

# Mathematical Neuroscience

## A personal perspective

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# Outline

Introduction

Hodgkin Huxley

Deriving the H-H model ab initio

Ephaptic interactions

Glial cells

Conclusion

## Introduction

Hodgkin Huxley

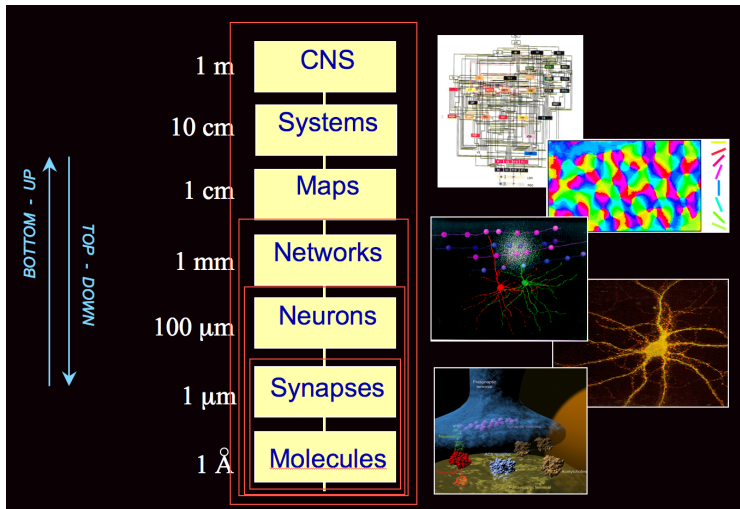
Deriving the H-H model ab initio

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# Hierarchy and Complexity in the CNS

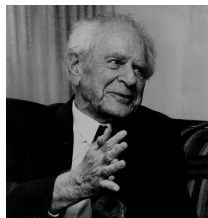


## How different are the viewpoints of biologists, physicists, and mathematicians?

- ▶ Induction and deduction
- ▶ Biologists make observations, measurements, run computational models on data. More induction than deduction.
- ▶ Physicists develop computational models, make simulations - do not provide proofs - discover what happens with reasonable certainty. More deduction than induction.
- ▶ Mathematicians attempt to provide rigorous proofs - sometimes of results that are "known" by another community - tough when most results bear upon situations considered easy (if not trivial) by the physicists or the biologists. Emphasis on deduction.

## Predictive mathematical models for Neuroscience

- ▶ The goal of mathematical neuroscience is to develop predictive, falsifiable, pieces of mathematics (Karl Popper).
- ▶ In neuroscience and in biology more generally all (mathematical) models are (at least partially) wrong
- ▶ Mathematics rigorously proves facts helping to circumscribe the domain of validity of models



## Example: The work of Hodgkin and Huxley



- ▶ One of the most famous mathematical models is that of **Hodgkin and Huxley (1952), Nobel prize in physiology (1961)**
- ▶ It has been falsified: some of its predictions are incorrect (**Hodgkin and Huxley (1952), Jane Cronin (1987, p.66)**).
- ▶ It is valid for a large number of experimental conditions.

Introduction

**Hodgkin Huxley**

Deriving the H-H model ab initio

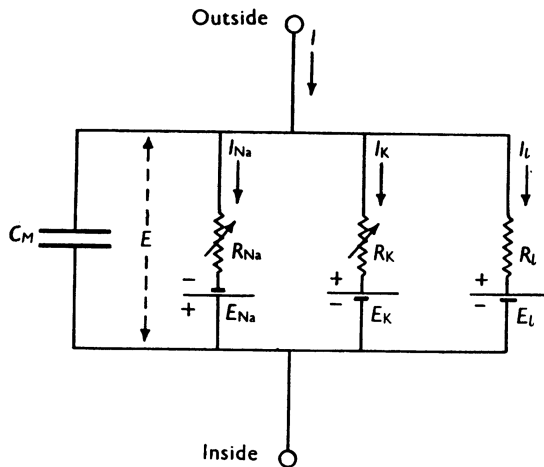
Ephaptic interactions

Glial cells

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# The flow of electric current through the surface membrane of a giant nerve fibre



From Hodgkin  
Huxley (1952)

## The equations

$$I = C_m \frac{dV_m}{dt} + \bar{g}_K n^4 (V_m - V_K) + \bar{g}_{Na} m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l),$$

