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Institut Thématique Multi-Organismes
Technologies pour la santé

Traitement du signal & modélisation pour les maladies neurologiques

Fabrice Wendling

INSERM U1099 - LTSI- Université de Rennes 1

Equipe « Systèmes épileptogènes: signaux et modèles »

http://perso.univ-rennes1.fr/fabrice.wendling/

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Modélisation bio-inspirée pour les maladies neurologiques: application à l'épilepsie

Fabrice Wendling

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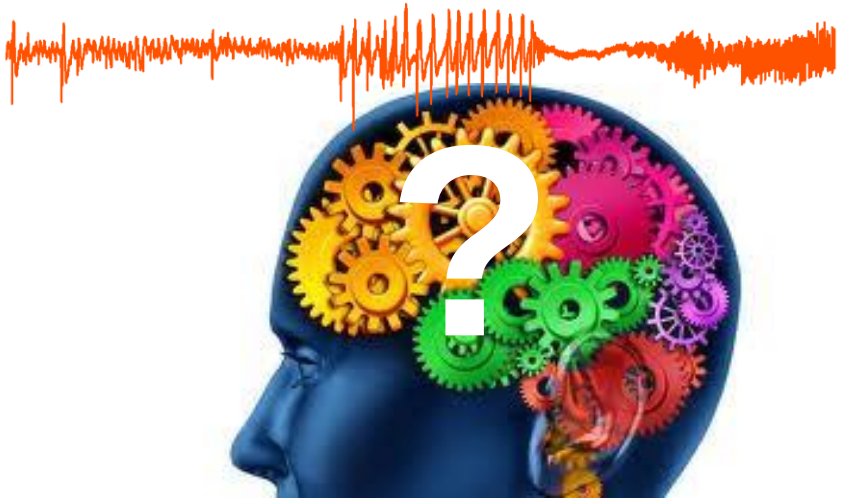
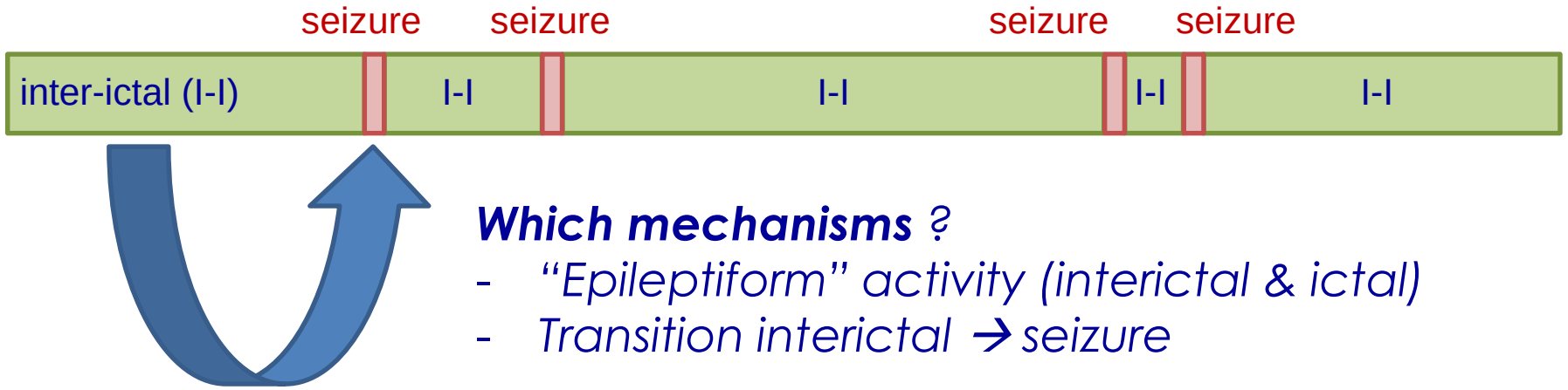
« Epilepsy is a complex dynamical disease » F. Lopes da Silva

- Epileptogenic Zone: **large-scale network** organization (extended, distributed)



- **Complexity of involved neuronal systems** (« networks of networks »)
  - . **Non linear** mechanisms
  - . **Spatial scales** : sub-cellular, cellular, networks, brain area
  - . **plasticity** (short/long term), **homeostatic** control

- Pathophysiological mechanisms at **different temporal scales**
  - . **Epileptogenesis**: long-time process (days, years)
  - . **Ictogenesis**: short-time process (seconds, minutes)



Which mechanisms *?*

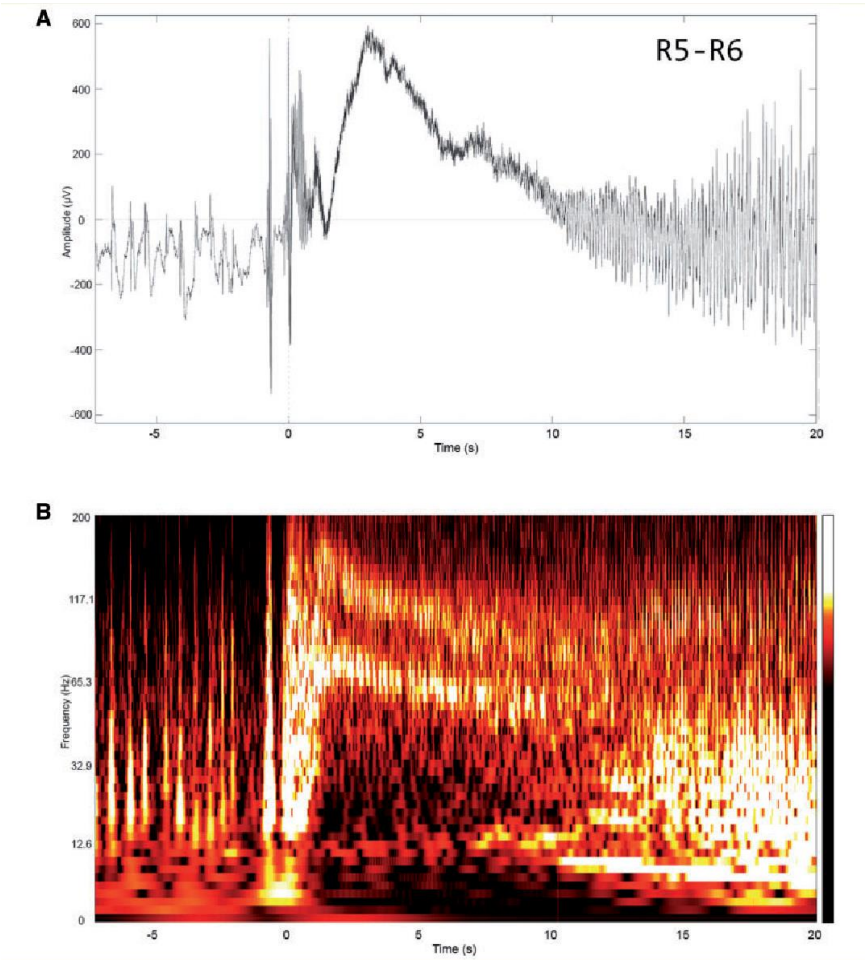
- *"Epileptiform" activity (interictal & ictal)*
- *Transition interictal → seizure*

Inter-ictal to ictal transition

Human (TLE)

Mouse (kainate)

Guinea pig (bic.)



- **Pre-ictal spikes**
- **Suppression of low-frequency oscillations**
- **Occurrence of a fast discharge**

« Epileptogenicity index »: ***Bartolomei, Chauvel, Wendling, Brain 2008***
« Fingerprint »: ***Grinenko, …, Chauvel, Brain 2017***

Wendling et al., EJN, 2012

Epileptic activity: many alterations at multiple levels …

- **Pyramidal cells**: **excitability ++** due to **potassium & chloride regulation** (KCC2--, NKCC1++), synchronization ++ due to increased collateral GLU excitation
- **Interneurones**: « dendritic-projecting » vs. « somatic-projecting », role of INs at seizure onset, INs ➔➔ HFOs
- **GLU synaptic transmission** : crucial role of AMPA et NMDA receptors, plasticity of excitatory synapses
- **GABA synaptic transmission** : « dis-inhibition », depolarizing GABA (GABA ➔ GABAa receptors controlling [Cl-]i ➔ Cl- reversal potential ++)
- **Extracellular space** : [K+]o increase (multiple excitatory effects), ephaptic interactions (synchronization++), astrocytes (GLU release/uptake)
- And also: extrasynaptic receptor activation / potentiation; gap junctions

Not mutually exclusive, can act synergistically …

Neurophysiology-inspired computational models can help!

