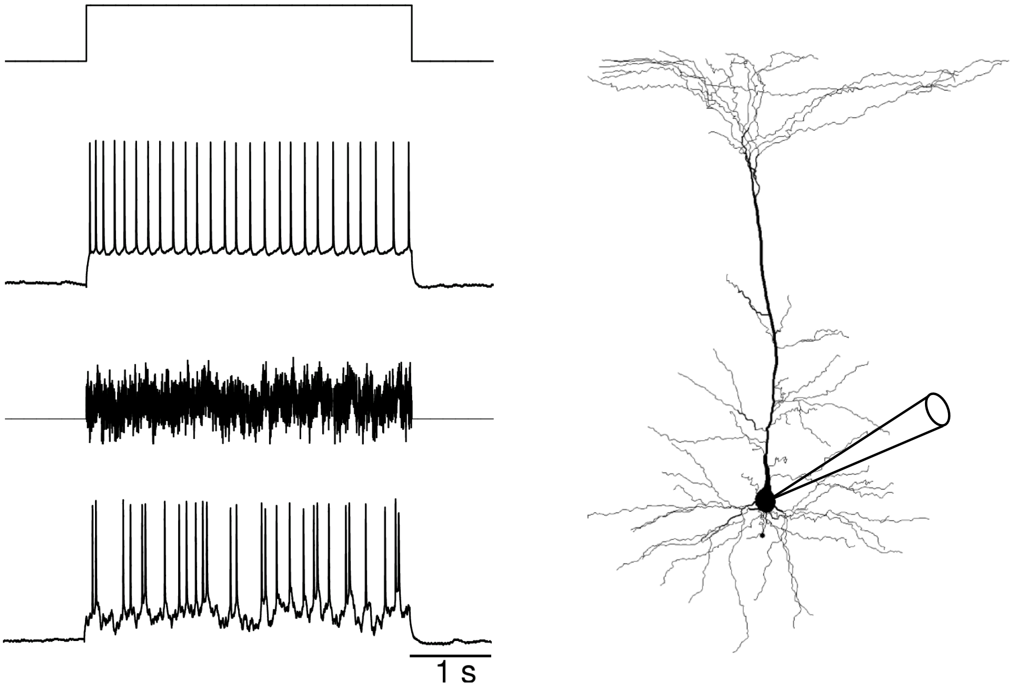
Holt, Softky, Koch, Douglas, J. Neurophysiol. 1996



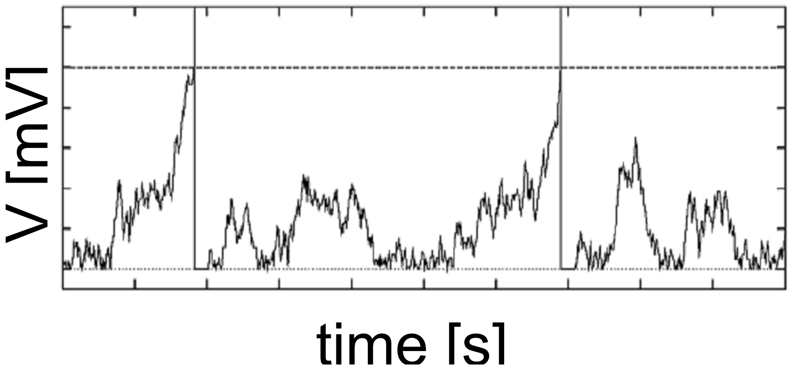


Giugliano et al., 2008, Biological Cybernetics
Arsiero et al., 2007, J Neuroscience
Giugliano et al., 2004, J Neurophysiology

Restore *in vivo*-like activity, *in vitro*??