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

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

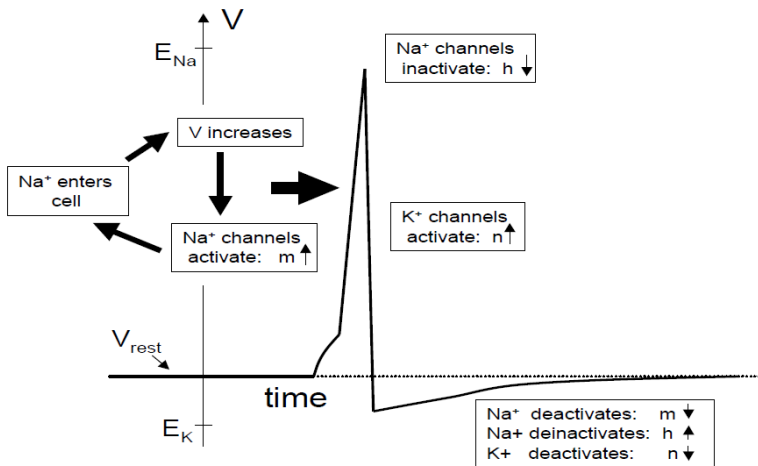
$$\frac{dh}{dt} = \alpha_h(V_m)(1 - h) - \beta_h(V_m)h$$

$n$ ,  $m$  are activation variables

$h$  is an inactivation variable

They also wrote the action potential propagation equation

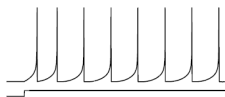
# The action potential



## Neurons behaviours

This model and variations thereof have been immensely successful in predicting neurons behaviours (**Izhikevitch (2005)**)

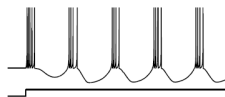
(i) Tonic Spiking



(ii) Phasic Spiking



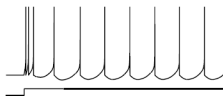
(iii) tonic bursting



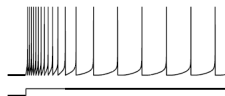
(iv) phasic bursting



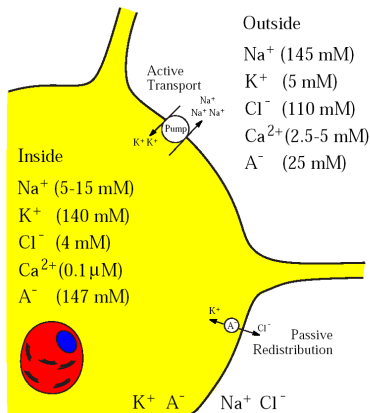
(v) Mixed mode



(vi) Spike freq. adaptation



# Today's view: ions and gates



## Equilibrium Potentials

$$\text{Na}^+ \quad 62 \log \frac{145}{5} = 90 \text{ mV}$$

$$62 \log \frac{145}{15} = 61 \text{ mV}$$

$$\text{K}^+ \quad 62 \log \frac{5}{140} = -90 \text{ mV}$$

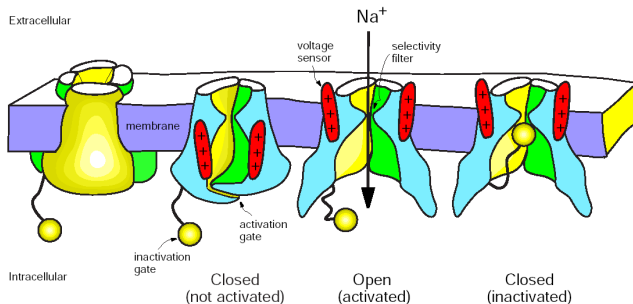
$$\text{Cl}^- \quad -62 \log \frac{110}{4} = -89 \text{ mV}$$

$$\text{Ca}^{2+} \quad 31 \log \frac{2.5}{10^{-4}} = 136 \text{ mV}$$

$$31 \log \frac{5}{10^{-4}} = 146 \text{ mV}$$

From Izhikevich 2005

# Ion channels



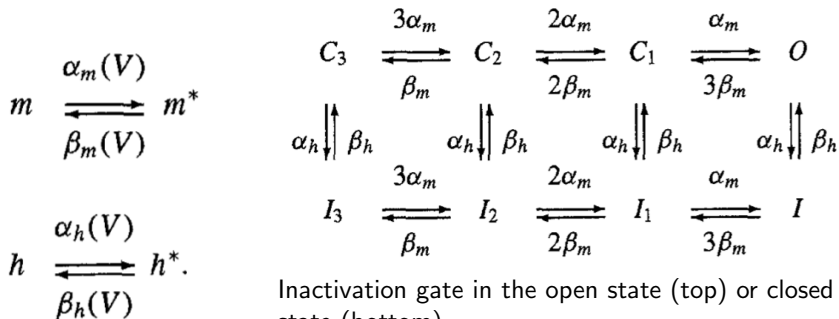
From [Izhikevich 2005](#)