RECORDING TECHNIQUE

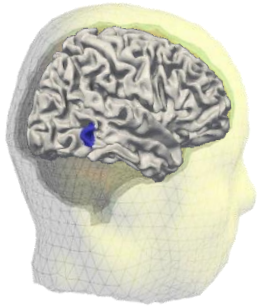
MODELS

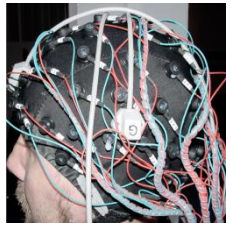
SIMULATED SIGNALS

REAL

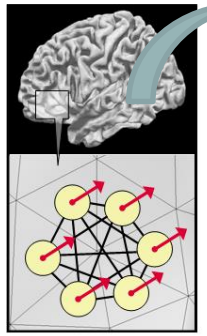
meso- to macroscopic

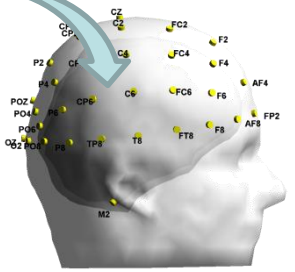
BRAIN

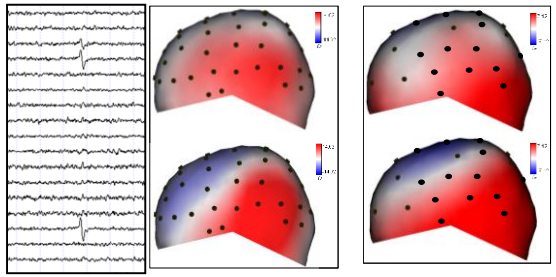




1 cm

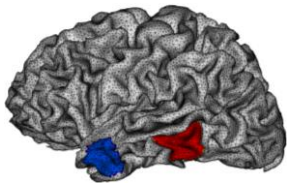


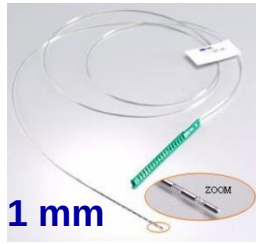




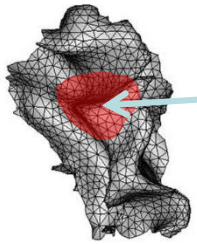
EEG

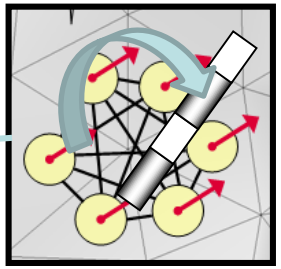
CORTICAL REGION



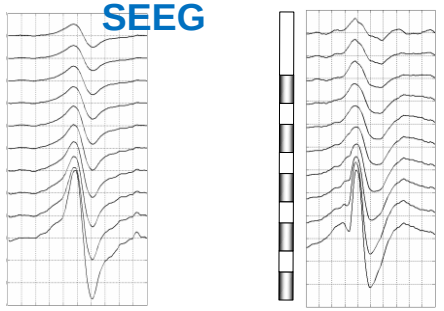


1 mm



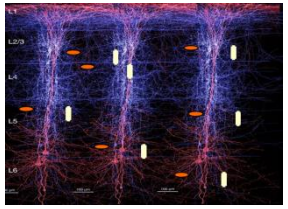


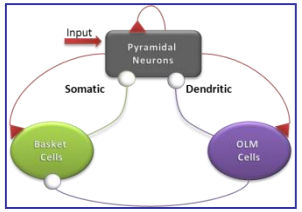
SEEG



NEURONAL POPULATION

100 µm

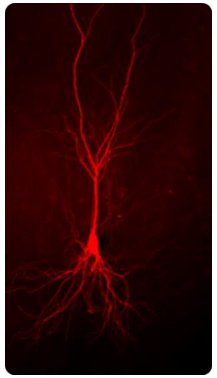




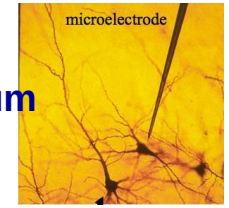
LFP/SEEG

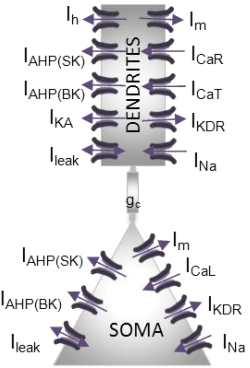
microscopic

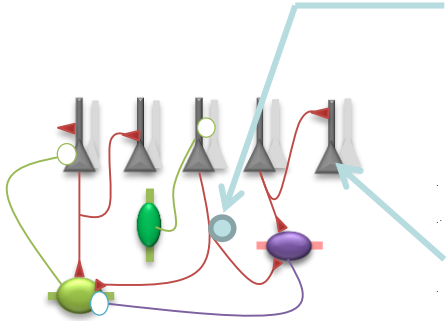
NEURONS & NETWORKS



10 µm

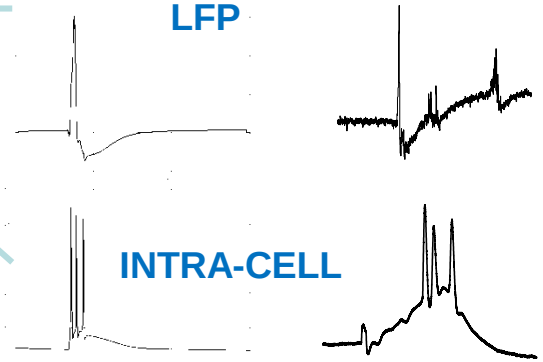






LFP

INTRA-CELL



Wendling, Benquet, Bartolomei, Jirsa, JNM, 2016

microscopic

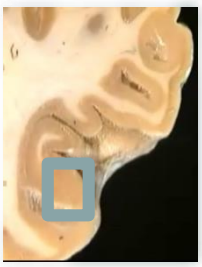
meso- to macroscopic

NEURONS & NETWORKS

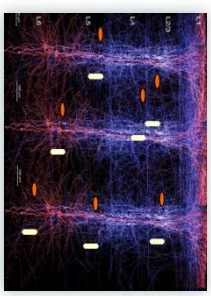
NEURONAL POPULATION

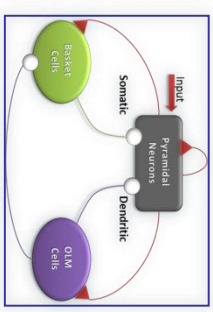
CORTICAL REGION

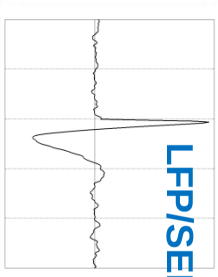
BRAIN



100 µm

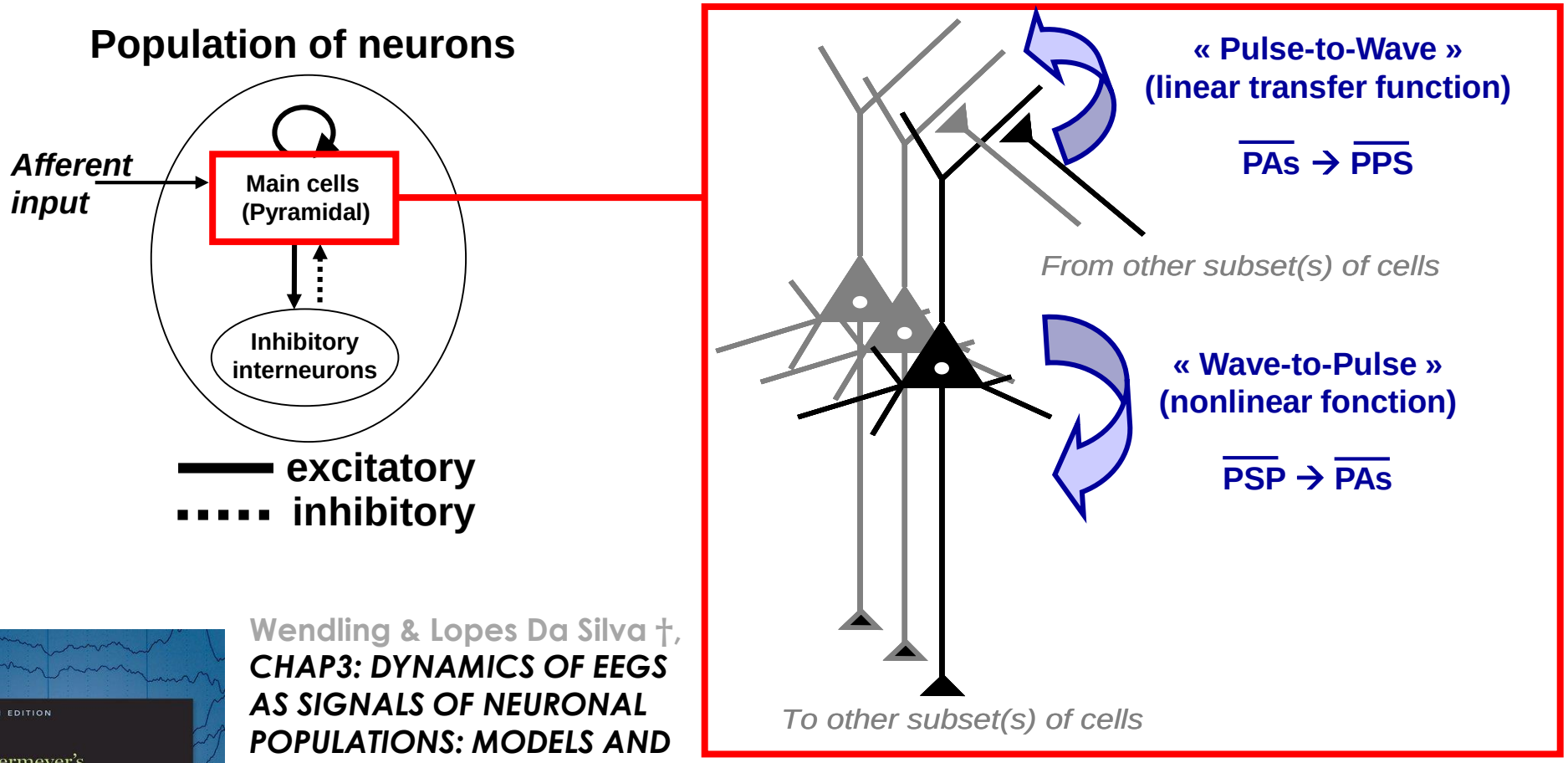


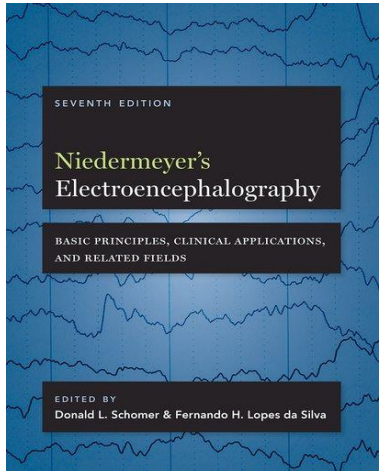




LFP/SEEG

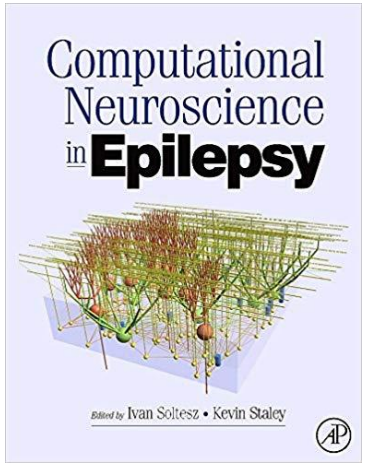
Neural Mass Modeling approach (macro-scale)





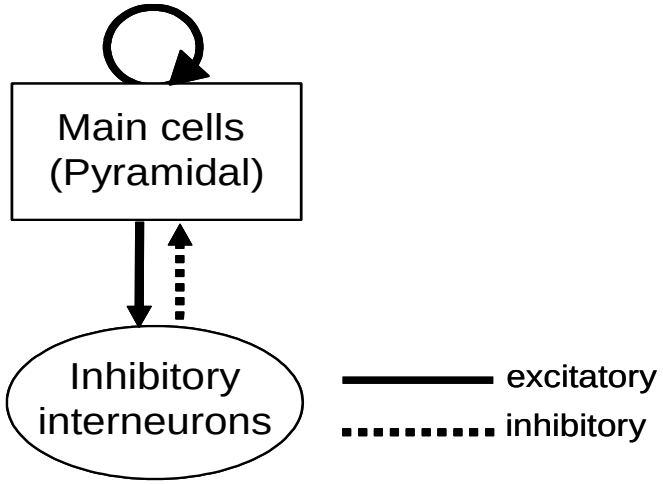
Wendling & Lopes Da Silva †, ***CHAP3: DYNAMICS OF EEGS AS SIGNALS OF NEURONAL POPULATIONS: MODELS AND THEORETICAL CONSIDERATIONS*** Electroencephalography, Basic Principles, Clinical Applications, and Related Fields
7th edition 2018

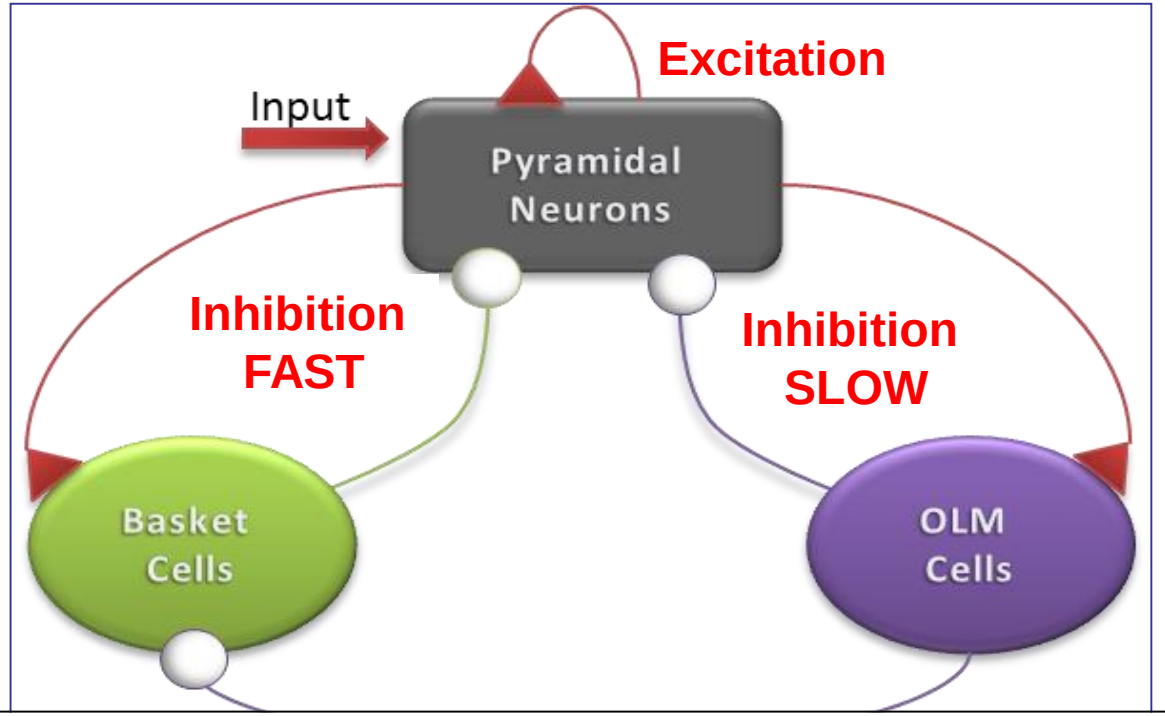
Wendling, Chauvel, ***"Transition to ictal activity in Temporal Lobe Epilepsy: insights from macroscopic models"***, in Computational Neuroscience in Epilepsy. I. Soltesz & K. Staley eds., 2008



From generic to specific NMMs

« Generic » model (1970) ⟹ « Structure-specific » model (e.g. Hipp.)





OM&P

M. Desroches et al. Slow-Fast Transitions to Seizure States in the Wendling-Chauvel Neural Mass Model

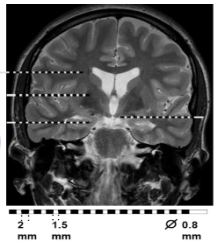
Slow-Fast Transitions to Seizure States in the Wendling-Chauvel Neural Mass Model

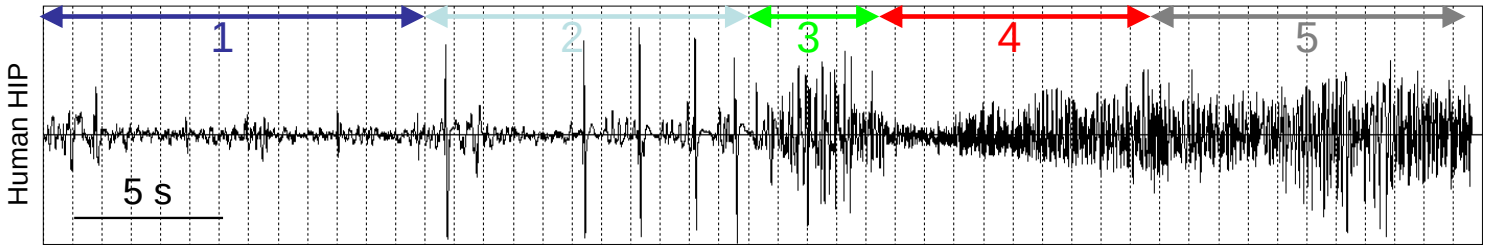
Mathieu Desroches[*1], *Olivier Faugeras*[2], *and Martin Krupa*[1]

2016

Incterictal to ictal transition in TLE: real versus simulated

Real
(human hip, SEEG)



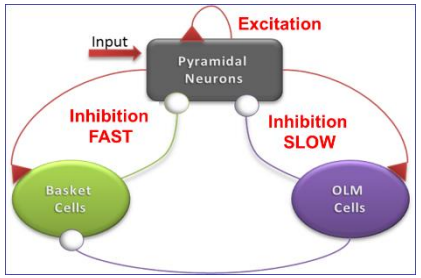


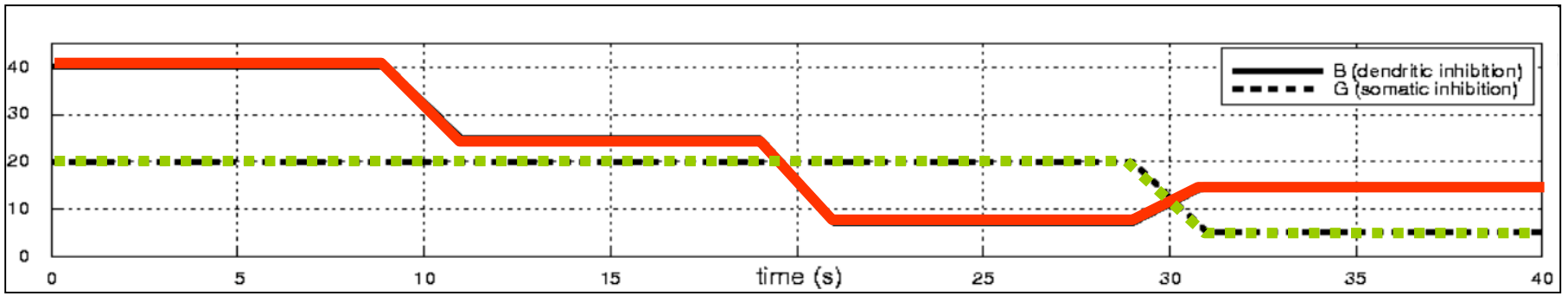
Adapted from: Suffczynski P, Wendling F, Bellanger J-J, Lopes Da Silva FH, Some insights into computational models of (Patho)physiological brain activity. Proceedings of the IEEE 94(4):784- 804, 2006

