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Realistic modeling and interpretation of depth-EEG signals recorded during inter-ictal to ictal transition in temporal lobe epilepsy

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Epilepsies

- Neurological disorder characterized by recurrent seizures

- Excessive firing in neuronal cells, abnormally-high synchronization processes in neuronal networks

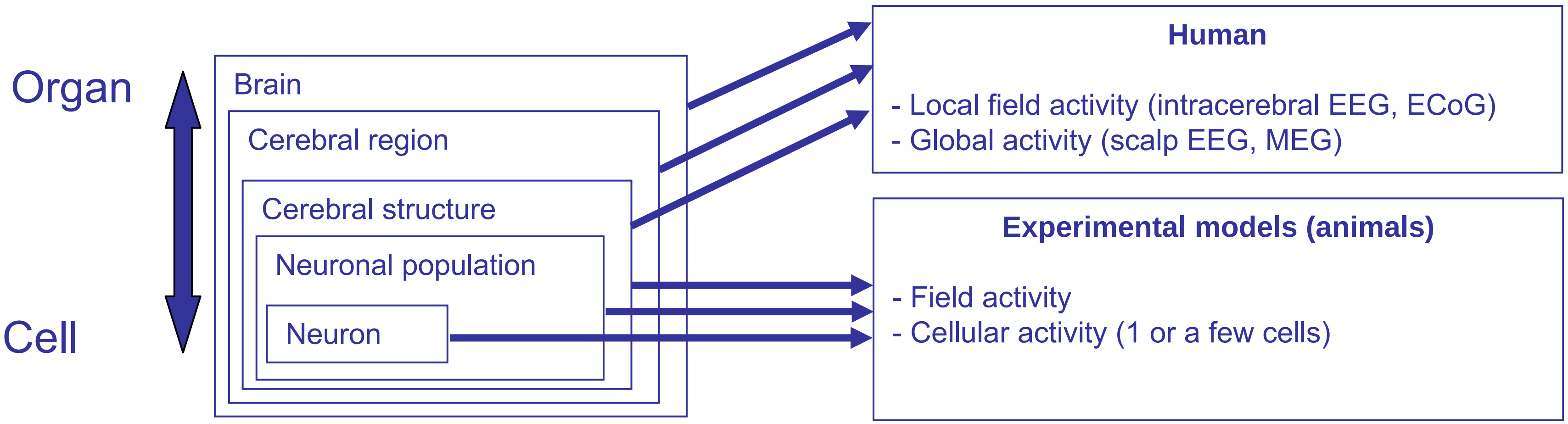
- Imbalance between excitation- and inhibition-related processes

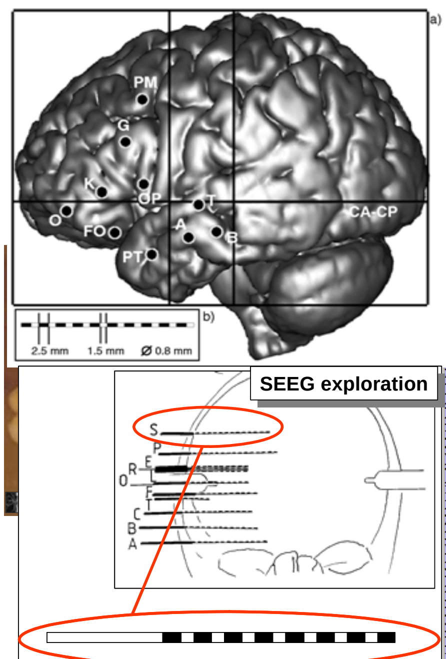
- Poorly understood mechanisms of:
    - **epileptogenesis** (property of a neuronal tissue to become epileptic)
    - **ictogenesis** (transition from interictal to ictal activity)

➡ Development of models

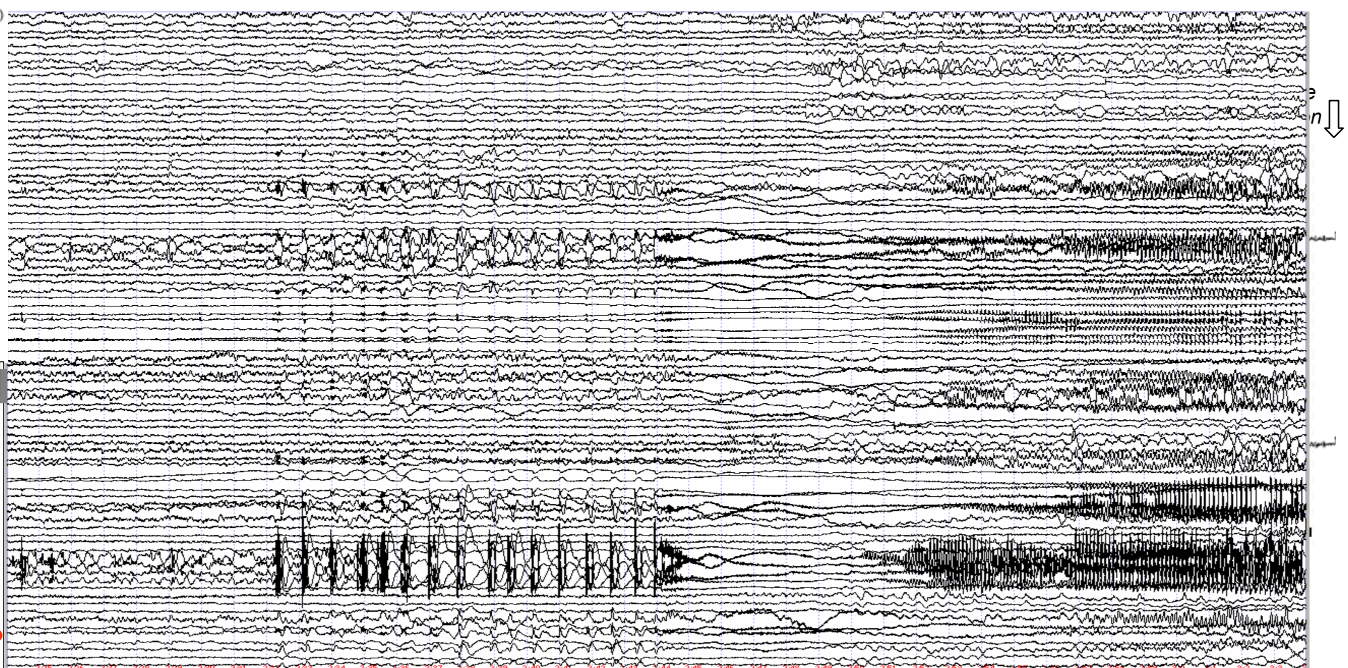
➡ Development of numerous techniques allowing for the observation of neuronal activity