A sodium channel is a molecule with 4 gates, 3 activation and 1 inactivation

The channel conductance is simply the product  $g_{\text{Na}} = \bar{g}_{\text{Na}} m^3 h$

## Ion channels

## Markov chain formalism



Inactivation gate in the open state (top) or closed state (bottom)

Three, two, one, or none of the activation gates closed (left to right)

From [A. Destexhe et al. \(1994\)](#)

## Propagation of the action potential along the axon

The theory of a cable consisting of a resistive core rounded by a membrane offering capacitance and variable resistance to currents is of central importance in neuron physiology

In a series of papers **J. Evans** studied the class of equations:

$$\begin{aligned}\frac{\partial V}{\partial t} &= \frac{\partial^2 V}{\partial x^2} + g^0(V, W^1, \dots, W^n) \\ \frac{\partial W^i}{\partial t} &= g^i(V, W^1, \dots, W^n) \quad i = 1, \dots, n\end{aligned}$$

$W^i(x, t)$  are the conductances of various ion channels

Diffusion equation with a nonlinear source term



## Propagation of the action potential along the axon

The existence, uniqueness and continuous dependence on initial values of the solutions **J. Evans and N. Shenk 1970**

Stability of the resting state and travelling pulse solutions were proved in three papers published in 1972 and one in 1975, all in the Indiana University Mathematics Journal. **J. Evans 1972,1975**

## Impact

Physiology: Huge

Mathematics: Important in dynamic system analysis

J. Guckenheimer and Ricardo A. Oliva, *SIAM J. Applied Dynamical Systems*, 2002

J. Guckenheimer and I.S. Labouriau, *Bulletin of Mathematical Biology*, 1993

Type "bifurcations Hodgkin-Huxley" in Google Scholar

## A bit of history

Ion channels are stochastic

How much does channel noise matter?

It took long to come up with a mathematically precise analysis of the Hodgkin-Huxley model when considered at several scales

T. Austin (2008) building on work by T.G. Kurtz (1971, 1981), S.N. Ethier and T.G. Kurtz (1986), M.H.A. Davis (1984), followed by M. Thieullen and collaborators K. Pakdaman et al. (2010), A. Genadot and M. Thieullen (2012), M. Riedler et al. (2012)

## Austin's work

Linear axon  $I = [-1, 1]$

Axon state:  $v : I \rightarrow \mathbb{R}$  Lipschitz and in  $H_0^1(I)$

All ion channels are identical

Finite set  $E$  of channel states

Channel driving/reversal potential  $v_\xi, \xi \in E$

Channel at position  $x$  goes  $\xi \rightarrow \zeta$  at rate  $\alpha_{\xi,\zeta}$

## Austin's work

$N$  stochastic models

$[2N]$  – 2 channels at positions  $\frac{1}{N} (\mathbb{Z} \cap N I^0)$ ,  $I^o = (-1, 1)$

Ion channel conductance  $\frac{1}{N} c_\xi$

$\Xi_t^{(N)} \in E^{\mathbb{Z} \cap N I^0}$  state of all channels at time  $t$

$p_\xi(x)$  proportion of those channels in state  $\xi$  in a neighbourhood of  $x$

# The deterministic Hodgkin-Huxley equations

## Regularity

A continuous function  $\mathbf{v} : [0, T] \rightarrow H_0^1(I)$  and a family  $(p_\xi)_{\xi \in E}$  of continuous functions  $\mathbf{p}_\xi : [0, T] \rightarrow \text{Lip}(I, [0, 1])$  is a solution of the deterministic Hodgkin-Huxley equation if

$$\begin{aligned} \frac{d}{dt} \mathbf{v} &\in L^2_{H^{-1}(I)}[0, T], \\ \frac{d}{dt} \mathbf{p}_\xi &\in L^\infty_{C(I)}[0, T] \quad \forall \xi \in E \end{aligned}$$