Simulated LFP for the identified scenario

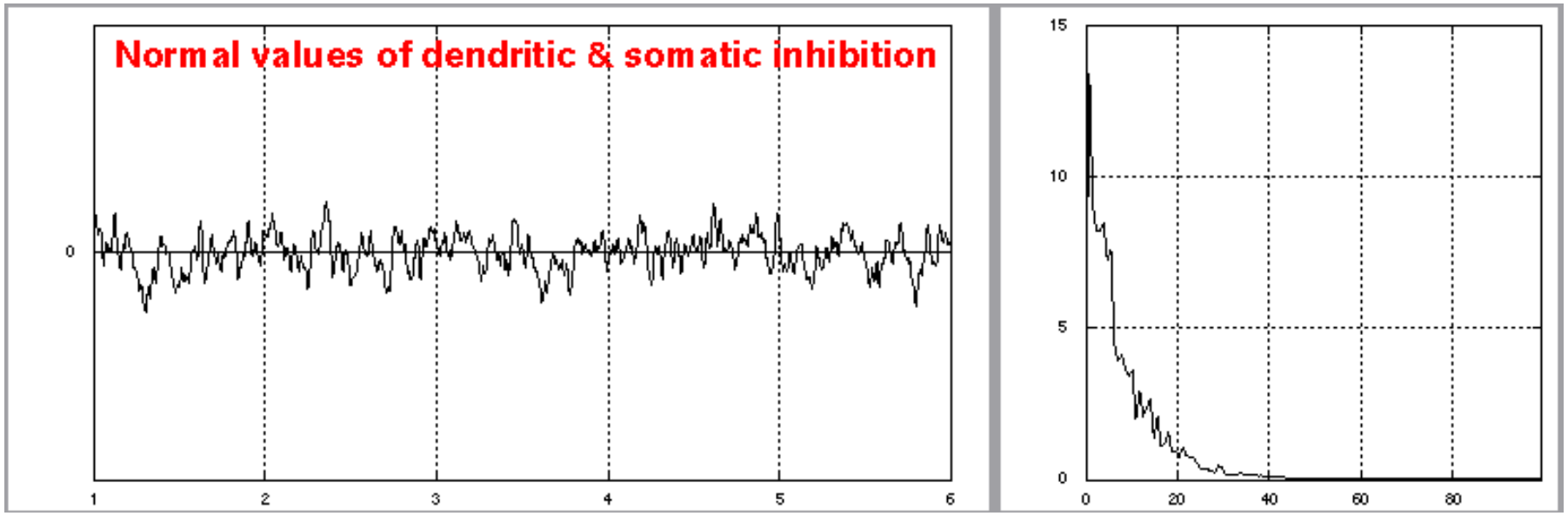
Slow dendritic inhibition

Fast somatic inhibition

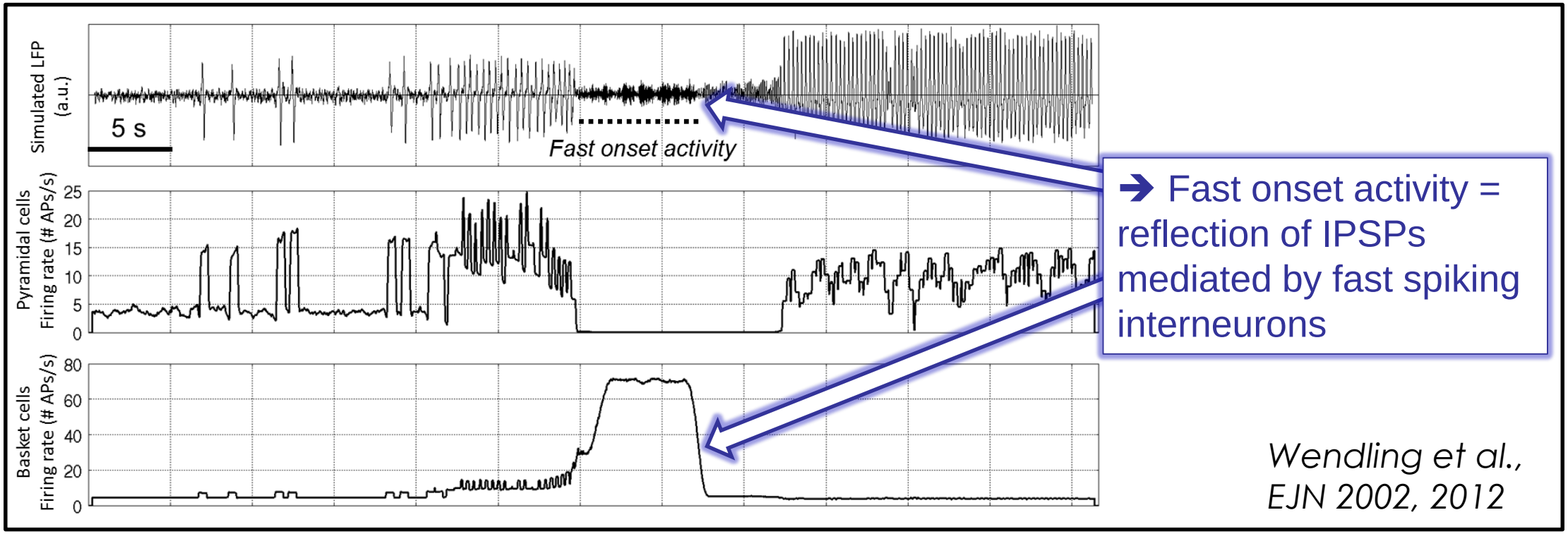




Simulated LFP



From prediction to validation



➔ Fast onset activity = reflection of IPSPs mediated by fast spiking interneurons

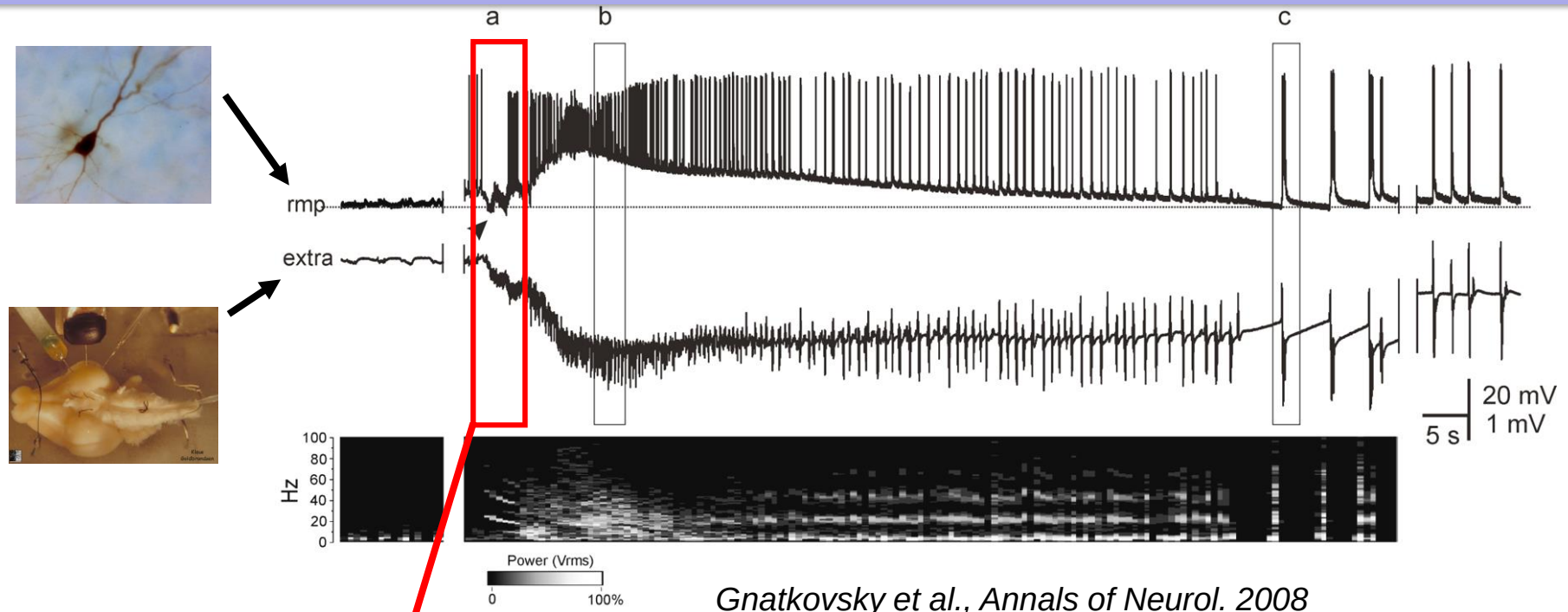
Wendling et al., EJN 2002, 2012

● **Experimental validation confirmed model prediction (M. de Curtis' team,** *Annals of Neurology 2008*)

Fast Activity at Seizure Onset Is Mediated by Inhibitory Circuits in the Entorhinal Cortex In Vitro

Vadym Gnatkovsky, MD, PhD, Laura Librizzi, PhD, Federica Trombin, PhD, and Marco de Curtis, MD

Experimental validation (in vitro)

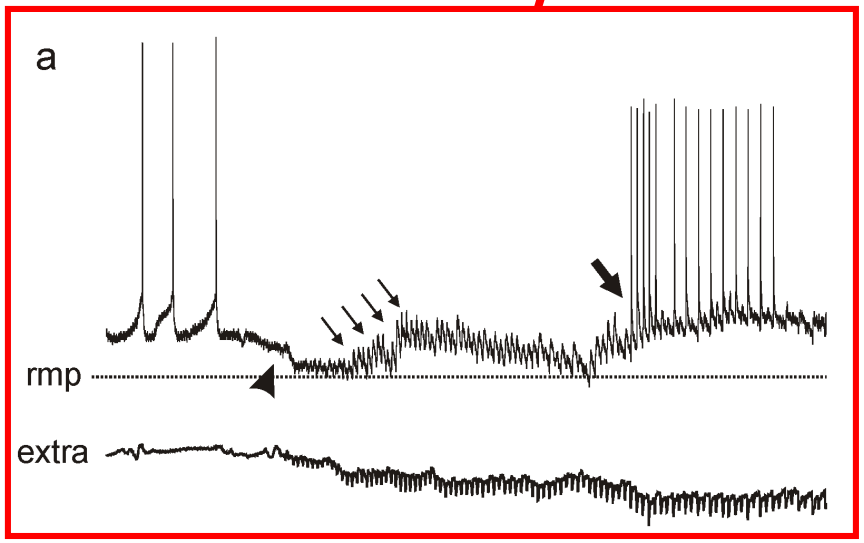


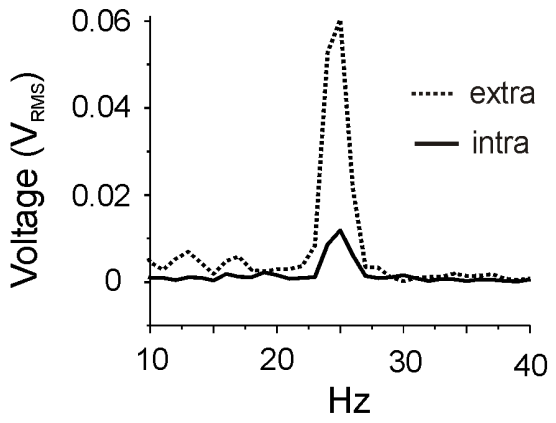
Intra-cellular

LFP

Time-frequency

Gnatkovsky et al., Annals of Neurol. 2008





Also shown in human epilepsy…

Human data (macro- and micro-electrode contacts)

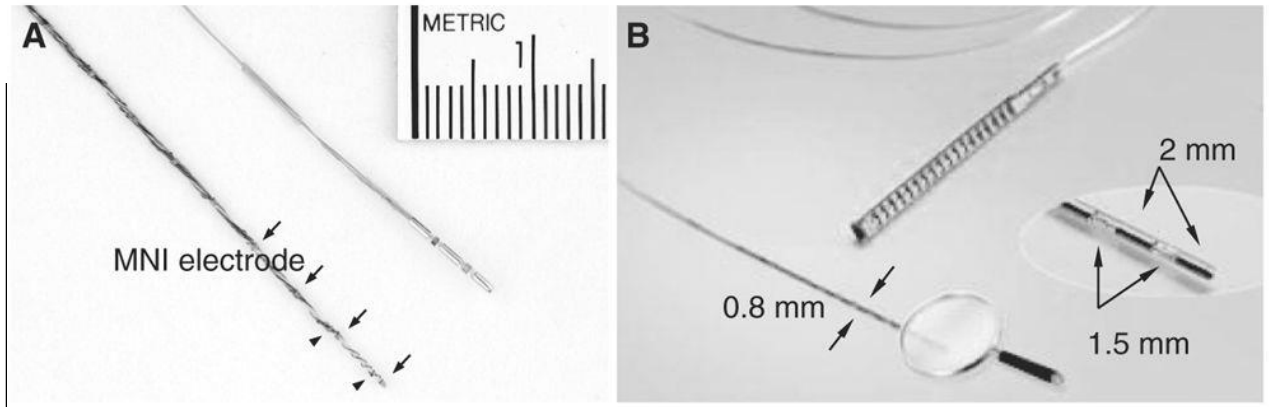
Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
AMERICAN NEUROLOGICAL ASSOCIATION