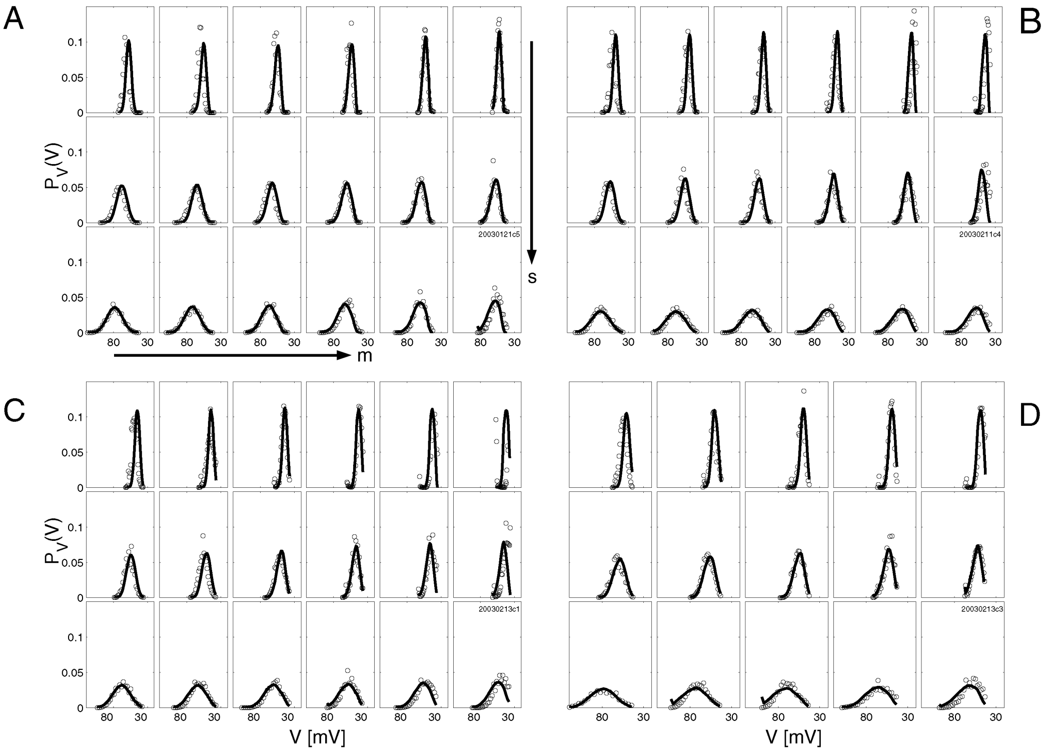
Leaky Integrate-and-Fire neuron model

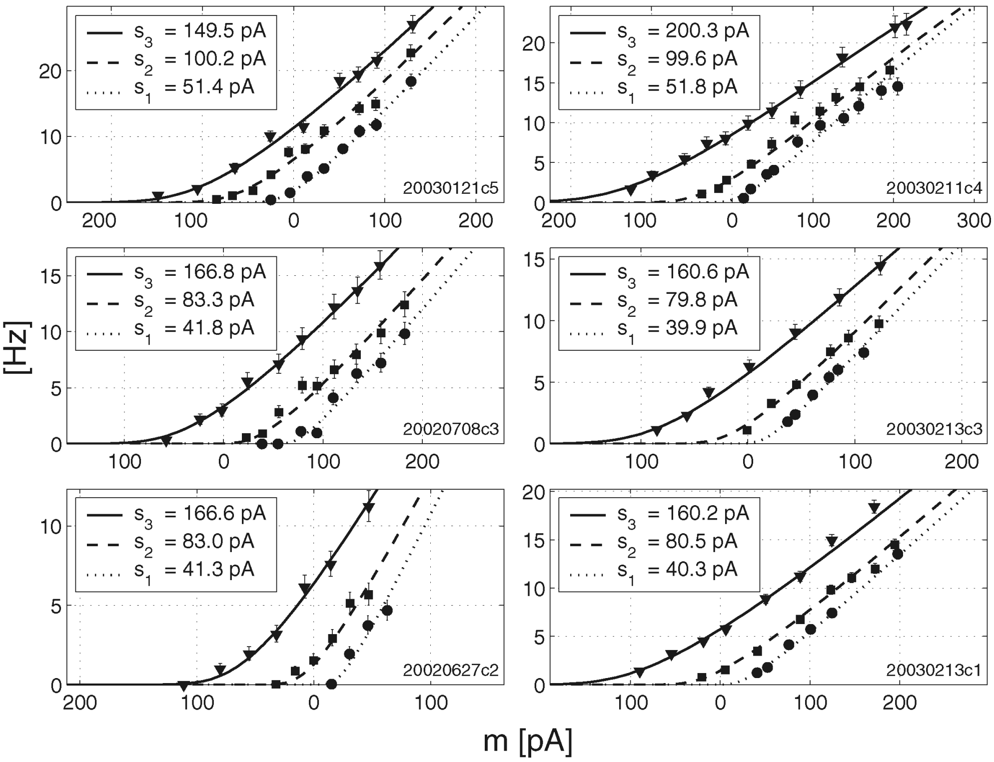


$$r_0 = f(\mu, \sigma, \tau)$$

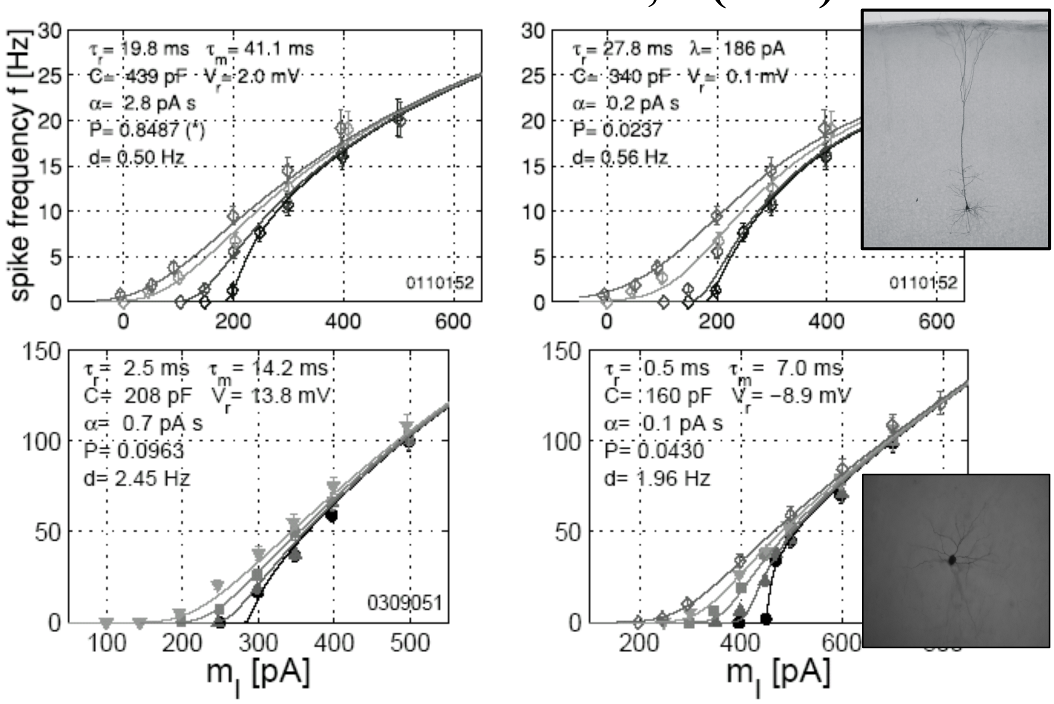
Giugliano et al., 2008, Biological Cybernetics
Arsiero et al., 2007, J Neuroscience
Giugliano et al., 2004, J Neurophysiology

Destexhe & co. ; Gerstner & co. ; and many others
McCormick et al., 1985; Powers and Binder, 2001