# The deterministic Hodgkin-Huxley equations

## The equations

$$\frac{d}{dt} \mathbf{v}_t = \Delta \mathbf{v}_t + \sum_{\xi \in E} c_{\xi} \mathbf{p}_{\xi,t} (v_{\xi} - \mathbf{v}_t) \quad \forall t \in [0, T]$$

$$\frac{d}{dt} \mathbf{p}_{\xi,t} = \sum_{\zeta \in E \setminus \{\xi\}} \alpha_{\zeta,\xi}(\mathbf{v}_t) \mathbf{p}_{\zeta,t} - \alpha_{\xi,\zeta}(\mathbf{v}_t) \mathbf{p}_{\xi,t} \quad \forall \xi \in E, \forall t \in [0, T]$$

with some initial and boundary conditions:

$$\mathbf{v}_0 = v_0 \quad \mathbf{p}_{\xi,0} = p_{\xi,0} \quad \mathbf{v}_t(\pm 1) = 0 \quad \forall t \in [0, T]$$

## The stochastic Hodgkin-Huxley equations

Given  $(\Omega, \mathcal{F}, (\mathcal{F}_t)_{0 \leq t \leq T}, \mathbb{P})$ , a càdlàg adapted process  $(\mathbf{V}_t, \Xi_t)$  such that each sample path is such that  $\mathbf{V}$  is a continuous mapping  $[0, T] \rightarrow H_0^1(I)$  and  $\Xi_t \in E^{\mathbb{Z} \cap N} I^0$  for all  $t \in [0, T]$  is said to be a solution of the stochastic Hodgkin-Huxley equations with initial conditions  $v_0, \Xi_0$  if the following conditions are satisfied:



## The stochastic Hodgkin-Huxley equations

Regularity: The map  $t \rightarrow \frac{d}{dt} \mathbf{V}$  is in  $L^2_{H^{-1}(I)}[0, T] \mathbb{P}$  a.s.

PDE:

$$\frac{d}{dt} \mathbf{V}_t = \Delta \mathbf{V}_t + \frac{1}{N} \sum_{i \in \mathbb{Z} \cap NI^0} c_{\Xi_t(i)} (v_{\Xi_t(i)} - V_t(i/N)) \delta_{i/N}$$

$$\forall t \in [0, T] \quad \mathbb{P} \text{ a.s.}$$

Jump:

$$\mathbb{P}(\Xi_{t+h}(i) = \zeta \mid \Xi_t(i) = \xi) =$$

$$\alpha_{\xi, \zeta} (\mathbf{V}_t(i/N)) h + o_{h \downarrow 0}(h) \quad \forall t \in [0, T], h \in (0, T-t]$$

with some conditional independence condition to first order in  $h$  on  $\mathcal{F}_t$  of the coordinate processes

$$(\Xi_{t+h}(i))_{h>0}$$

# The stochastic Hodgkin-Huxley equations

## Initial conditions

$$\mathbf{V}_0 = v_0, \quad \Xi_0 = \Xi_0, \quad \mathbf{V}_t(\pm 1) = 0 \quad \forall t \in [0, T]$$

## Convergence result

Let  $\varepsilon > 0$  and suppose given initial conditions  $v_0, p_{\xi,0}$ . Then for any  $N$  sufficiently large, there exists an initial condition  $\Xi_0$  for the stochastic Hodgkin-Huxley equations so that there is some "high-probability"  $\Omega_1 \subseteq \Omega$  with  $\mathbb{P}(\Omega \setminus \Omega_1) < \varepsilon$  and such that

$$\sup_{0 \leq t \leq T} \|\mathbf{V}_t - \mathbf{v}_t\|_{H_0^1(I)} < \varepsilon$$

$$\sup_{0 \leq t \leq T} \|\mathbf{C}_{\xi,N}(\Xi_t^{(N)}) - \mathbf{p}_{\xi,t}\|_{H^{-1}(I)} < \varepsilon,$$

on  $\Omega_1$ .

$\mathbf{C}_{\xi,N}(\Xi)$  is the empirical measure for  $\xi$ :

$$\mathbf{C}_{\xi,N}(\Xi) = \frac{1}{N} \sum_{i \in \mathbb{Z} \cap NI^0, \Xi = \xi} \delta_{i/N}$$

## Convergence result

### In words

As  $N \rightarrow \infty$  the stochastic ion-channel model of the axon gives a time-evolution of the potential difference along the axon that converges to that given by the deterministic model, uniformly up to a given finite time horizon, in probability.

## Convergence result

### Scales

Three scales: individual ions, ion channels, whole axon

Stochastic model is faithful at the second and third scales

It uses a simplified behaviour at the smallest (a continuum charge distribution evolving in time according to a parabolic PDE): it "averages away" the random behaviour at the smallest scale

The difference between the stochastic and deterministic models is one of resolution: although neither model can "see" the individual ions, the stochastic model can see single channels, whereas even these are beyond the deterministic model.