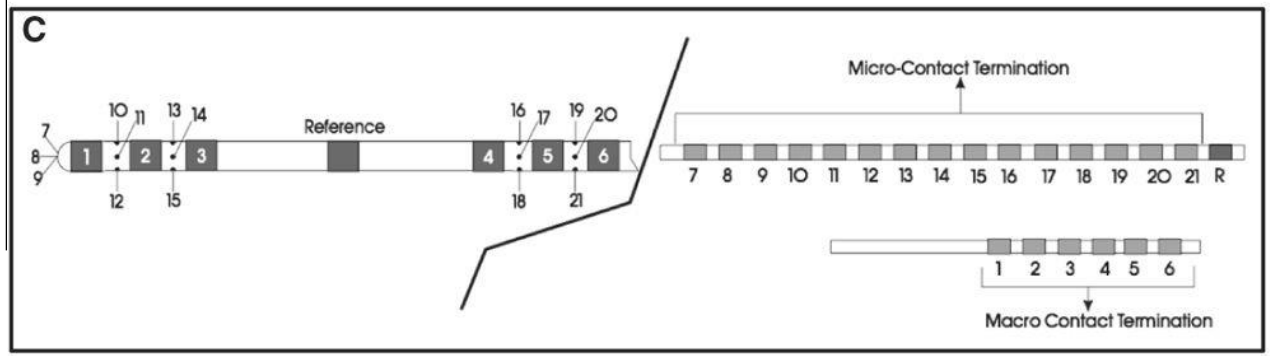
Oct. 2018

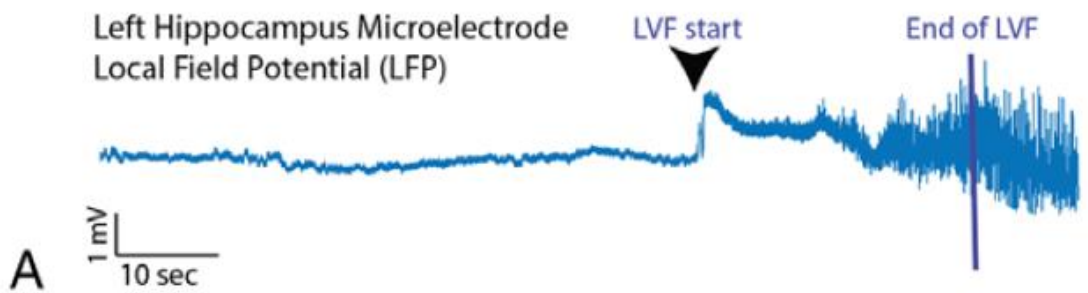
Research Article

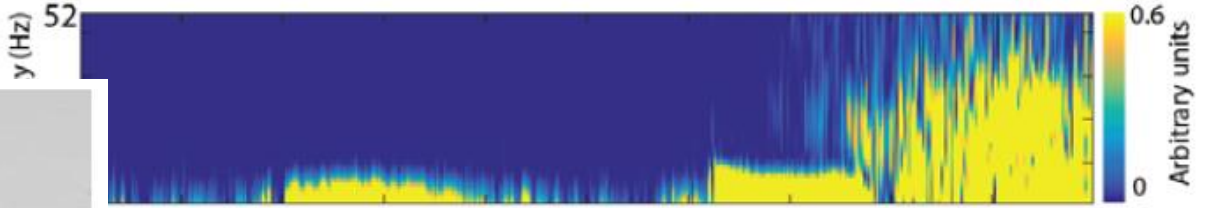
Low-voltage fast seizures in humans begin with increased interneuron firing

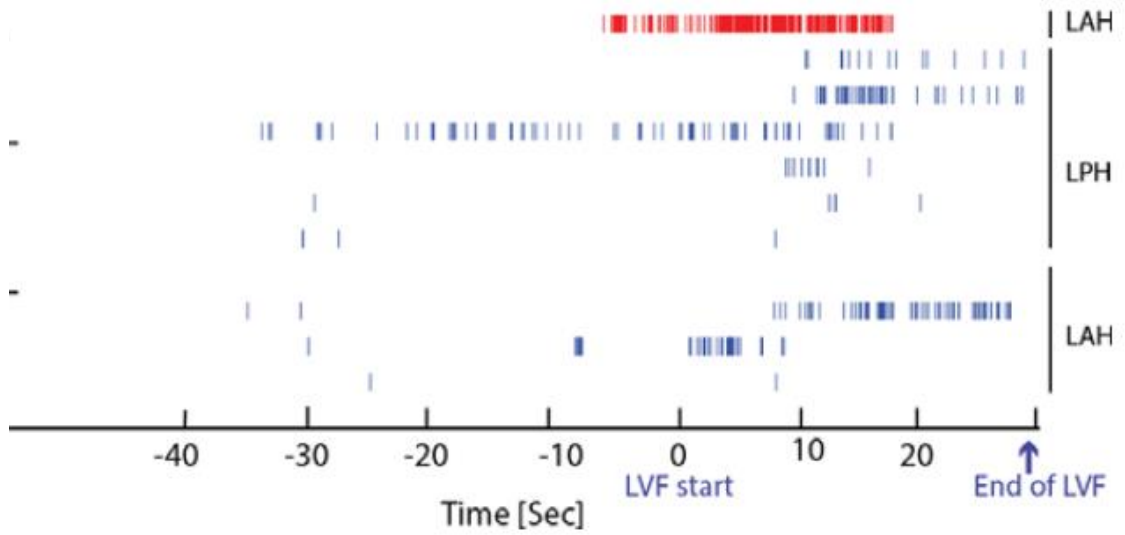
Bahareh Elahian PhD, Nathan E. Lado BA, Emily Mankin PhD, Sitaram Vangala MS, Amrit Misra MD, PhD, Karen Moxon PhD, Itzhak Fried MD, PhD, Ashwini Sharan MD, Mohammed Yeasin PhD, Richard Staba PhD, Anatol Bragin PhD, Massimo Avoli MD, PhD, Michael R. Sperling MD, Jerome Engel Jr MD, PhD, Shennan A. Weiss MD, PhD











From prediction to validation

- **2003**: **meso-scale model** can reproduce the transition from ongoing activity to seizure

- Model predictions about necessary conditions to generate **fast onset epileptic activity**:
    1. **Increased excitation**
    2. Decreased **slow inhibition**
    3. Preserved **fast inhibition**

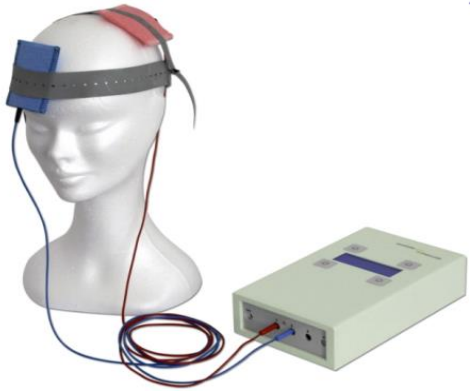
- **2008**: experimental evidence (isolated brain; guinea-pig)

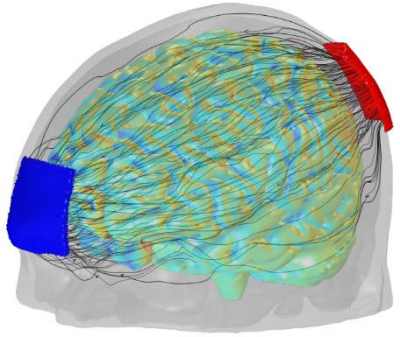
- **2018**: clinical evidence (depth-EEG recording; human)

➔ "Realistic" models provide relevant insights into pathophysiological mechanisms

Neural mass modeling for neurostimulation-based therapeutic approaches

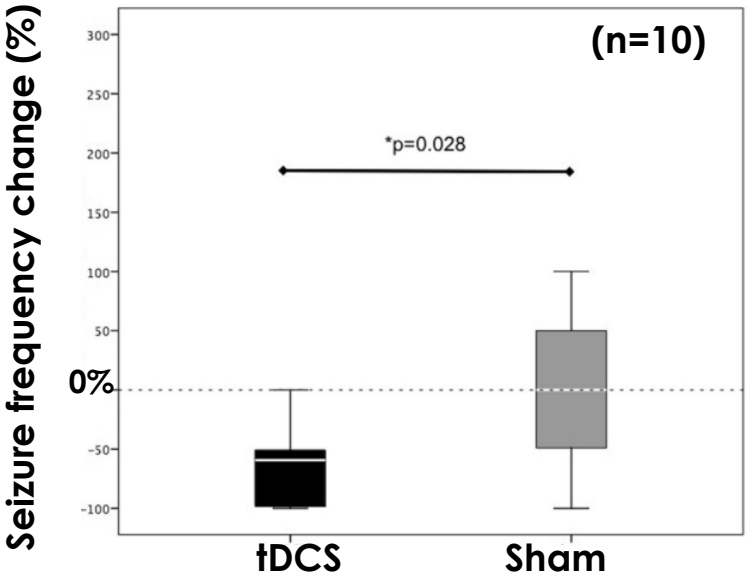
Transcranial current stimulation (tCS) in drug resistant epilepsies



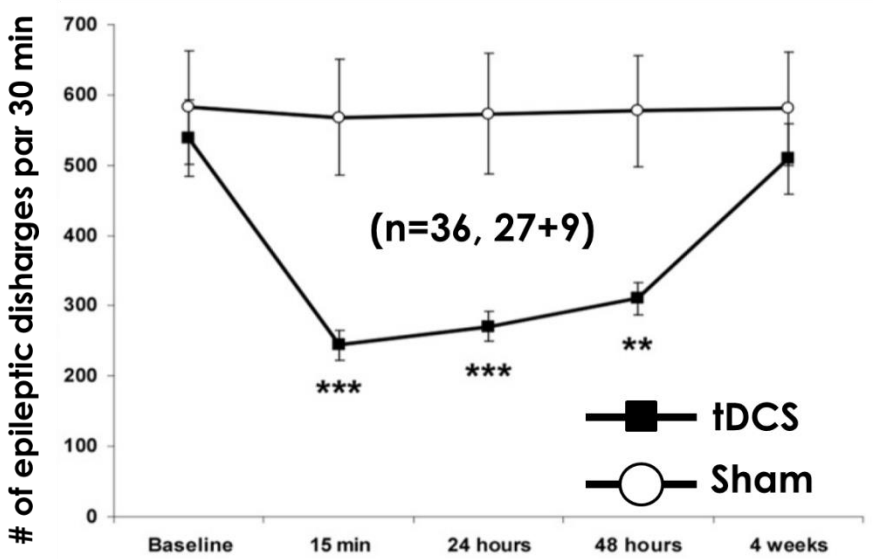


- **Bipolar cathodal tDCS** (for 20 min with cathode positioned over the seizure focus)
- Creates **weak electric fields** (~1 V/m): **subthreshold**
- Multiple **mechanisms of action (acute, lasting)**
- **Seizure reduction**, effect on **EEG discharges**
- **Non-invasive, no side-effects** (Auvichayapat et al, 013; San-Juan et al, 017)

Safe, high-potential technique, but mechanisms of action must be clarified



Assenza et al, 2017



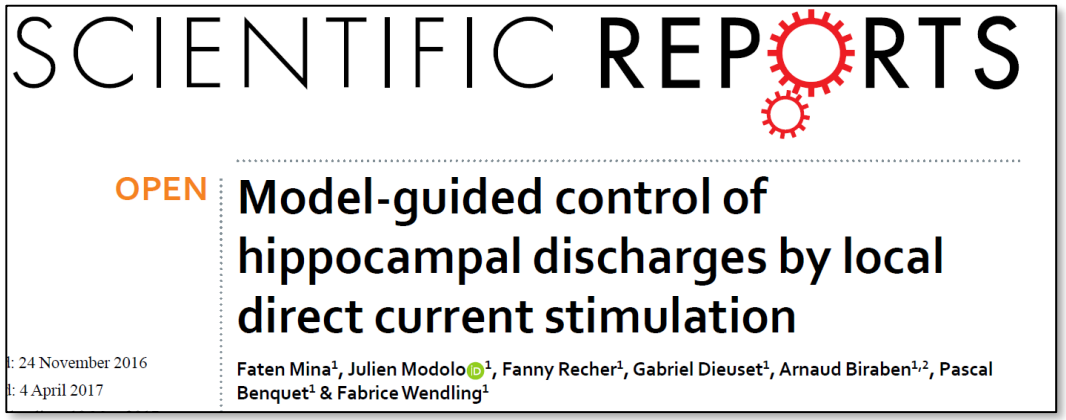
Auvichayapat et al, 2013

Model-based study of low intensity local stimulation

- **Direct local stimulation**
  - Extensively studied *in vitro* (Jefferys 1981)
  - Very few *in vivo* studies (Weiss et al. 1998)
  - Immediate membrane polarization effects well described (Bikson 2004)
  - Lasting effects related to neuroplasticity

- **Our objective** : ***in vivo*** exploration of the effects of **very low intensity DC stimulation (tDCS compatible)**

- **Combined approach** "in silico/in vivo"


SCIENTIFIC REPORTS

OPEN

Model-guided control of hippocampal discharges by local direct current stimulation

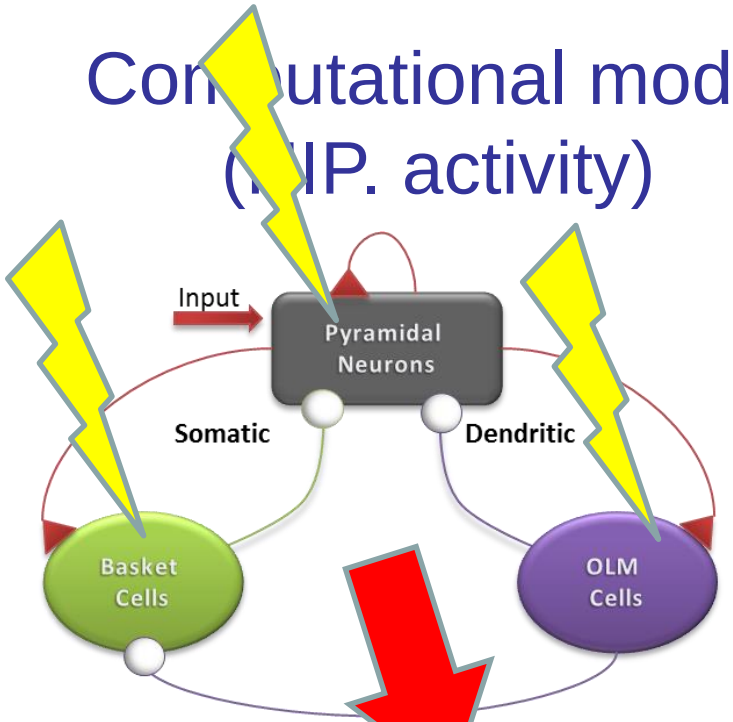
l: 24 November 2016
l: 4 April 2017

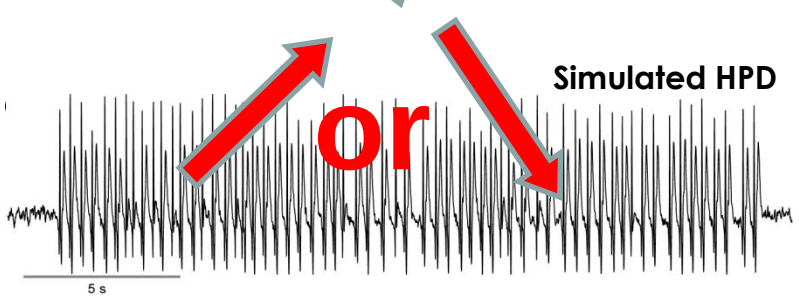
Faten Mina[1], Julien Modolo[1], Fanny Recher[1], Gabriel Dieuset[1], Arnaud Biraben[1,2], Pascal Benquet[1] & Fabrice Wendling[1]