A
B
C
D
$P_V(V)$
s
m
20030121c5
20030211c4
20030213c1
20030213c3
V [mV]

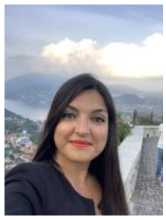

s_3 = 149.5 pA
s_2 = 100.2 pA
s_1 = 51.4 pA
20030121c5
s_3 = 200.3 pA
s_2 = 99.6 pA
s_1 = 51.8 pA
20030211c4
s_3 = 166.8 pA
s_2 = 83.3 pA
s_1 = 41.8 pA
20020708c3
s_3 = 160.6 pA
s_2 = 79.8 pA
s_1 = 39.9 pA
20030213c3
s_3 = 166.6 pA
s_2 = 83.0 pA
s_1 = 41.3 pA
20020627c2
s_3 = 160.2 pA
s_2 = 80.5 pA
s_1 = 40.3 pA
20030213c1
[Hz]
m [pA]

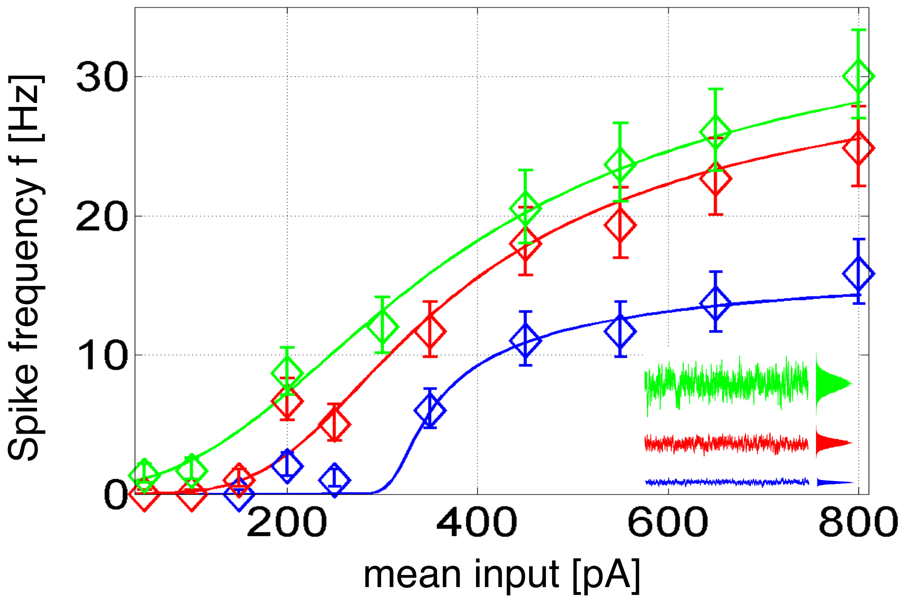
PYR/FS neurons L2-3, 5 (SSC)



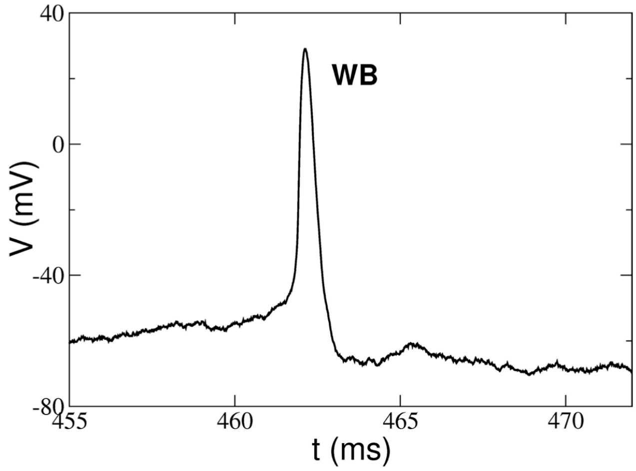
La Camera et al., 2006; Rauch et al., 2003