Electrophysiological observations





Intracerebral multiple lead electrodes
(lead: ∅ 0.8 mm, L 2mm)



Epilepsy Unit, CHR La timone, Marseille

Objective of this work: "To interpret" depth-EEG signals

A difficult issue:

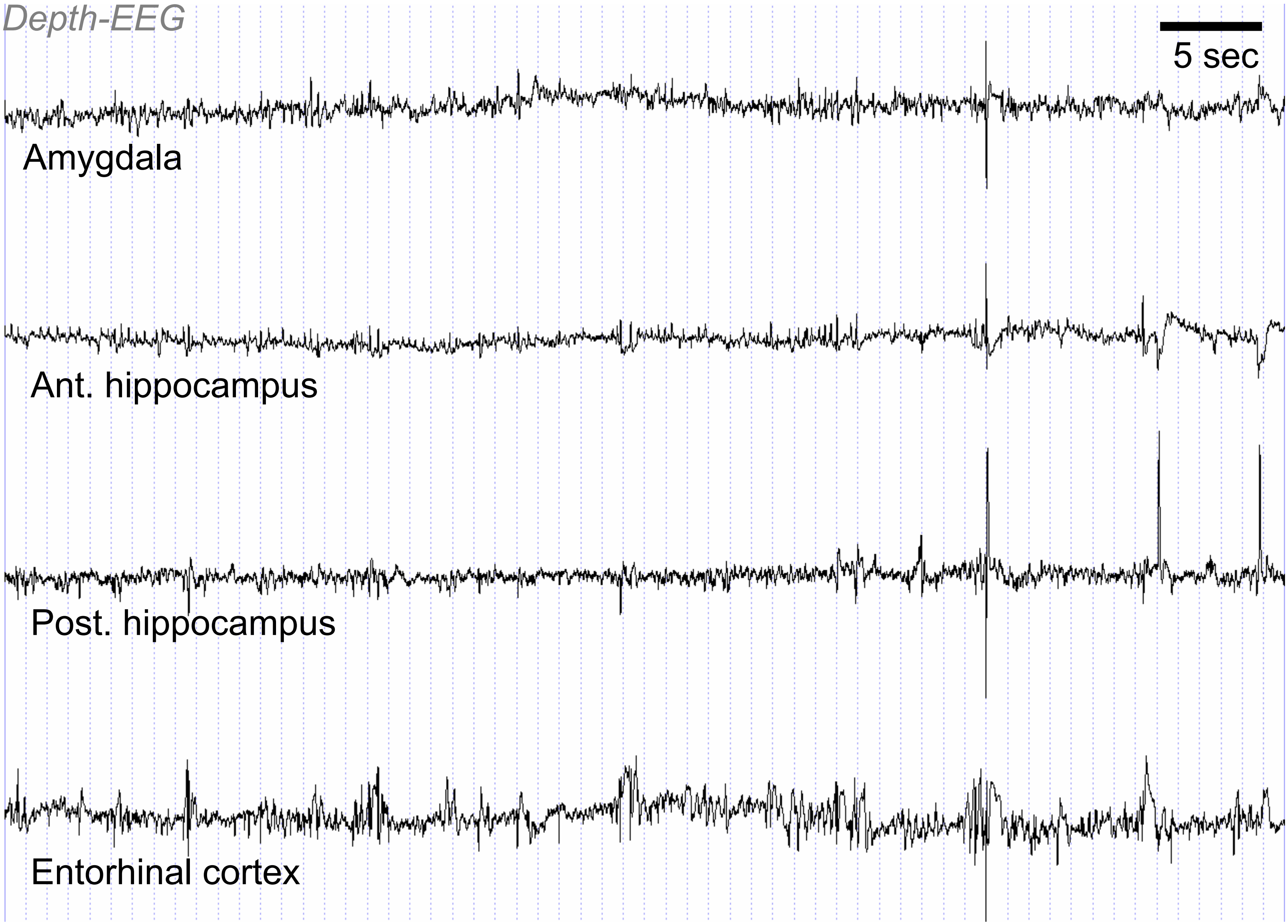
● Observations are **incomplete**
- In time: epilepsy = progressive disease, observation window is limited
- In space: spatial undersampling, some structures can not be recorded (difficult access)

● Pathophysiological mechanisms occur at different **temporal scales**
- Epileptic « spikes »: a few hundred of ms
- Seizures: a few tens of seconds up to several minutes (**prediction?**)
- Frequency of seizures : a few/day up to a few/month (**regulations** ?)