- **Long-term perspective**: explore the effects of **AC** stimulation

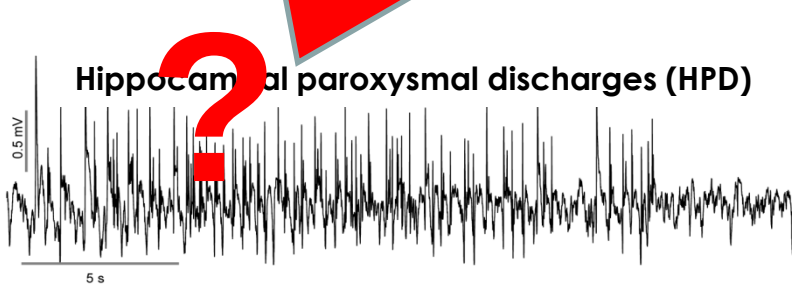
Combined approach

Computational model (HIP. activity)





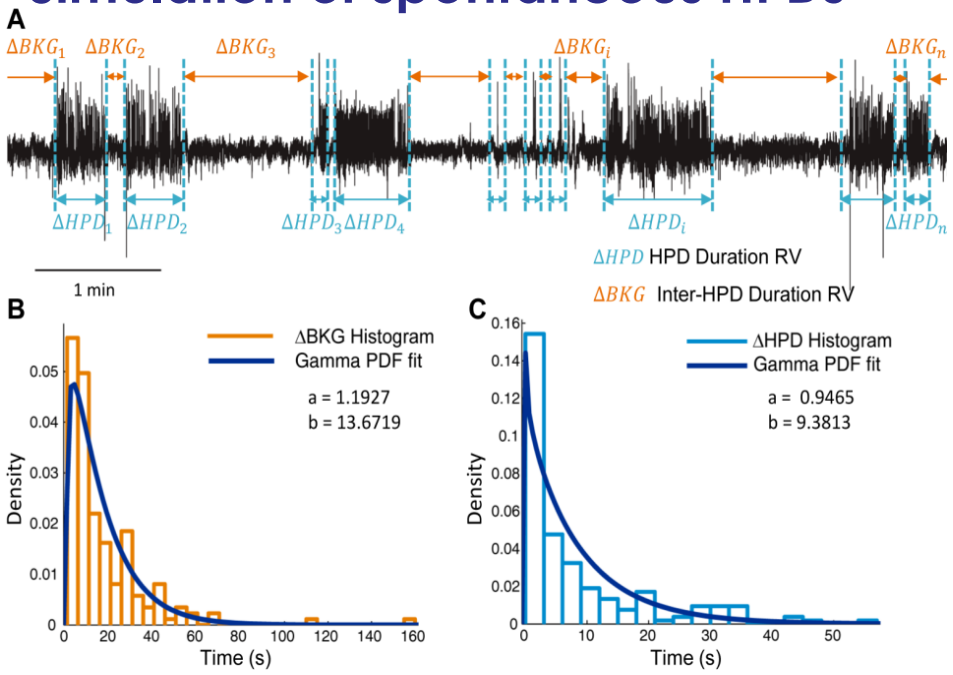
Experimental model (mouse, TLE)

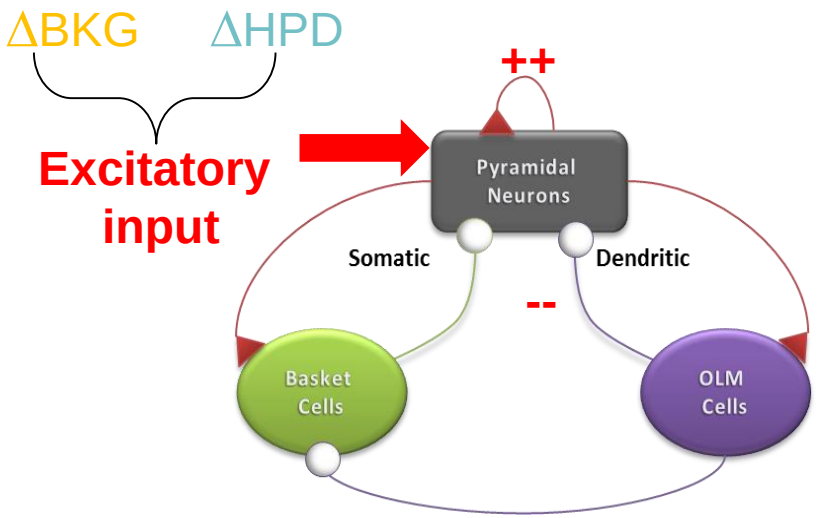


Methodology: **experimental test** of **model predictions**

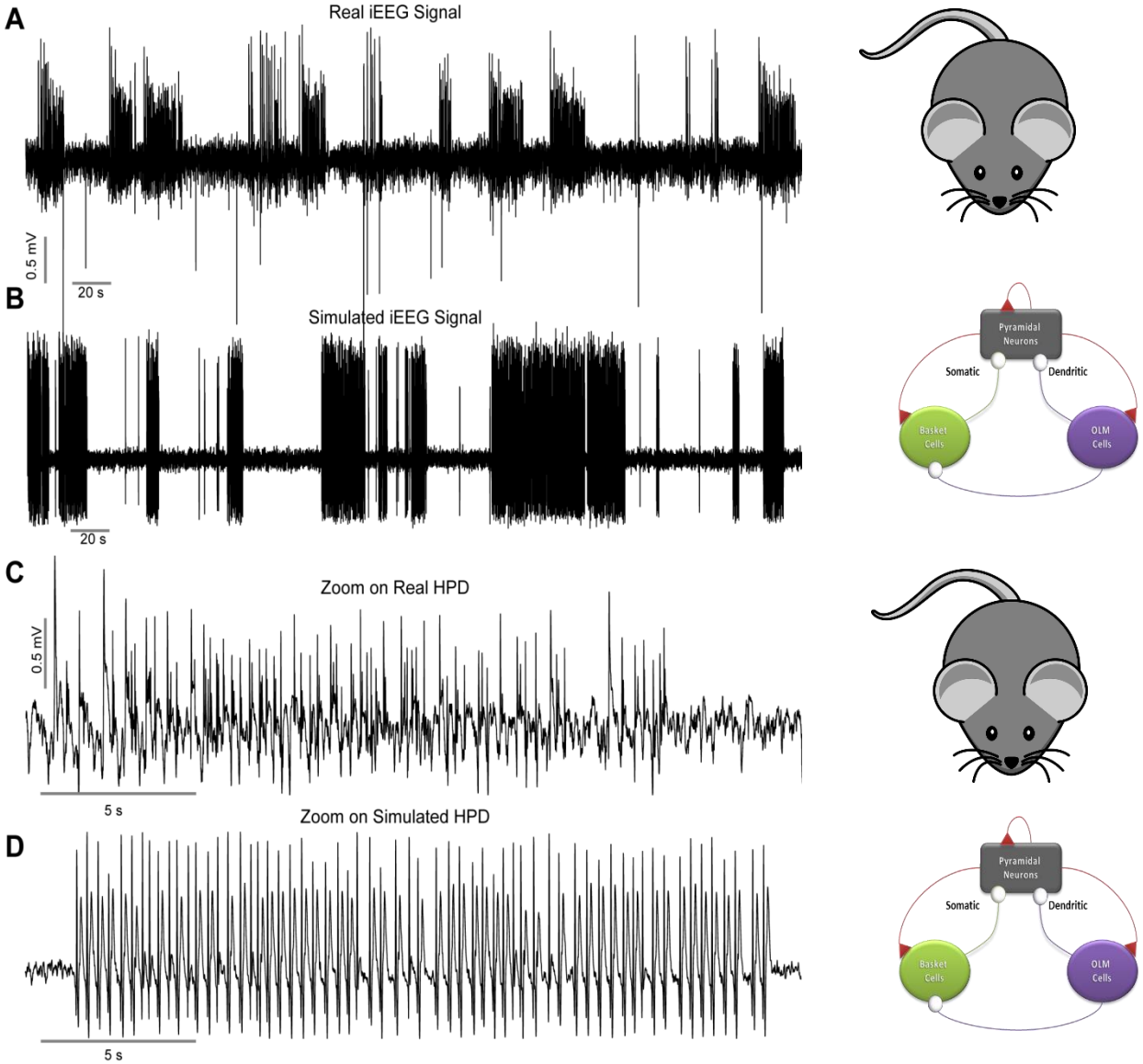
Modeling of epileptic discharges (HPDs)