Medial prefrontal cortical L5 pyramids

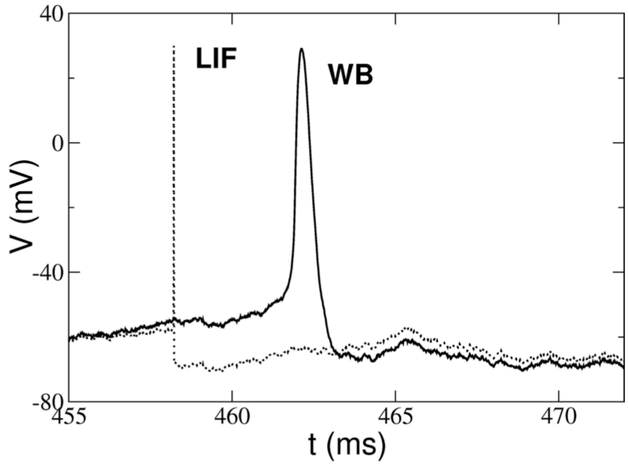




What about predicting AP times?



The LIF fails…

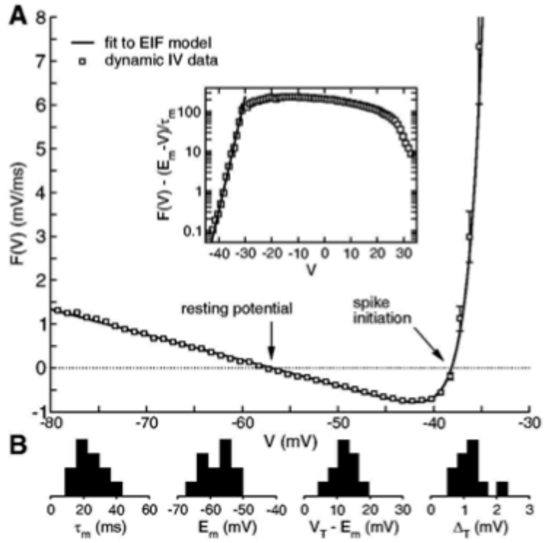


LIF

$$C\frac{dV}{dt} = -g_L(V - V_L) + I_{syn}(t)$$

Extending the LIF model

$$
\begin{aligned}
\frac{dV}{dt} &= F(V) + \frac{I_{in}(t)}{C} \\
F(V) &= \frac{1}{\tau_m}\left(E_m - V + \Delta_T \exp\left(\frac{V - V_T}{\Delta_T}\right)\right)
\end{aligned}
$$



Badel et al 2008

Extending the LIF model

$$
C\frac{dV}{dt} = -g_L(V - V_L) + \psi(V) + I_{syn}(t)
$$

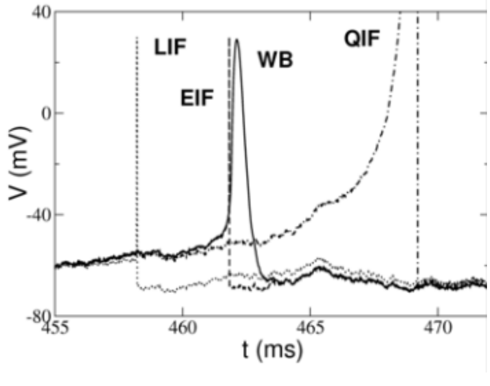
QIF: quadratic integrate-and-fire neuron

$$
\begin{aligned}
C\frac{dV}{dt} &= -g_L(V - V_L) + \psi(V) + I_{syn}(t) \\
\psi(V) &= \frac{g_L}{2\Delta_T}(V - V_T)^2 + g_L(V - V_L) - I_T
\end{aligned}
$$