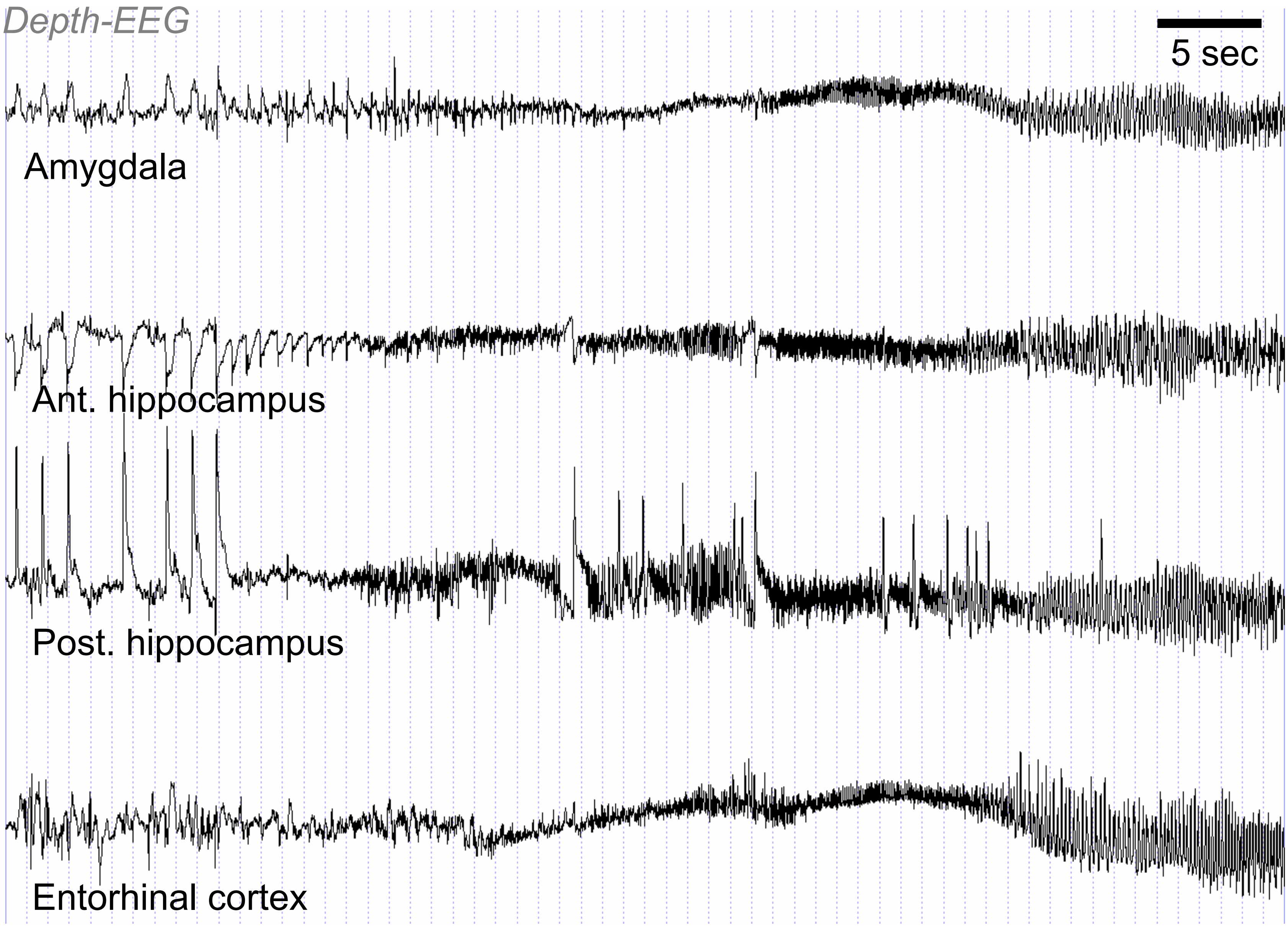
● **Complexity** of recorded systems (specific **cytoarchitectonics**, **nonlinear** mechanisms, different **spatial scales**, short/long term **plasticity**)

⇨ **Depth-EEG** is a **non-stationary** signal with **transient events** and **ruptures** of dynamics (more or less abrupt)

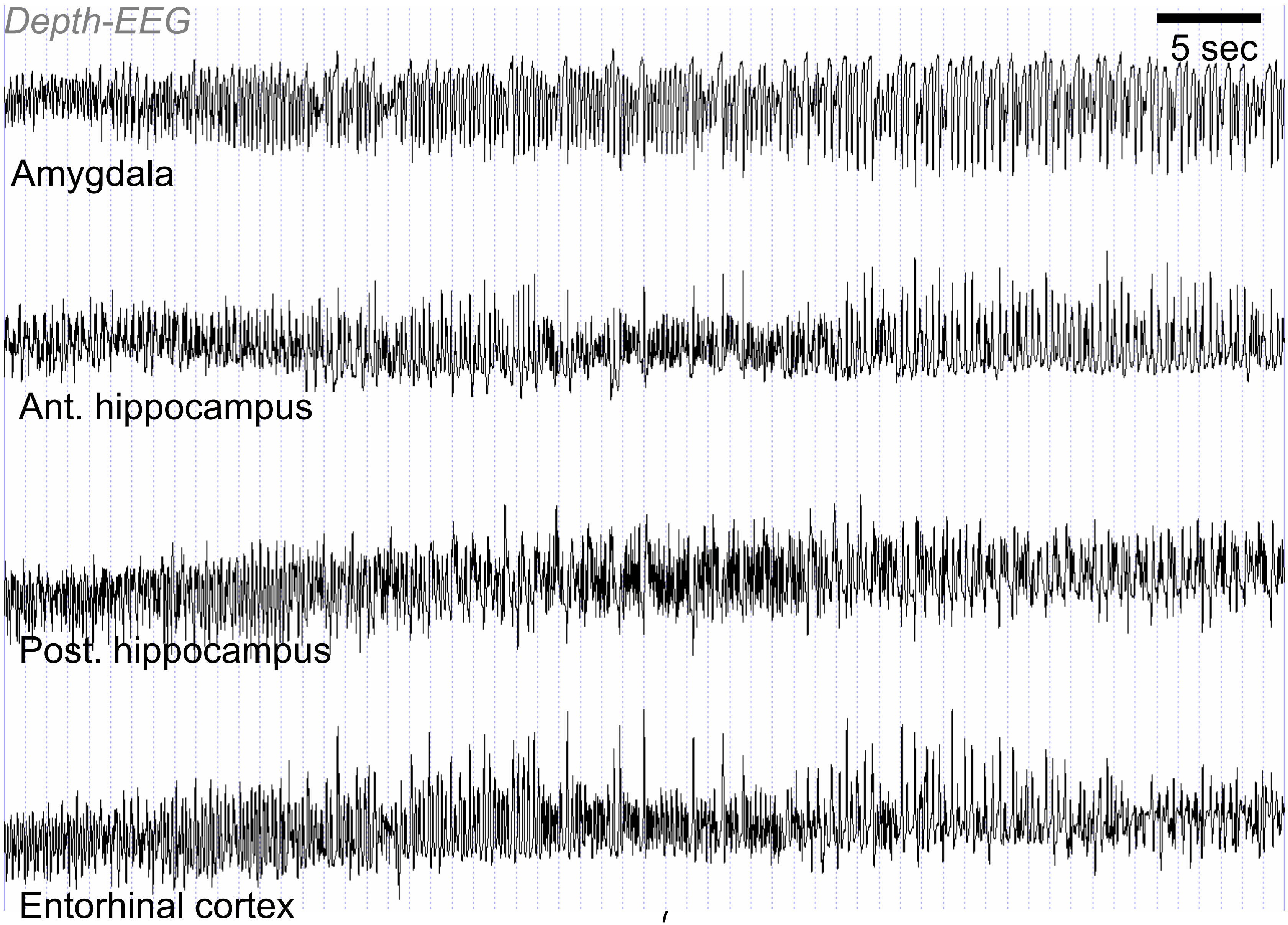
Interictal and pre-onset activity (TLE)