• Simulation of spontaneous HPDs



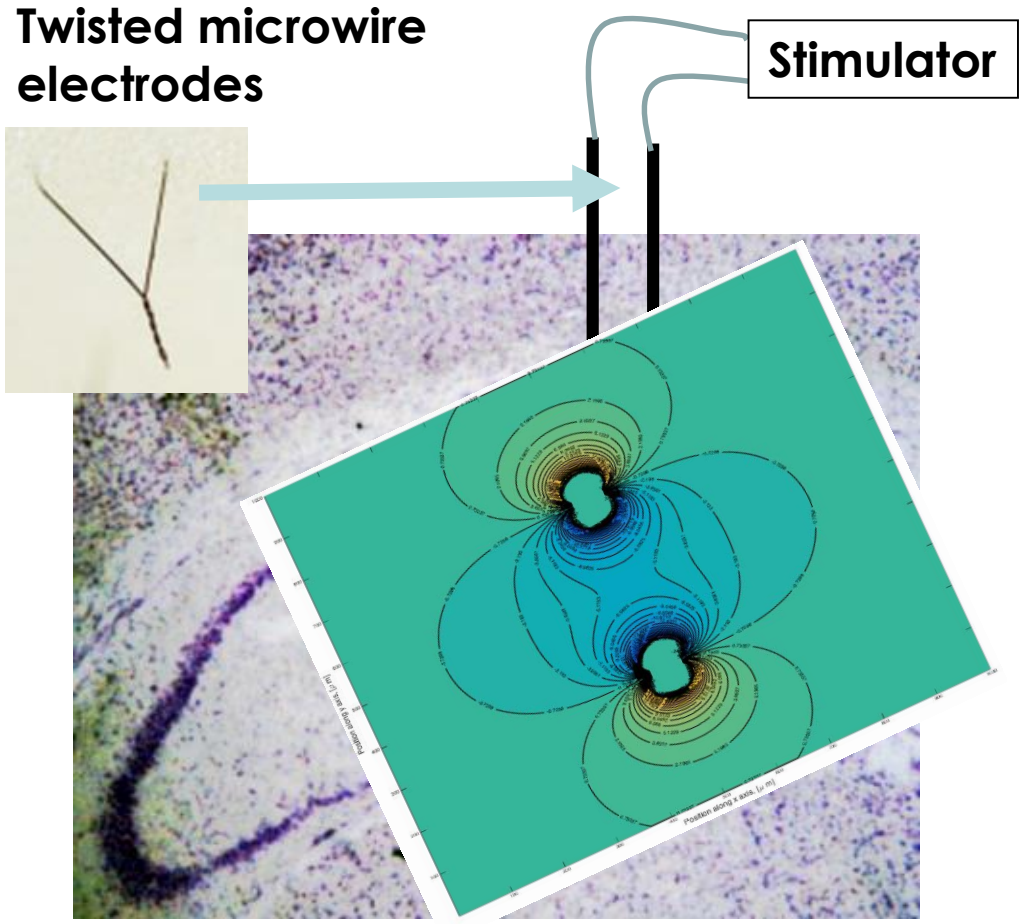


• Real versus simulated



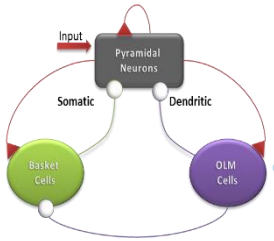
Modeling of electric field effects

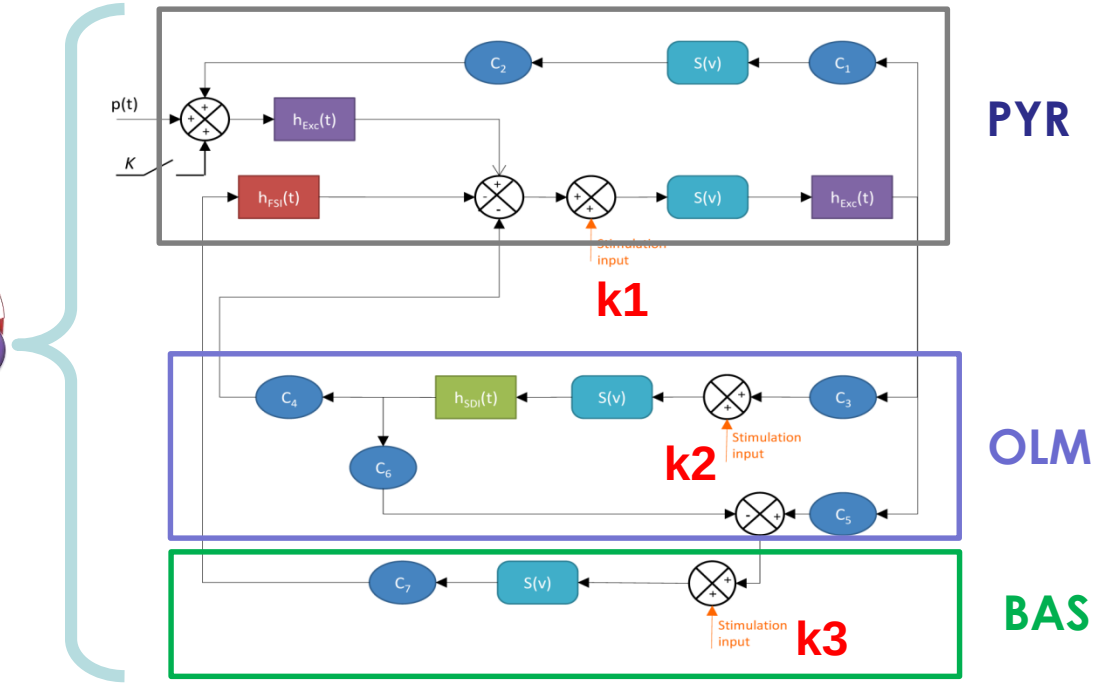
- **In vivo experimental setup**



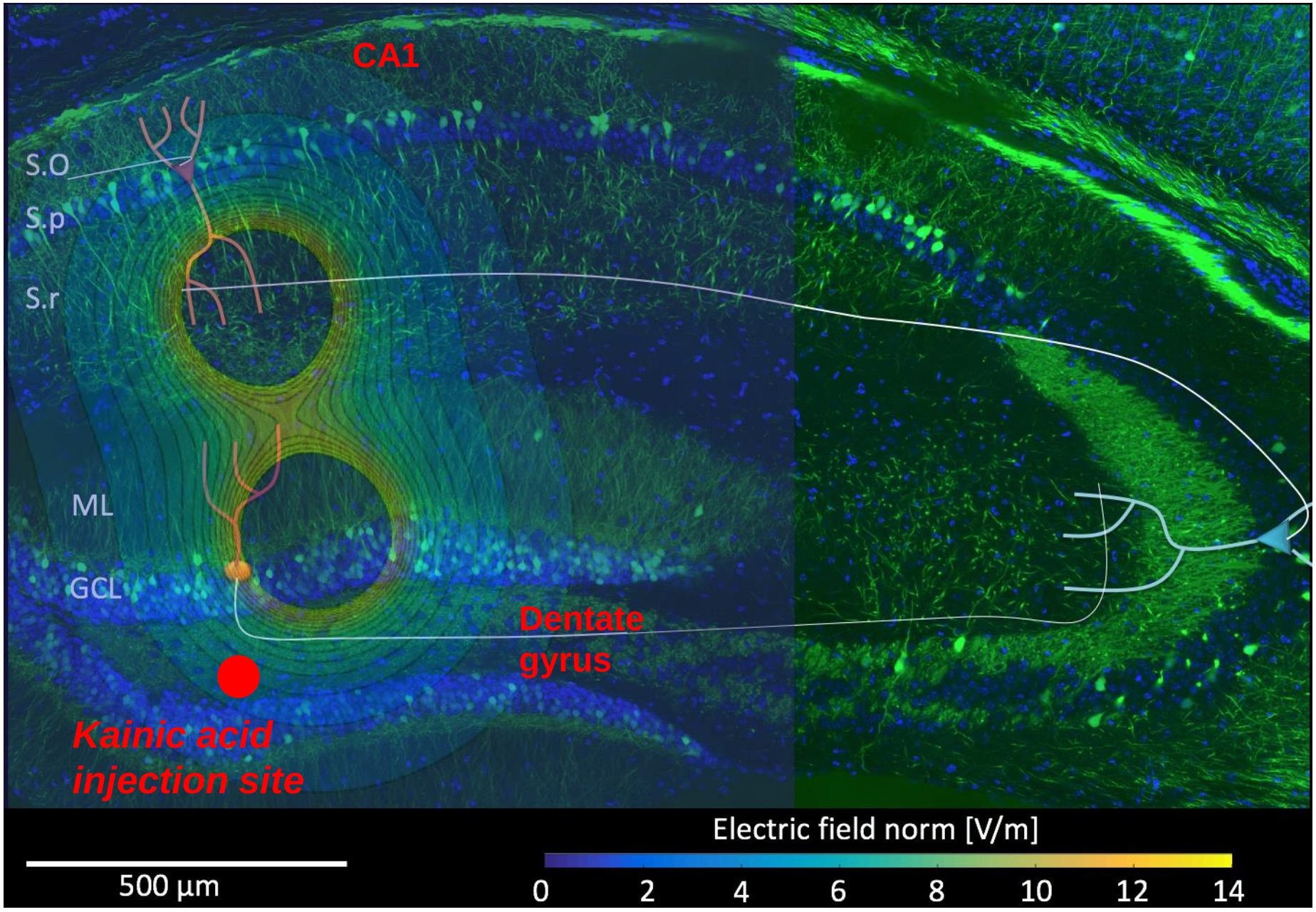
Hypotheses

- Immediate polarisation effects
- Affects the mean membrane (additive model)
- Both PYRs et INs are impacted

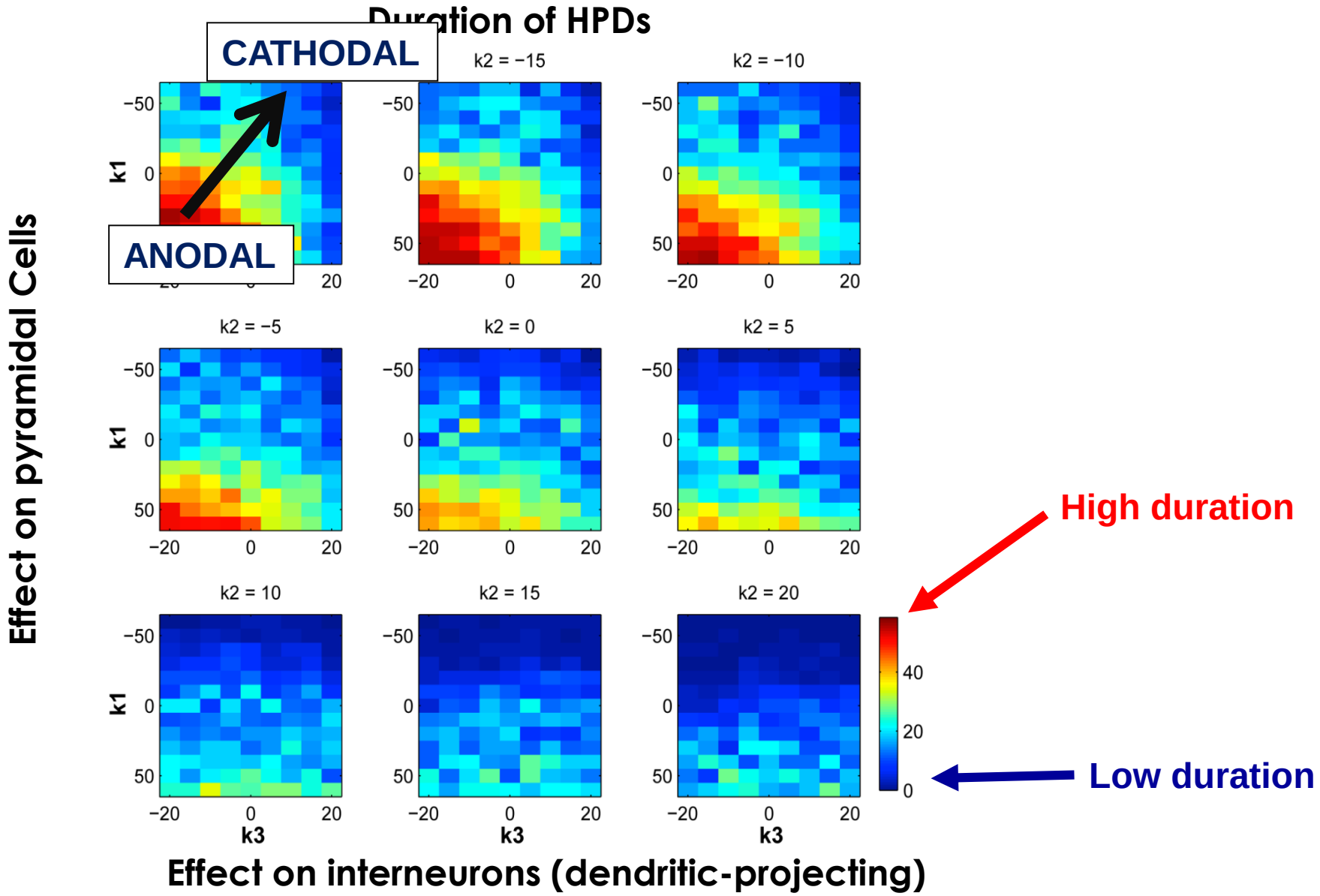




Dosimetry: **I = 1µA**

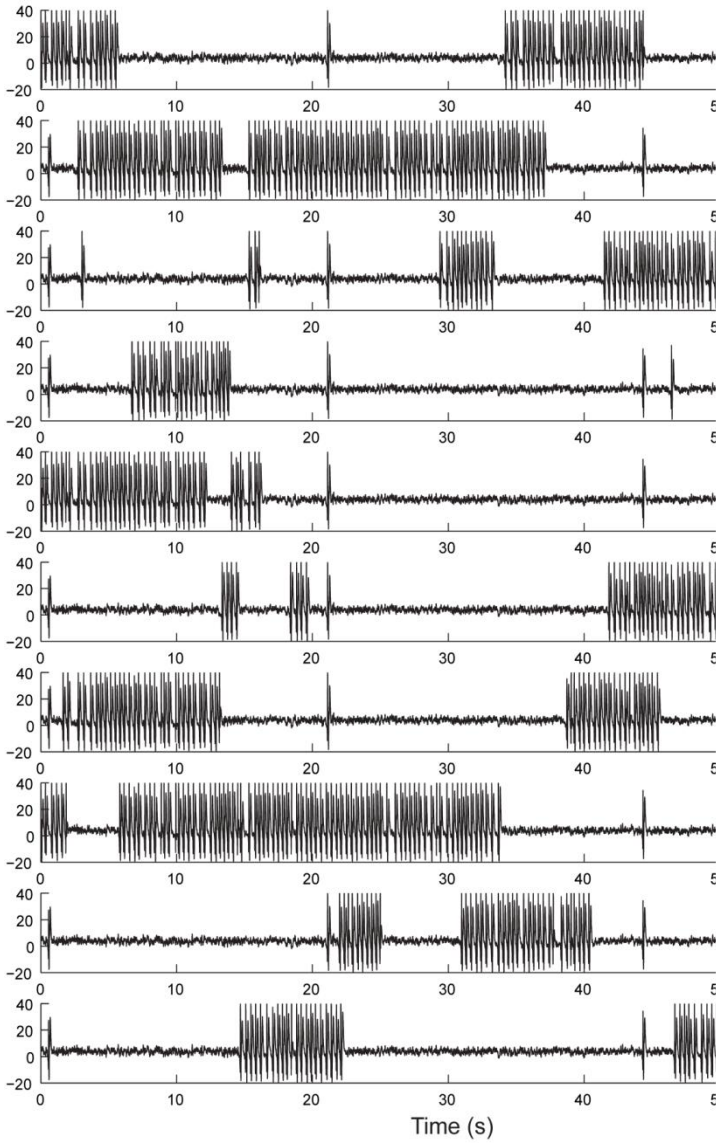


Results: model predictions (polarity)

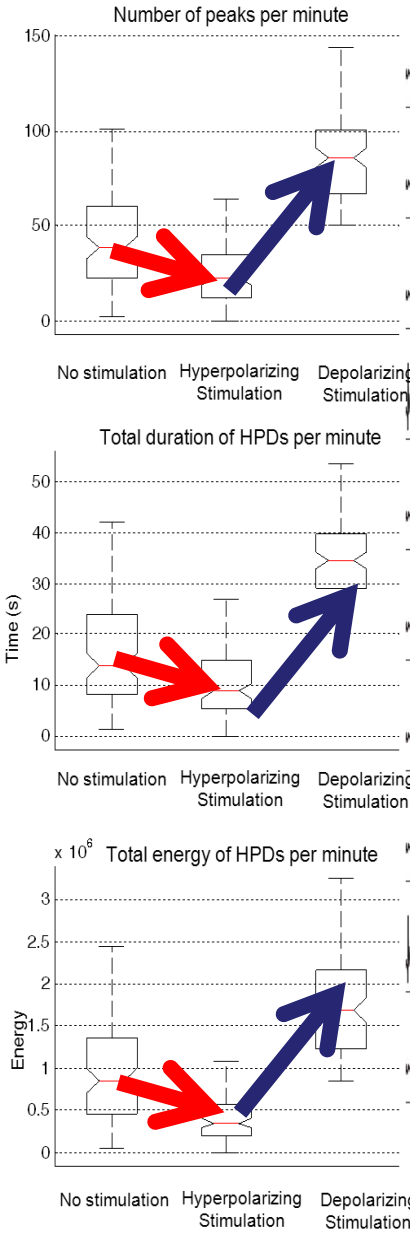


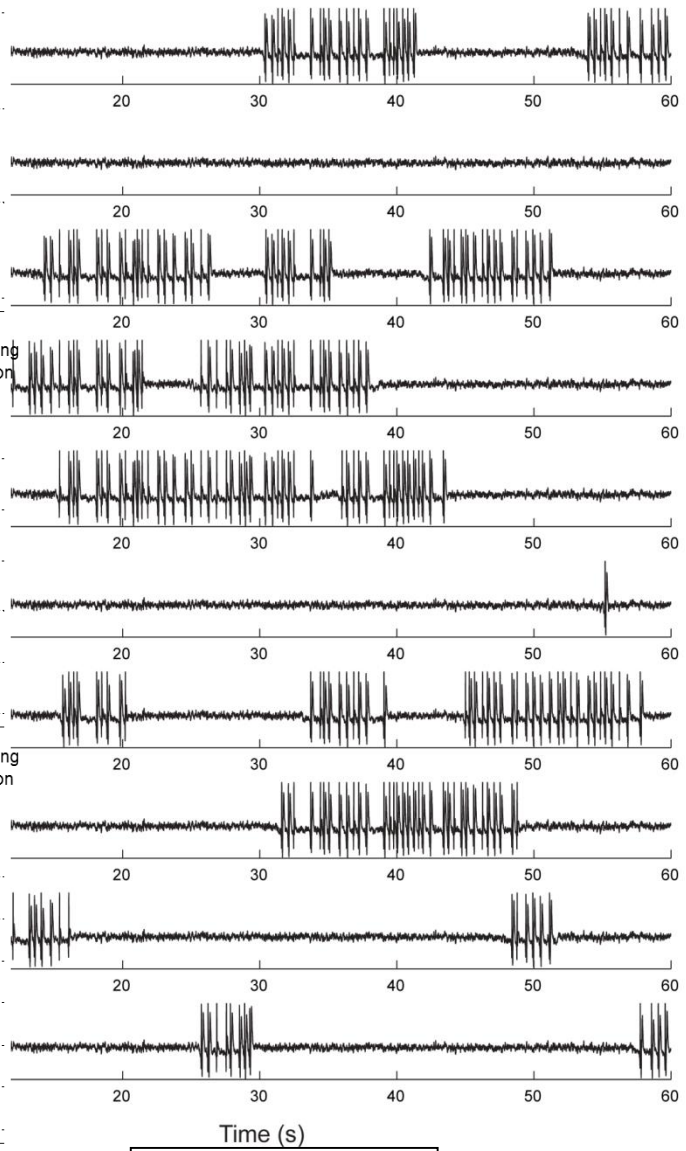
Mina F., J. Modolo, … , Benquet P., Wendling F. Model-guided control of hippocampal discharges by local direct current stimulation. Scientific Reports, 2017.