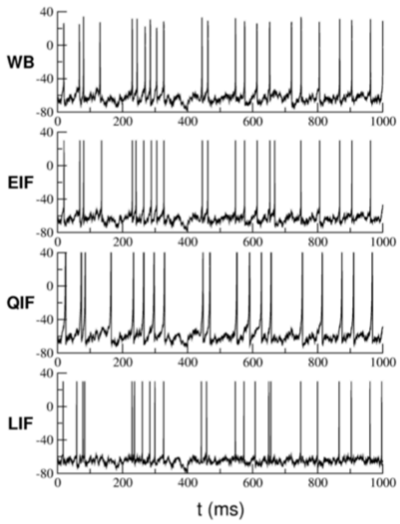
Ermentrout and Kopell 1986

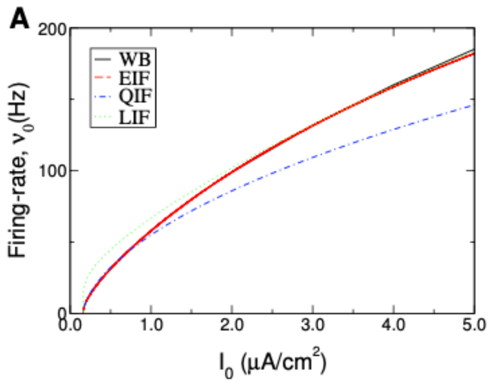
$$
\begin{aligned}
C\frac{dV}{dt} &= -g_L(V - V_L) + \psi(V) + I_{syn}(t) \\
\psi(V) &= g_L \Delta_T \exp\left(\frac{V - V_T}{\Delta_T}\right)
\end{aligned}
$$

(Fourcaud-Trocmé et al 2003)



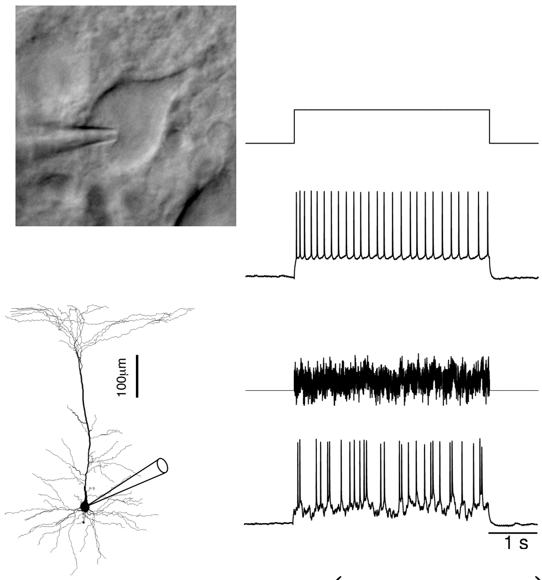
Extending the LIF model



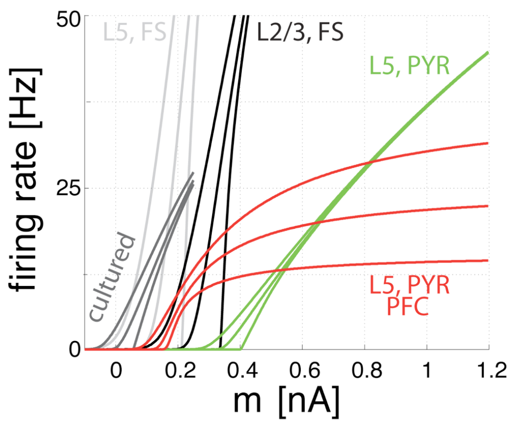


Response to (stationary) fluctuating inputs

generalising the f-i curve



$$F = \Phi(\mu, \sigma, \tau)$$



Giugliano et al., 2008, Biological Cybernetics
Arsiero et al., 2007, J Neuroscience
Giugliano et al., 2004, J Neurophysiology

Destexhe & co. ; Gerstner & co. ; and many others
McCormick et al., 1985; Powers and Binder, 2001