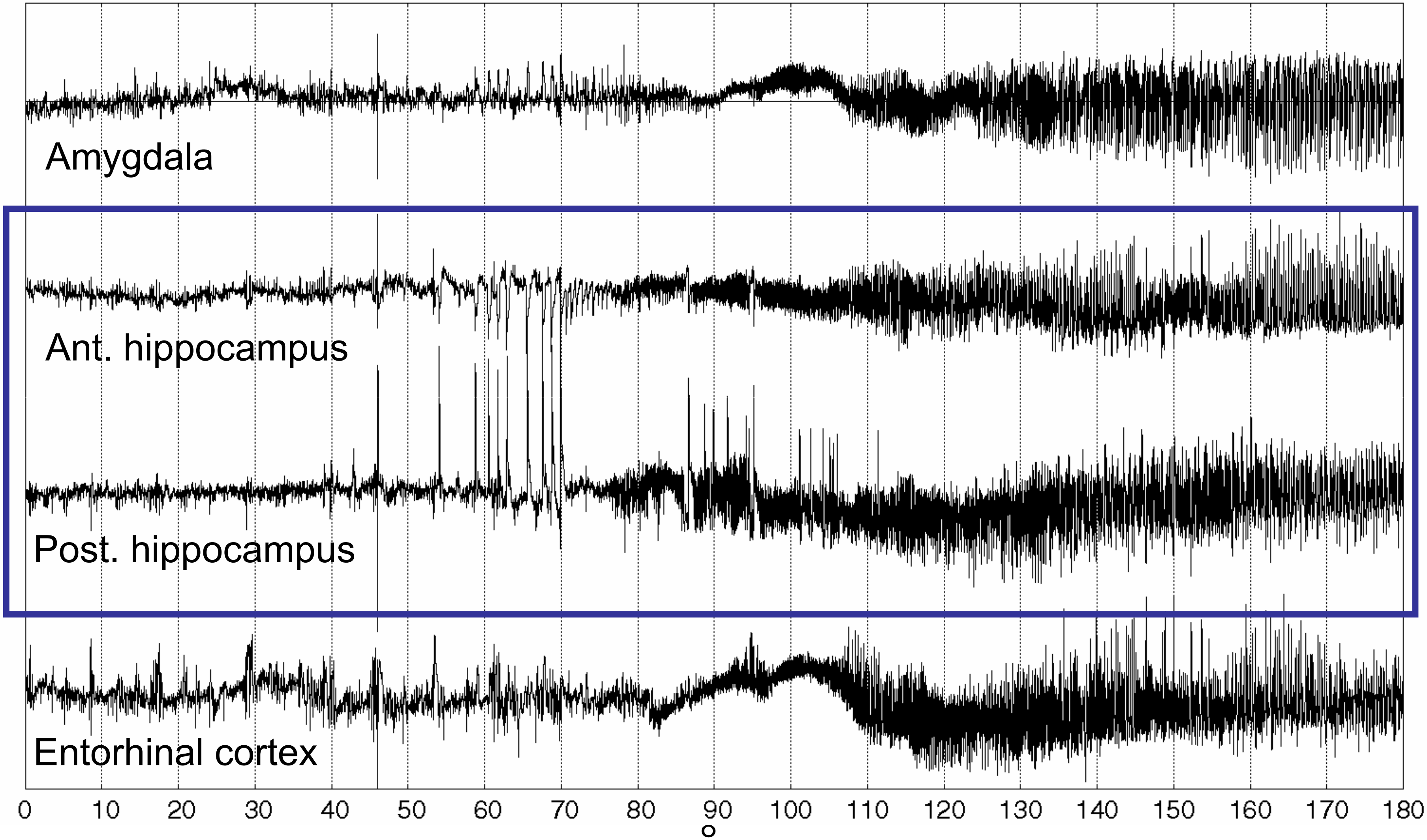
Seizure onset



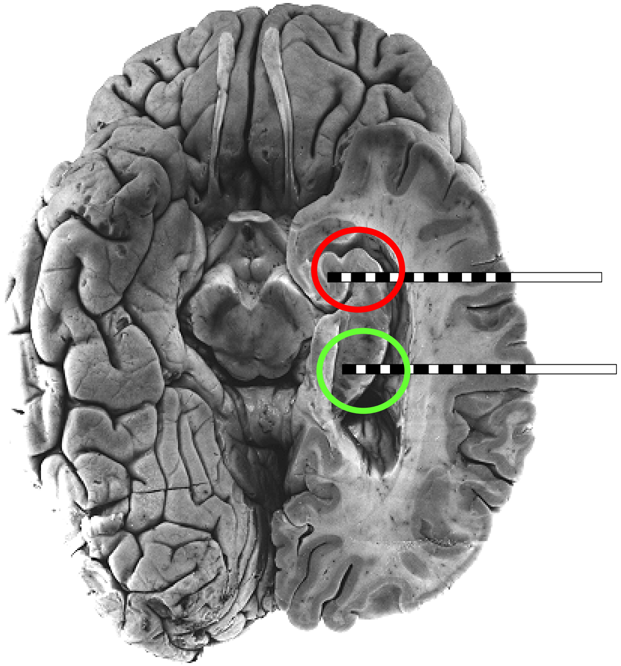
Ictal activity

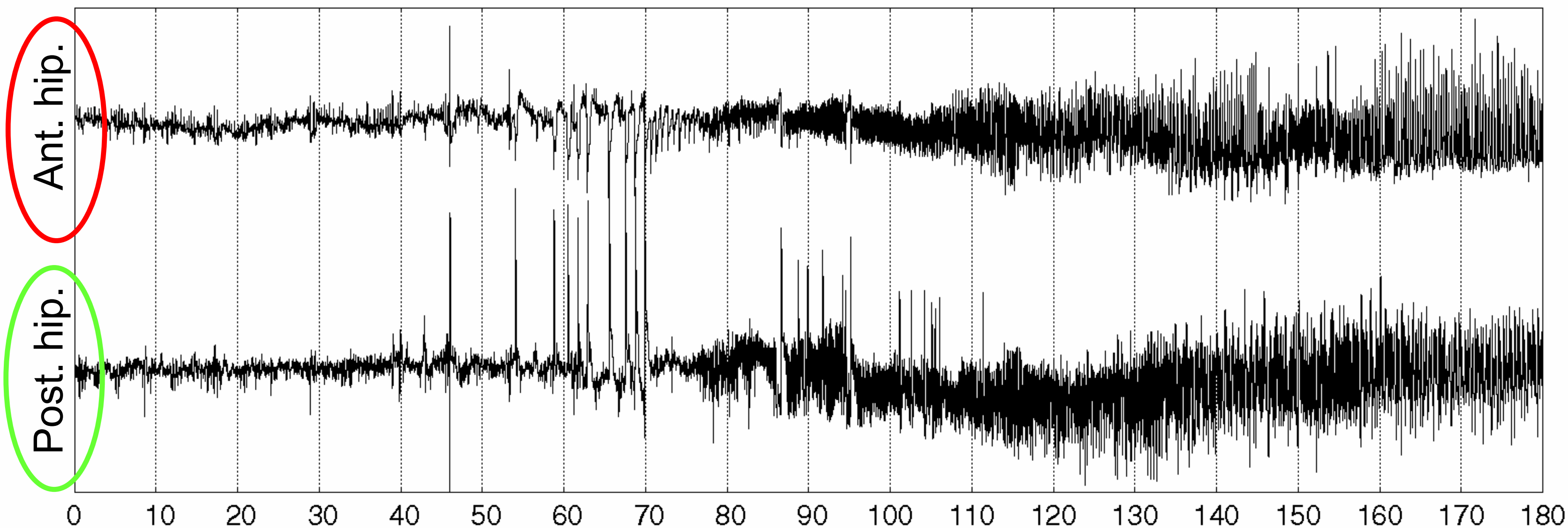


Interictal / ictal transition

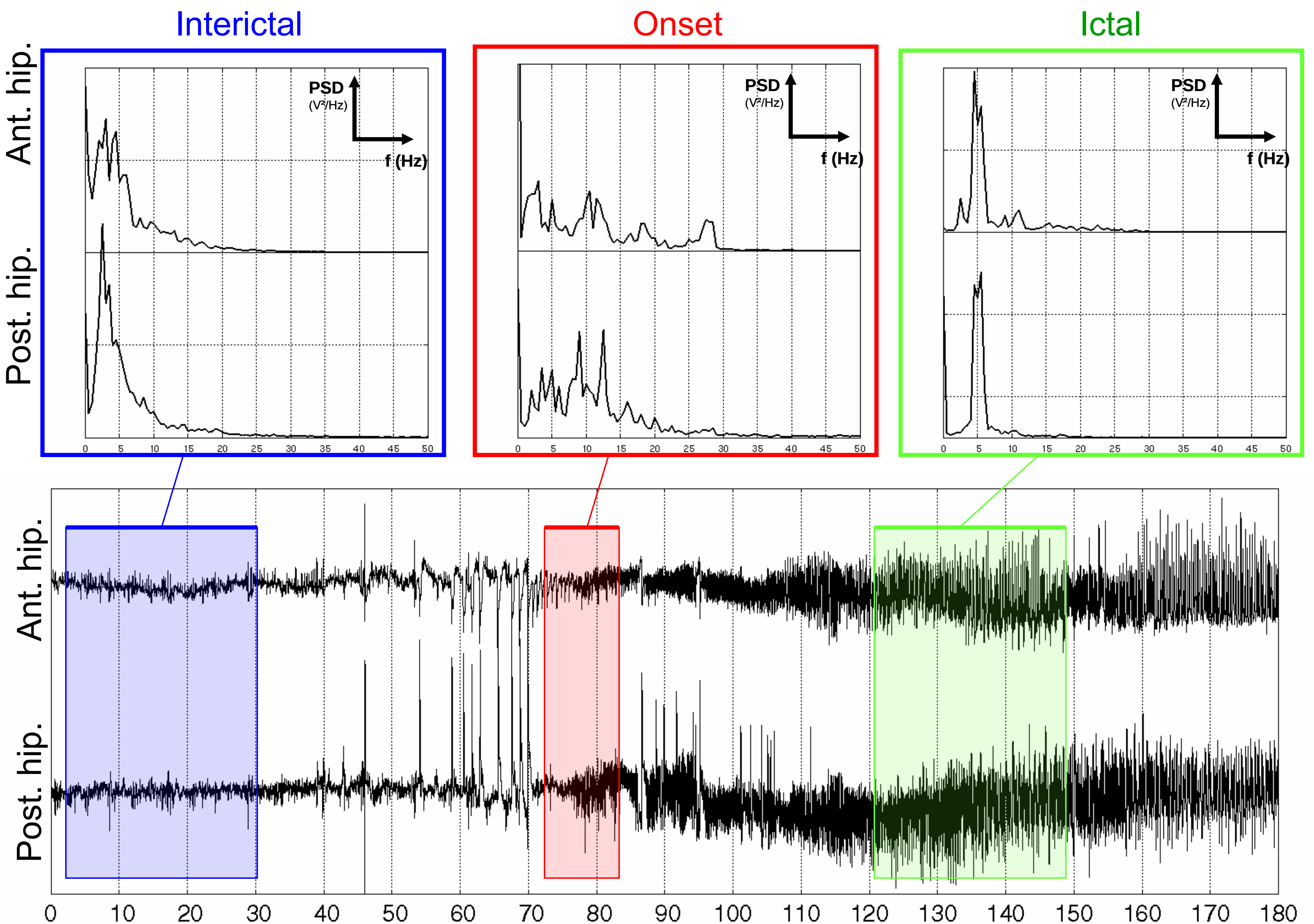