Results: model predictions (polarity)

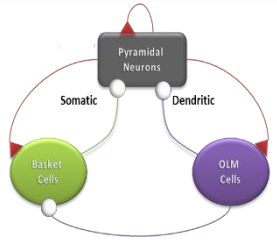


CONTROL (no stim.)

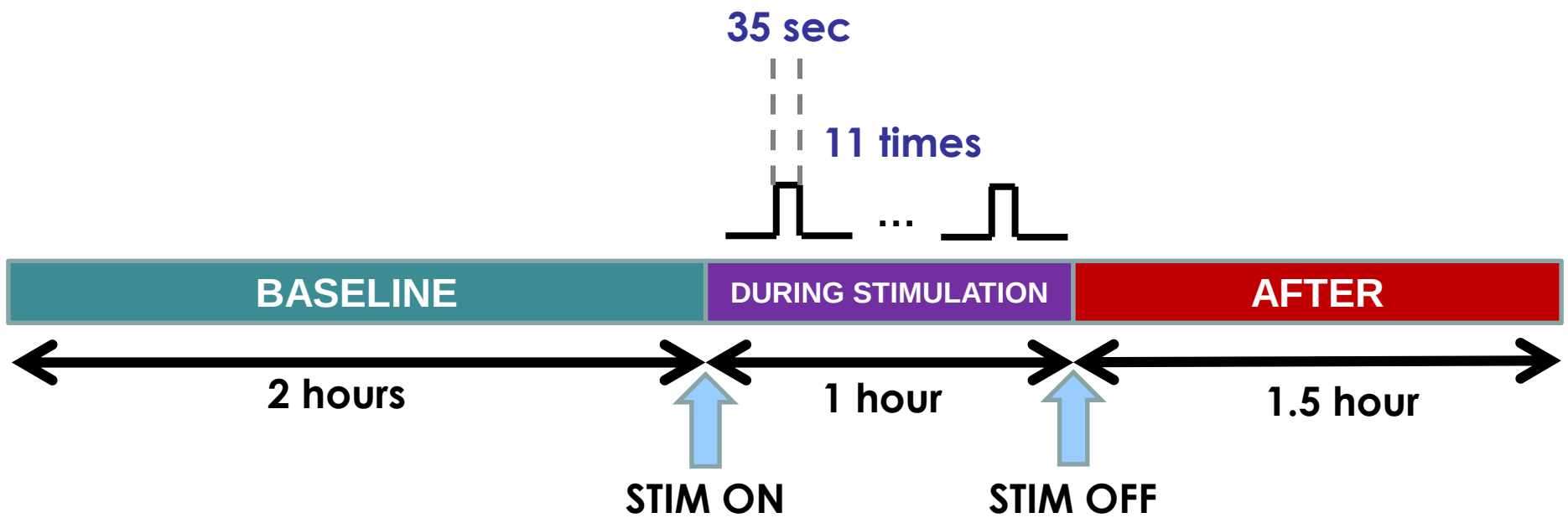




CATHODAL



Experimental test of model predictions



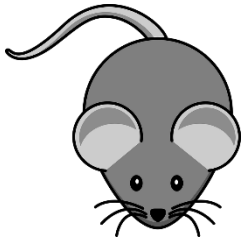
- Stimulation protocol: 1 hour; 11 times 35 seconds (~every 5 min)

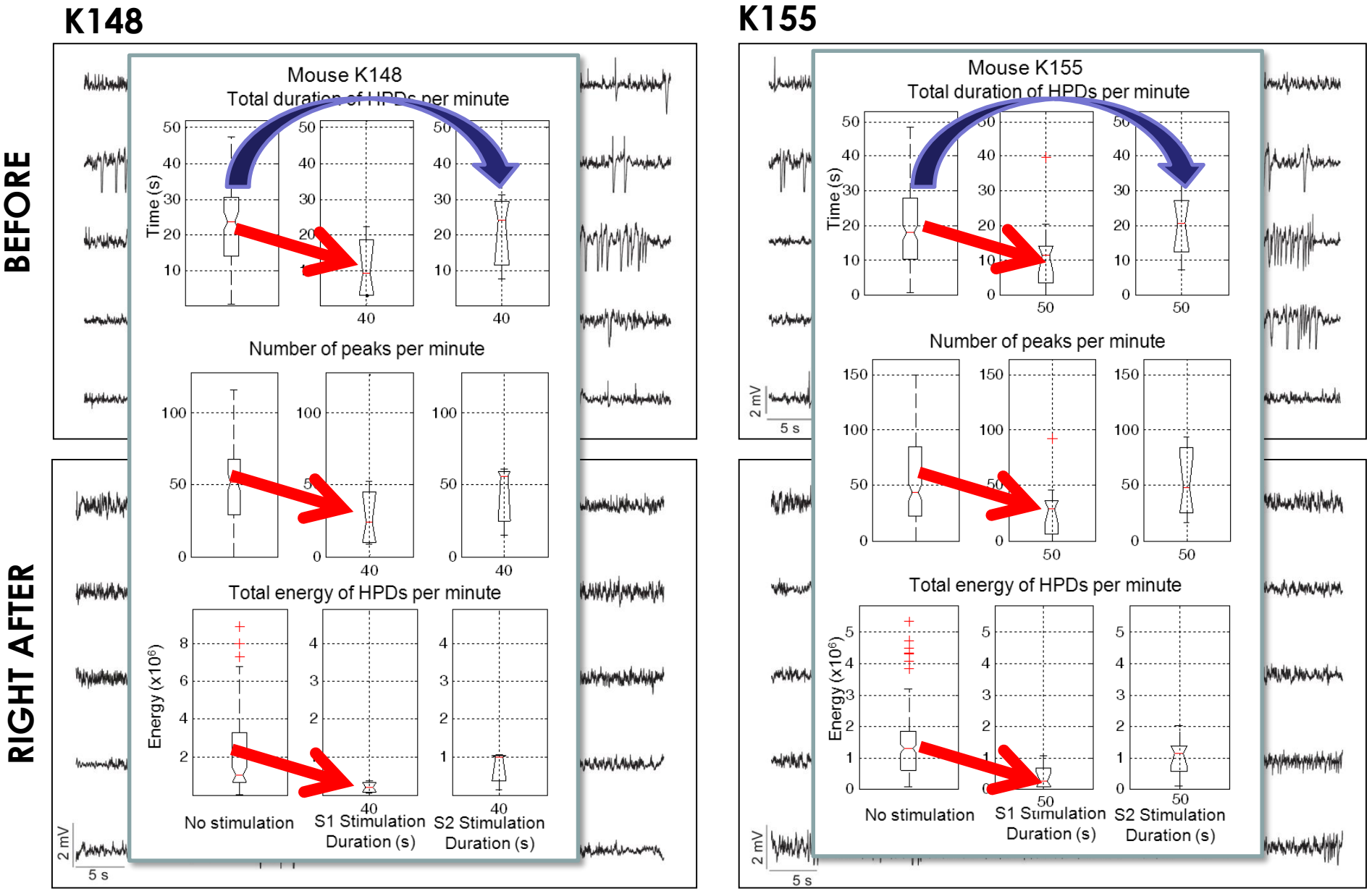
- Cumulated stim. duration : 6 min 25 sec over the 60 min stimulation period

- DC (cathodal), 1 µA

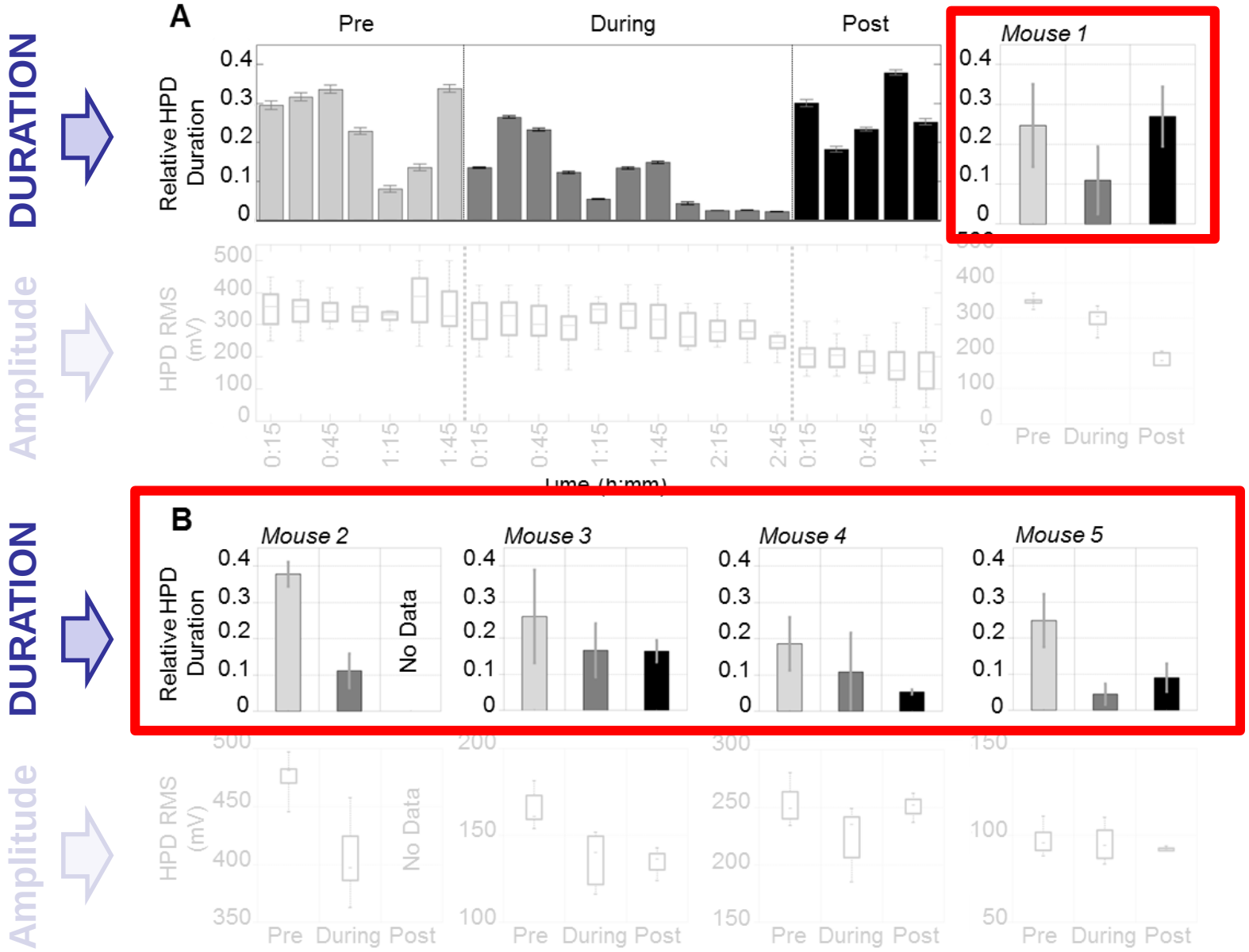
Impact on epileptic discharges?