## Extension of the work

This work has been extended by Pakdaman, Thieullen and Wainrib, [Pakdaman et al. \(2010\)](#), in the space clamped case and by Riedler, Thieullen and Wainrib, [Riedler et al. \(2012\)](#), in the space extended case to describe the fluctuations of the stochastic model around the limit.

Two important innovations: use of Markov jump processes coupled to an ODE or PDE, piecewise deterministic Markov processes (PDMPs) [M. Davis \(1984\)](#), [D. Vermes \(1985\)](#).

Proof of functional central limit theorems.

## Impact

**Physiology:** Significant, e.g. importance of fluctuations/noise on neural encoding

Introduction of a rigorous treatment of "noise" in neuroscience, e.g.:

the work of Stannat on stochastic nerve equations **Stannat 2013, Sauer & Stannat 2015**

**Mathematics:** Important, e.g. new theorems on PDMPs.

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**Ephaptic interactions**

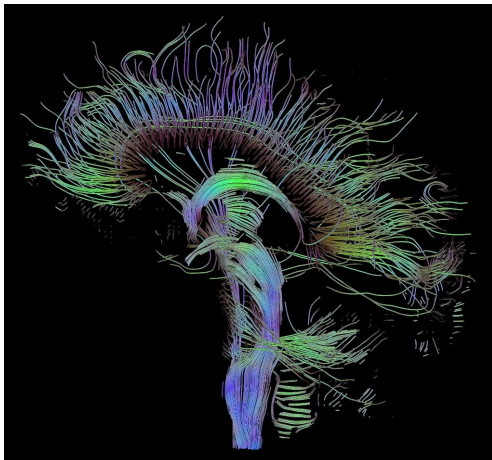
Glial cells

Conclusion



## Connectome

Diffusion Tensor Imaging (DTI) allows to recover bundles of myelinated axons in the brain at a resolution of about 1mm  
Roughly 1000 axons in a bundle



## Cross-talk between axons

Ephaptic interaction between axons of the white matter tracts

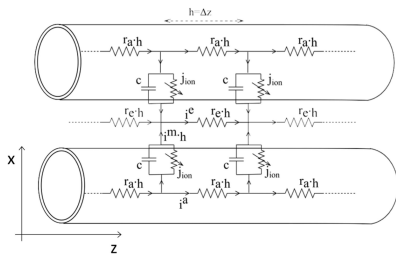
Signals exchanged between different brain regions may not be faithfully transmitted along the white matter tracts through axons that can be modelled as passive electric cables

Nonsynaptic electrical interaction between adjacent nerve fibers  
(Katz & Schmitt, 1940)

## Two adjacent axons

Work of Hiba Sheheitli and Viktor K. Jirsa

J. Sheheitly and V.K. Jirsa (2020)



$$\gamma \frac{\partial^2 v_1^m}{\partial z^2} - \alpha \frac{\partial^2 v_2^m}{\partial z^2} = c \frac{\partial v_1^m}{\partial t} + j_{ion,1} - I_1,$$

$$\gamma \frac{\partial^2 v_2^m}{\partial z^2} - \alpha \frac{\partial^2 v_1^m}{\partial z^2} = c \frac{\partial v_2^m}{\partial t} + j_{ion,2} - I_2,$$

$$\text{where } \gamma = \left( \frac{r_a + r_e}{2r_a r_e + r_a^2} \right), \quad \alpha = \left( \frac{r_e}{2r_a r_e + r_a^2} \right)$$

$j_{ion,i}$ ,  $i = 1, 2$  is given by

$$j_{ion,i} = -g^i (v_i^m - (v_i^m)^3/3 - w_i) := f(v_i^m, w_i^m)$$

FitzHugh Nagumo model, reduction of the Hodgkin-Huxley model

$r_e = 0$ , the two axons are uncoupled

## The resulting equations for $N$ axons

$$4(R+1) \sum_{s=1}^N \alpha_{ps} \frac{\partial^2 v_s}{\partial z^2} = \frac{\partial v_p}{\partial t} + f(v_p, w_p) - I_p,$$