Power spectral densities

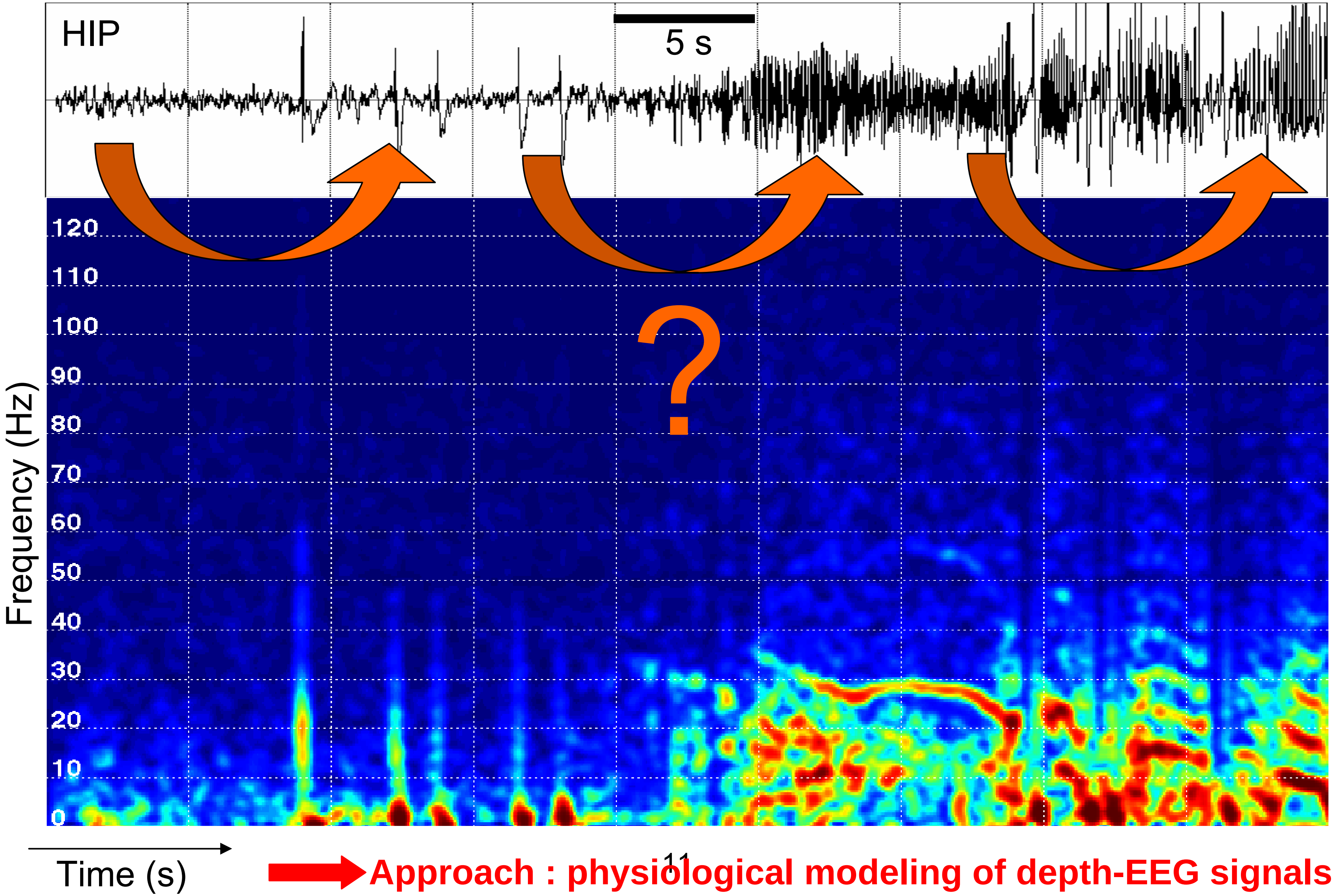




Power spectral densities

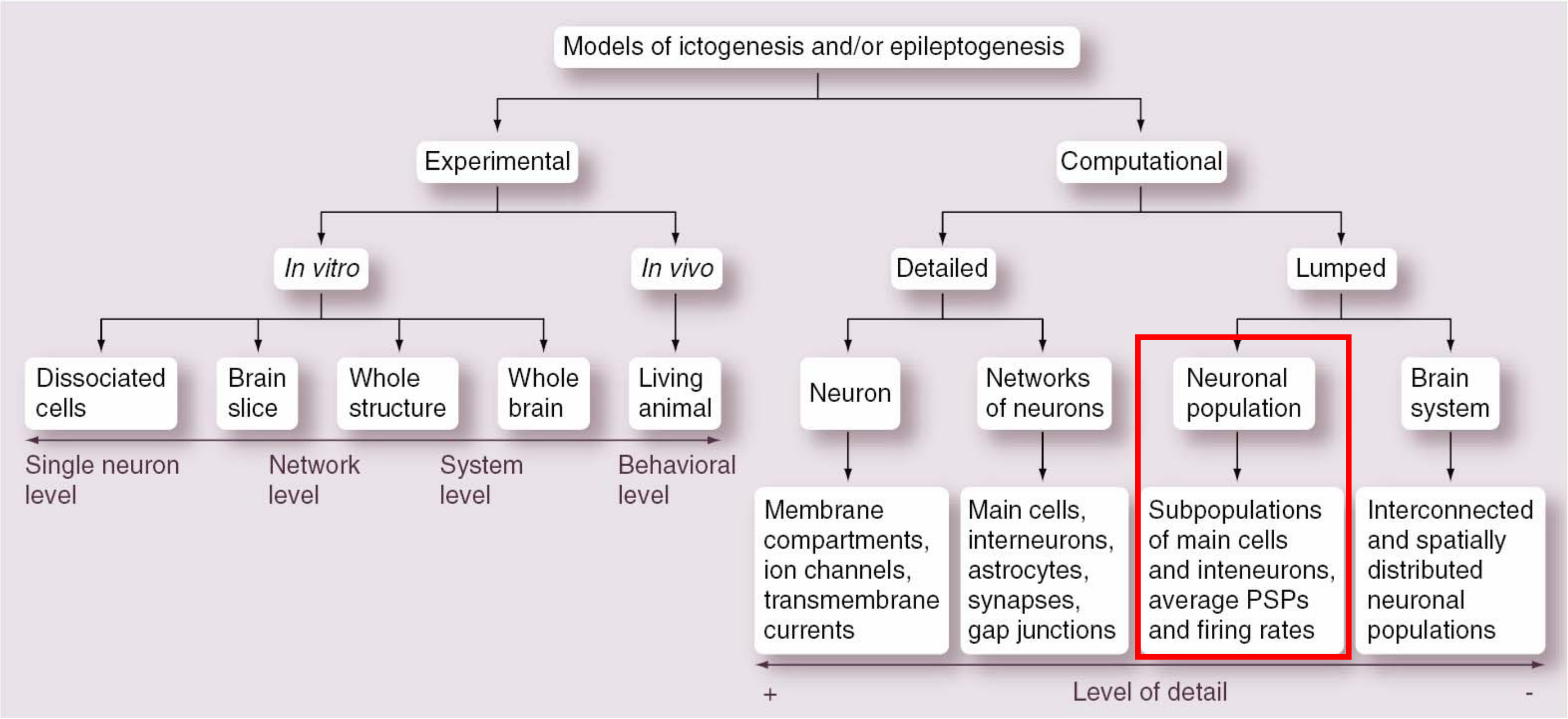


Time-frequency representation



Approach : physiological modeling of depth-EEG signals

Models used in the study of epileptic phenomena



F. Wendling, *Computational models of epileptic activity: a bridge between observation and pathophysiolocial interpretation*, Expert Review of Neurotherapeutics (2008)

Why a 'population-oriented' approach ?