Results : *in vivo* model (immediate effects)



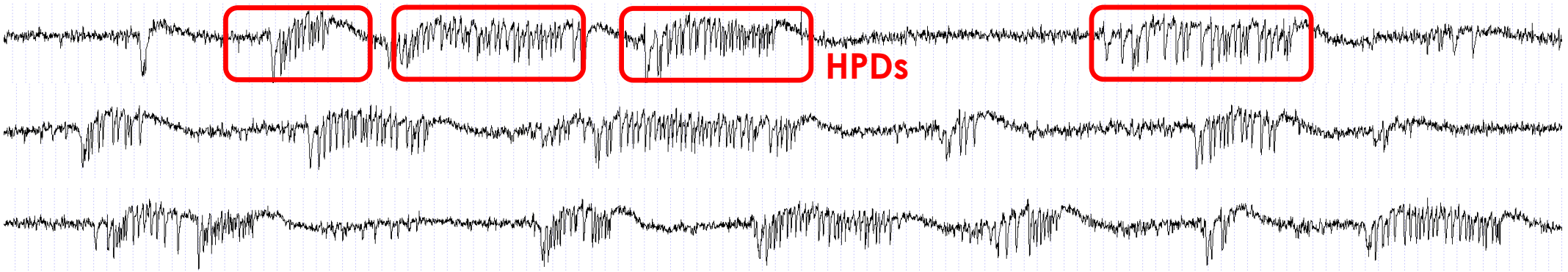


Results : *in vivo* model (immediate & lasting effects)

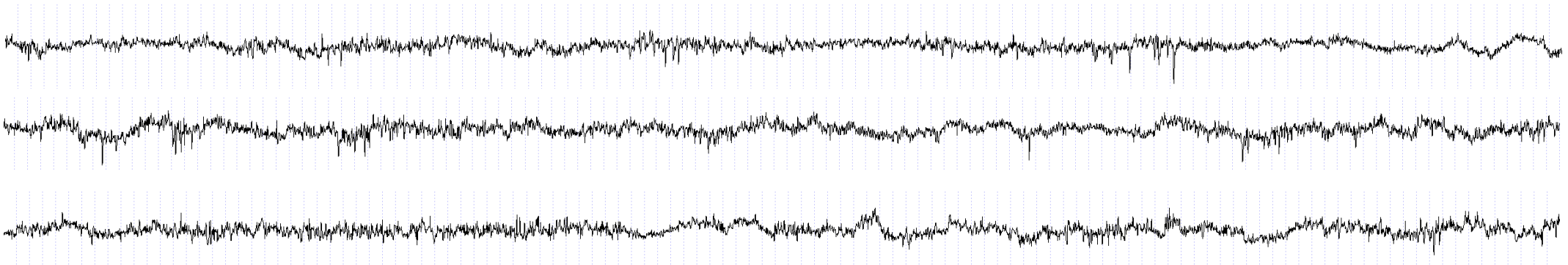


Work in progress : from DC to AC local direct stimulation

Before stimulation (2 mins time series)



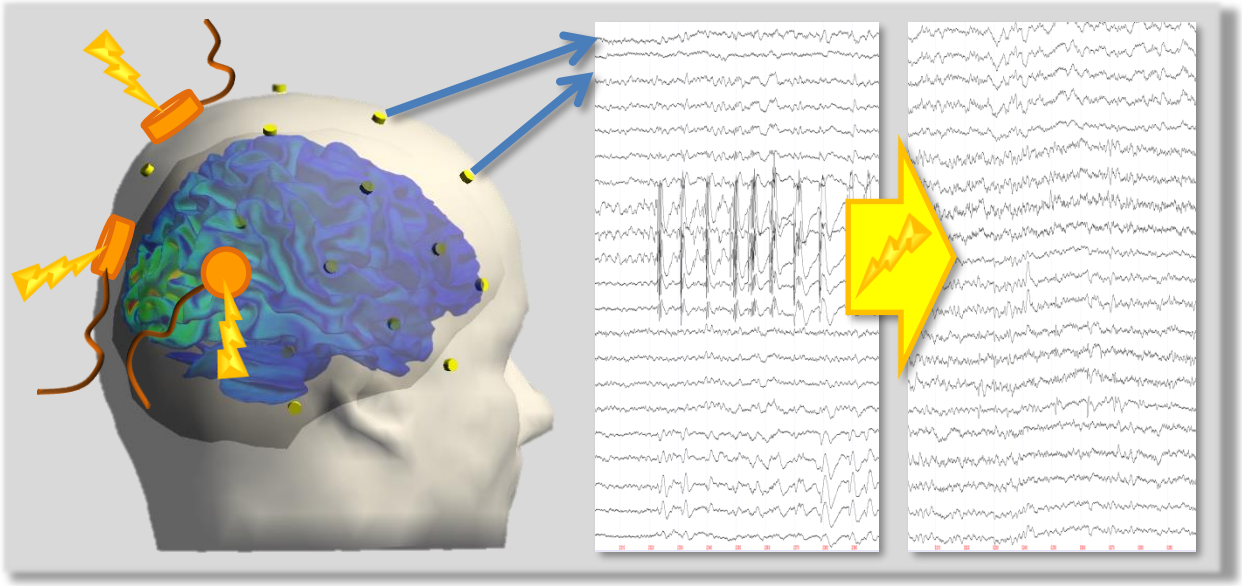
Between stimulation blocks (2 mins time series)



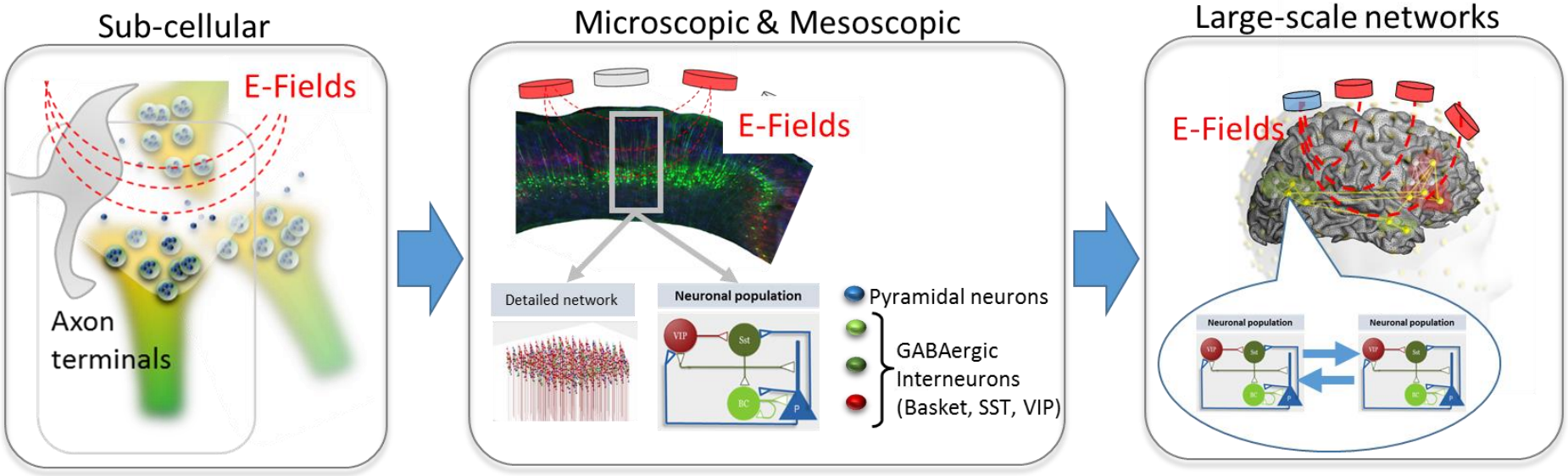
Benquet P., Modolo J., Wendling F. Brain tissue stimulation method, apparatus and computer program. European Patent EP 16000751.4, 2016.

Application to therapeutic tDCS for epilepsy

The Hope…



Multi-scale approach:

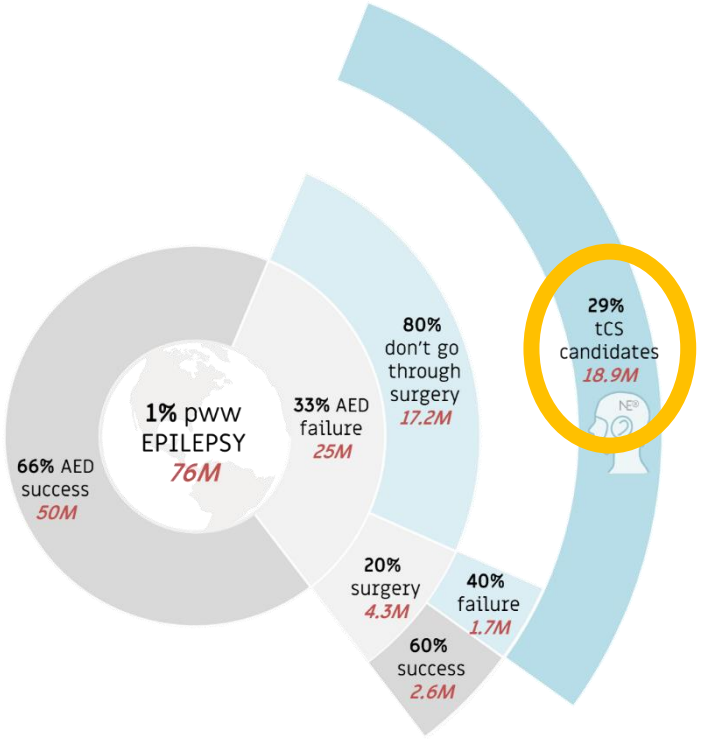


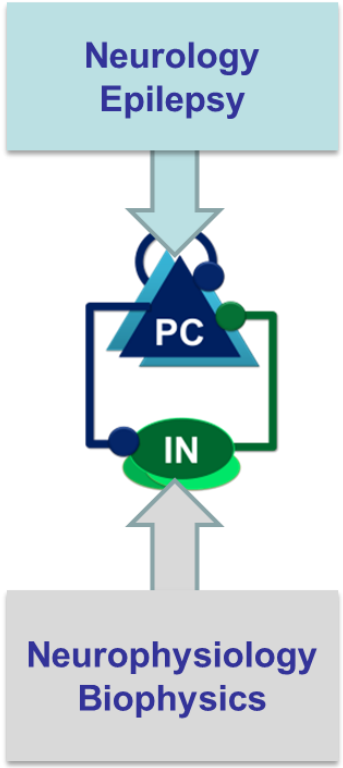
Wendling et al. - Unpublished

« Take home message »

- Computational models can lead to **efficient neuromodulation** protocols, i.e. able to reduce epileptiform activity

- Mice: DC stimulation showed efficacy at 1 µA, ➔ **2 à 10 V/m** between the 2 electrodes





- **In patients**: high therapeutic potential but still a long way to go….

- Need for **hybrid models** (neurophysiology + biophysics), **personnalised** and **multi-level**

Thank you for your attention

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- F. Lopes da Silva †

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- Giulio Ruffini
- Roser Sanchez
- Ricardo Salvador

Fundings

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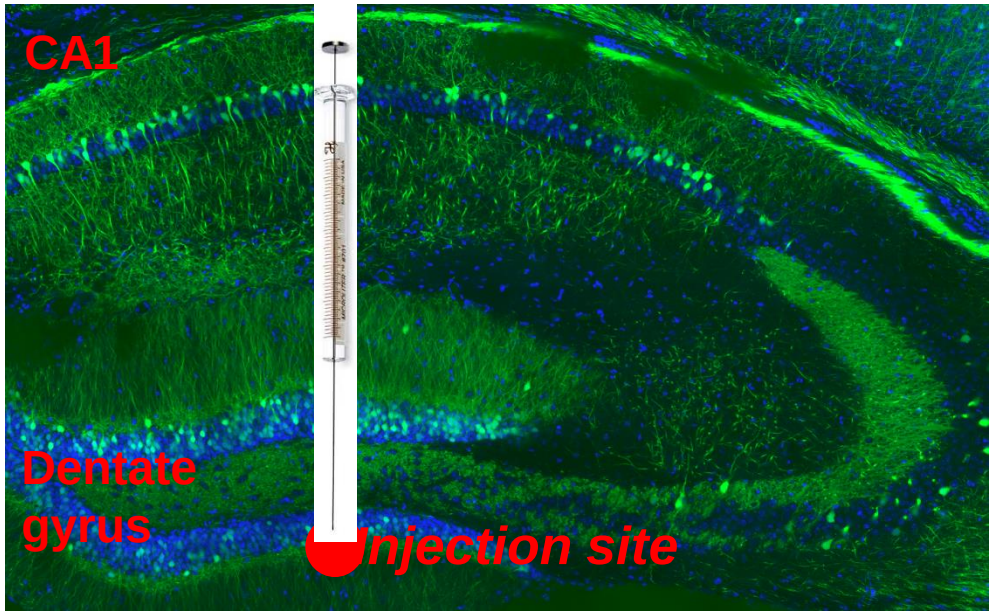
« Kainate » model – Temporal Lobe Epilepsy

C57BL/6J Mice

> 80 days

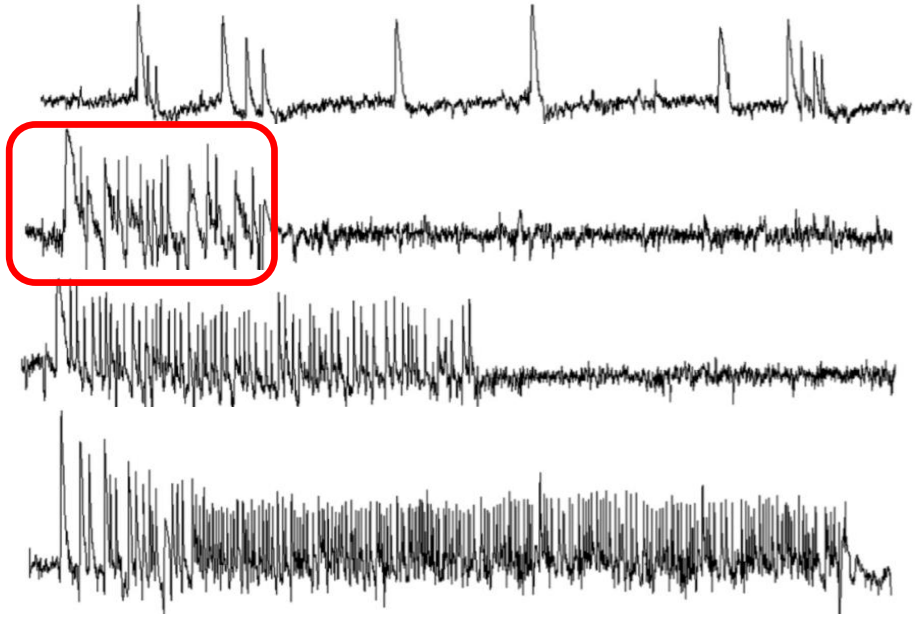
Stereotaxic surgery

Intra-hippocampal kainic acid micro-injection



"Hippocampal paroxysmal discharges" (HPD)

*HPD **number** and **duration** increase with **epileptogenesis***



D1

28 days (epileptogenesis): Gradual excitability increase

D28: ***chronic epilepsy***

Heinrich et al., Neurobiology of Disease, 2011