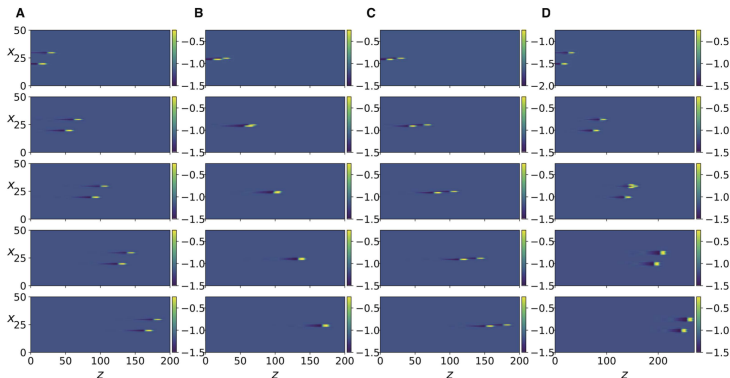
$$\frac{\partial w_p}{\partial t} = \varepsilon (v_p + a - bw_p).$$

for  $p = 1, \dots, N$

$v_s$  is the membrane potential of the  $s$ th neuron

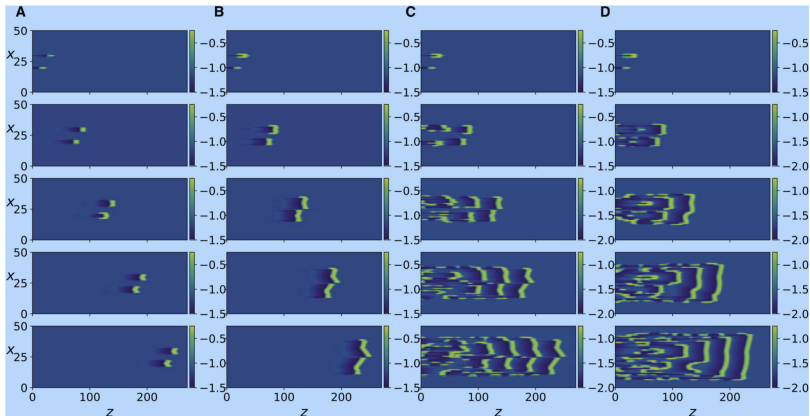
$R = r_a/r_e$ .

## Results of numerical simulations



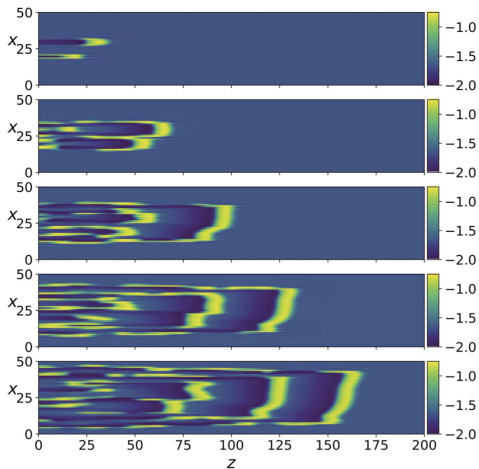
**Figure 3.** Numerical simulation of Equation 13. The color bar indicates the value of  $v$ , the  $x$  variable indicates the axon number. Each column corresponds to a simulation with a specific value of the parameter; snapshots show progress of time from top to bottom. (A)  $R = 0.8$ , axons number 30 and 20 are stimulated at  $t = 0$  and  $t = 10$ , respectively, and the panel rows from top to bottom correspond to  $t = 500, 1100, 1700, 2300, 2900$ . (B) Same as in A but with axons number 25 and 24 stimulated. (C) Same as in B but with stimulation at  $t = 0$  and  $t = 11$ . (D) same as in A but with  $R = 0.4$ , and panels show  $t = 500, 1400, 2300, 3200, 4100$ .

## Results of numerical simulations



**Figure 4.** (A, B) same as in Figure 3A but with  $R = 0.33$  and  $R = 0.191$ , respectively. (C, D) same as in Figure 3D but with  $R = 0.19$  and  $R = 0.15$ , respectively.

## Results of numerical simulations



Numerical simulation for  $R = 0.05$ . The panels from top to bottom correspond to  $t = 500, 1100, 1700, 2300, 2900$ .