- Main figures:
  - Cerebral cortex : 10 billions of neurons
  - Each neuron is connected to a large number of neurons (100 to 100 000 synapses/neuron)

- Interactions between subpopulations of cells → Ensemble dynamics (*positive or negative loops, feedback/feedforward)*

- EEG dynamics
  - reflection of these ensemble interactions
  - summation of PSP generated by a large number of cells activated quasi-synchronously

Background

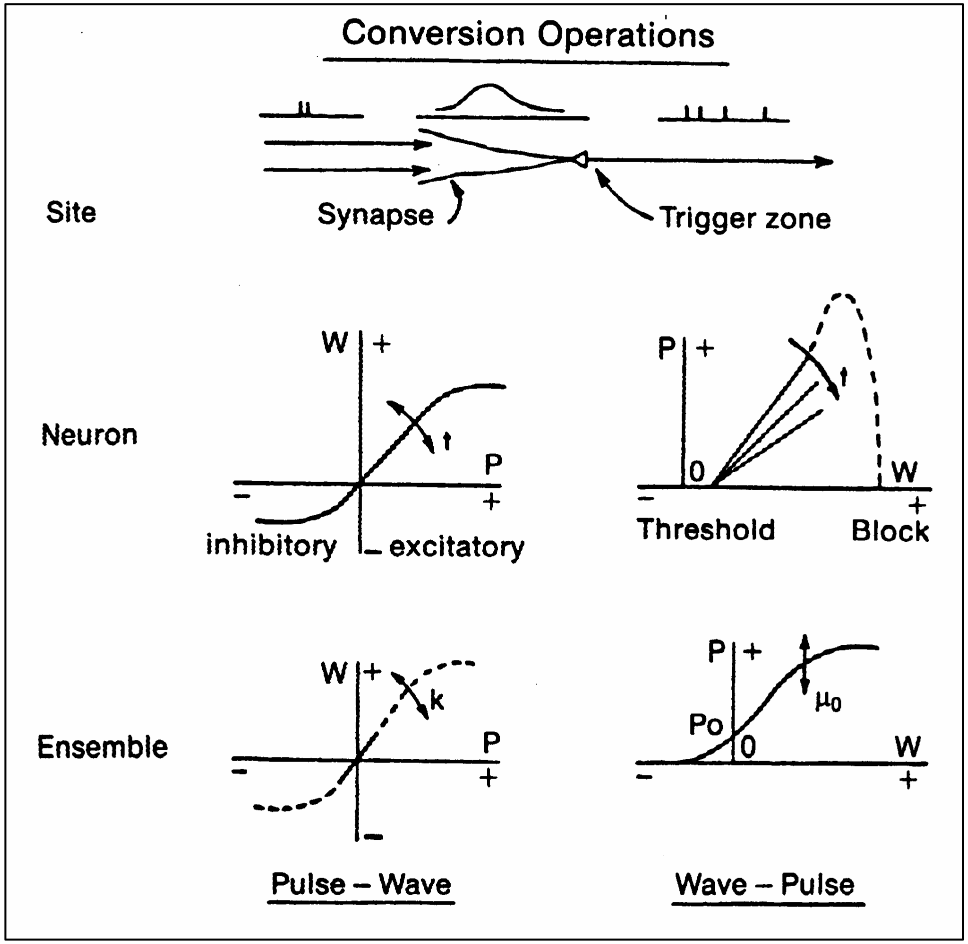
• Population models : Wilson & Cowan (1972), Freeman (~1970), Lopes da Silva (~1970), Jansen (1993, 1995), Wendling (2000), Suffczynski (2001), *and others*

• Main features

- Relevant variable: firing-rate

- Synaptic inputs sum linearly into the soma (mean-field approximation)

- Firing-rate computed from the total current delivered by synaptic inputs



W.J. Freeman, *Tutorial on neurobiology: From single neurons to brain chaos*, Int. J. Bif. Chaos, 1992

Example : Freeman 's model (1/2)

Olfactory system (*receptors → olf. bulb → Ant olf. nucleus → prepyiform cortex*)