## What is next?

More physiological checking is required

More modelling is to be done (role of myeline, nodes of Ranvier, ion channels, noise)

Everything remains to be done from the mathematical point of view



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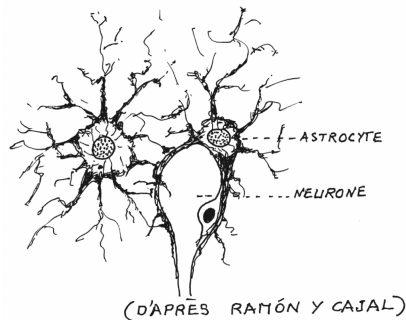
## Forgotten glial cells

85 billion of neurons in the human brain

More than 100 billion of glial cells (between 1.2 and 1.6 times more, [Herculano-Houzel 2009](#))

Three categories (review in [Barres 2008](#)):

1. microglia
2. oligodendrocytes: myelinate
3. astrocytes



[Y. Agid and P. Magistretti \(2018\)](#)

## Glial- or neuronal-man?

Glutamate evokes calcium concentration rises in astrocytes  
(Cornell-Bell et al. 1990)

$\text{Ca}^{2+}$  signalling can propagate along astrocytic processes and even between glial cells as waves

Glial  $\text{Ca}^{2+}$  waves might constitute an extraneuronal signalling system in the CNS

Increases in cytosolic (fluid that comprises cytoplasm)  $\text{Ca}^{2+}$  concentration of astrocytes could regulate the release of neuroactive molecules

All this led to the idea that astrocytes are powerful regulators of neuronal spiking, synaptic plasticity, and cerebral blood flow

## Glial- or neuronal-man?

Glial cells are electrically passive

$\text{Ca}^{2+}$  could be an effective code  
for stimulus

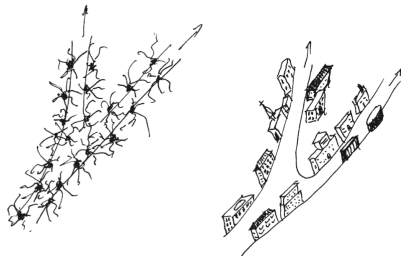
representation

interpretation

transformation

transmission

$\text{Ca}^{2+}$  signalling is stochastic



Y. Agid and P. Magistretti  
(2018)

## The role(s) of glial cells

Source of energy for neurons

Participate in the communication  
between all neural cells

Control synapse formation and  
creation of new neurons

Building up our behaviours

Y. Agid and P. Magistretti 2018



**Yves Agid  
Pierre Magistretti**

## L'Homme glial

**Une révolution dans  
les sciences du cerveau**



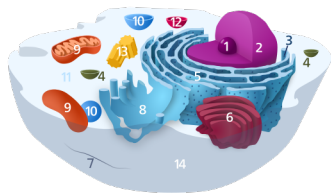
En accord avec le programme national de lecture pour les lycéens et les étudiants en médecine - 1992-2019 & 2020

## A (very) simple model (Stimberg , Goodman, Brette and De Pittà 2019)

Intracellular  $\text{Ca}^{2+}$  concentration is unanimously regarded as a prominent readout signal of astrocyte activity

$\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release (CICR) from the astrocyte's endoplasmic reticulum (ER) appears to be one of the main mechanisms

Astrocytic CICR is triggered by the intracellular second messenger inositol 1,4,5-trisphosphate (IP3)



5. Rough endoplasmic reticulum

8. Smooth endoplasmic reticulum

11. Cytosol (fluid that contains organelles; with which, comprises cytoplasm)

## A (very) simple model (Stimberg , Goodman, Brette and De Pittà 2019)

Two ordinary differential equations in the Hodgkin–Huxley form (Li and Rinzel 1994)

The first equation is a mass balance for  $\text{Ca}^{2+}$  ( $C$ ) in terms of three fluxes  $J_r$ ,  $J_l$ ,  $J_p$   
 CICR ( $J_r$ ),  $\text{Ca}^{2+}$  leak from the ER ( $J_l$ ), and  $\text{Ca}^{2+}$  uptake from the cytosol back to the ER by  $\text{Ca}^{2+}$ /ATPase pumps ( $J_p$ )

$$\frac{dC}{dt} = J_r + J_l - J_p$$

The second equation is for the gating variable ( $h$ ) of de-inactivation of the channels that are responsible for CICR

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h}$$

$J_r$ ,  $J_l$  and  $J_p$  are nonlinear functions of  $C$  and the IP3  $I$

## A (very) simple model (Stimberg , Goodman, Brette and De Pittà 2019)

The IP3  $I$  is governed by another mass balance equation (De Pittà et al. 2009)

$$\frac{dI}{dt} = J_{\beta}(\Gamma_A) + J_{\delta} - J_{3K} - J_{5P} + J_{ex}$$

$J_{\delta}$ ,  $J_{3K}$ ,  $J_{5P}$  and  $J_{ex}$  are nonlinear functions of  $C$  and  $I$ .

$\Gamma_A$  is the activated fraction of astrocytic metabotropic receptors which starts phospholipase  $C\beta$ -mediated IP3 production



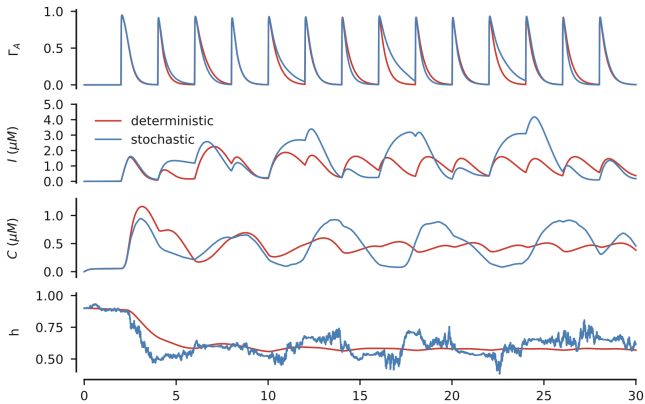
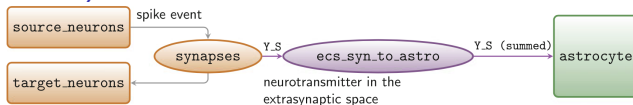
## A (very) simple model (Stimberg , Goodman, Brette and De Pittà 2019)

The fraction of activated astrocyte receptors  $\Gamma_A$  depends on the neurotransmitter concentration in the periastrcytic space  $Y_S$

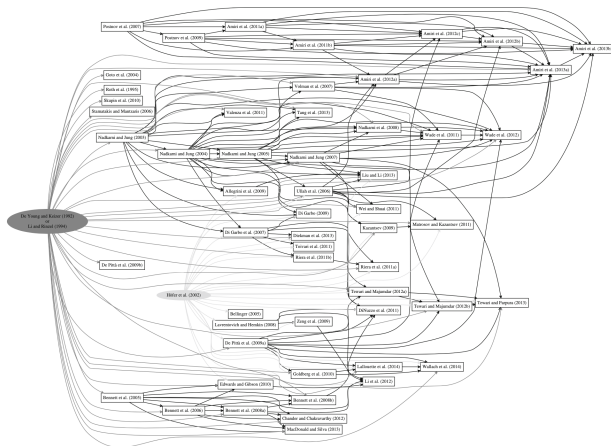
$$\frac{d\Gamma_A}{dt} = O_N Y_S (1 - \Gamma_A) - \Omega_N (1 - \zeta \mathcal{H}_1(C, K_{KC})) \Gamma_A$$

Dynamics of the astrocyte's state variables  $\Gamma_A$ ,  $l$ ,  $C$ ,  $h$  are governed by ODEs akin to neuronal state variables, although on a longer time scale

# A (very) simple model (Stimberg , Goodman, Brette and De Pittà 2019)



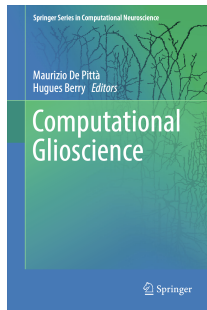
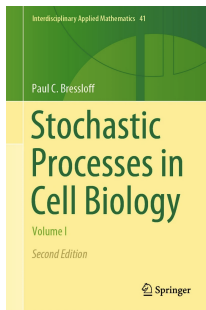
## Which models?



**Fig. 16.2** Evolution of astrocyte and astrocyte–neuron models from 1995 to 2014. An arrow starts from the model which was used as a reference for the model pointed by the arrowhead. Dark gray lines represent the models that were based on the models by De Young and Keizer (1992) and Li and Rinzel (1994). Light gray lines represent the models that were based on the model by Höfer et al. (2002)

## Where to go?

Read the books **P. Bressloff (2014)** and **M. De Pittà, H. Berry (2019)** and



Do the maths  
Put things into networks

Introduction

Hodgkin Huxley

Deriving the H-H model ab initio

Ephaptic interactions

Glial cells

Conclusion

## Topics I haven't had time to cover

- ▶ Plasticity, Learning (astrocytes seem to be important there)
- ▶ Models of cortical areas: neural fields (a lot of geometry)
- ▶ Mean field models of populations of neurons

## Miscellany

Unlike in, e.g., Physics, modelling is often unescapable for a mathematician in neuroscience: you usually can't jump on an equation and go away to study it: you HAVE to learn the biology

Interacting with experimentalists is important but very difficult because of the cultural gap (unlike in Physics)

Interacting with computational neuroscientists is also important but also very difficult because of their blind trust in computer simulations from which they acquire a "reasonable certainty"