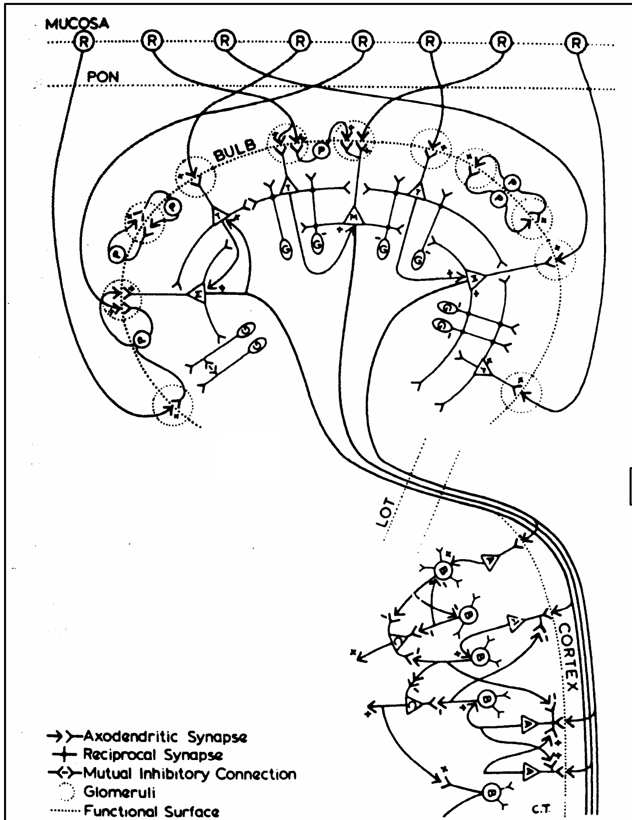
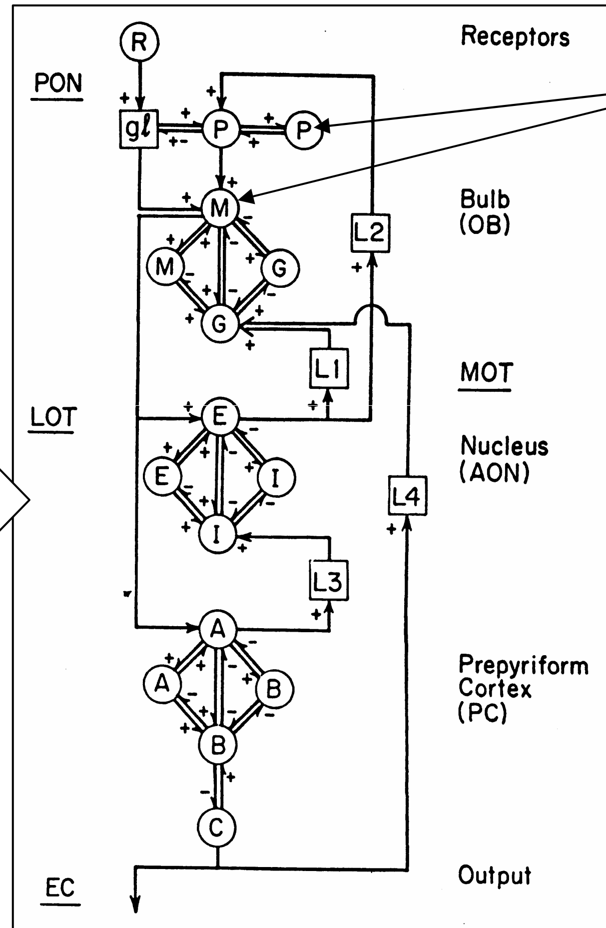


Figure 4.1. Diagram of the neuronal populations of the olfactory system according to Freeman (1975). Abbreviations as in Figure 4.2.



2nd order ordinary differential equation

Example : Freeman 's model (2/2)

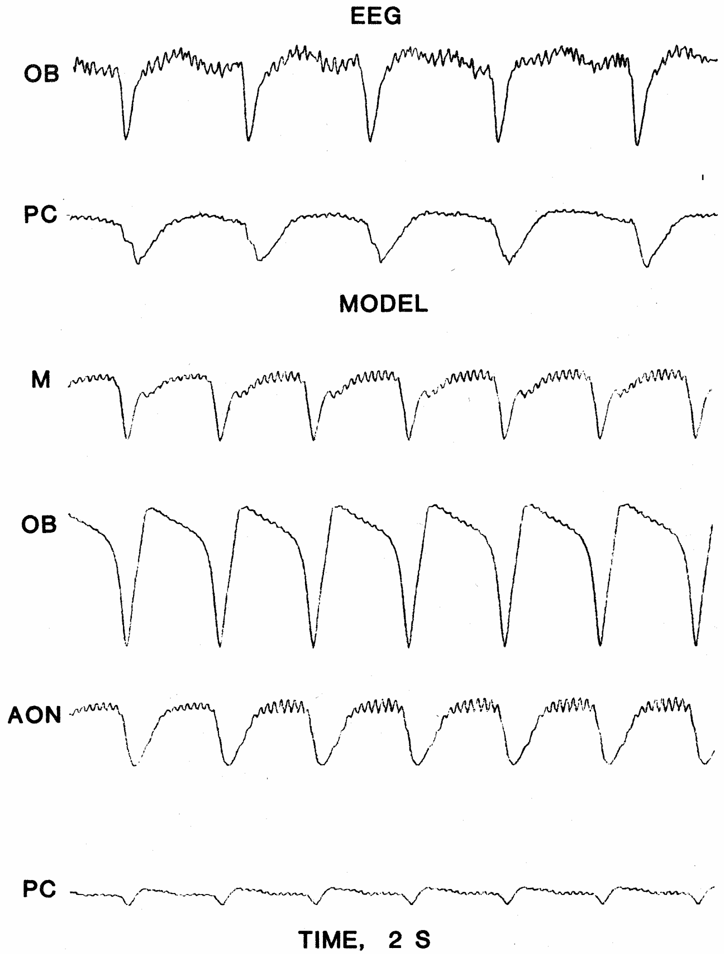


Fig. 8. Examples of 2-s time segments of EEGs recorded from a rat during a seizure, comparing these with the outputs of the model (see Fig. 3)

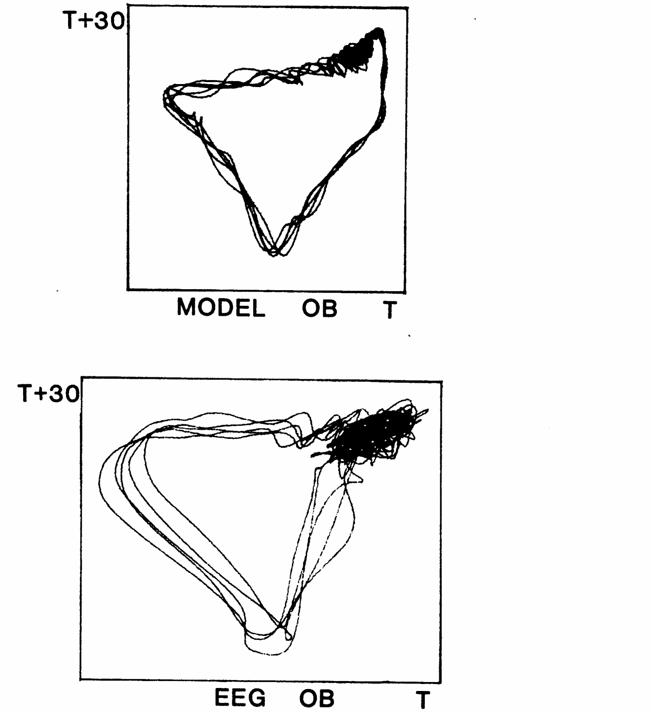
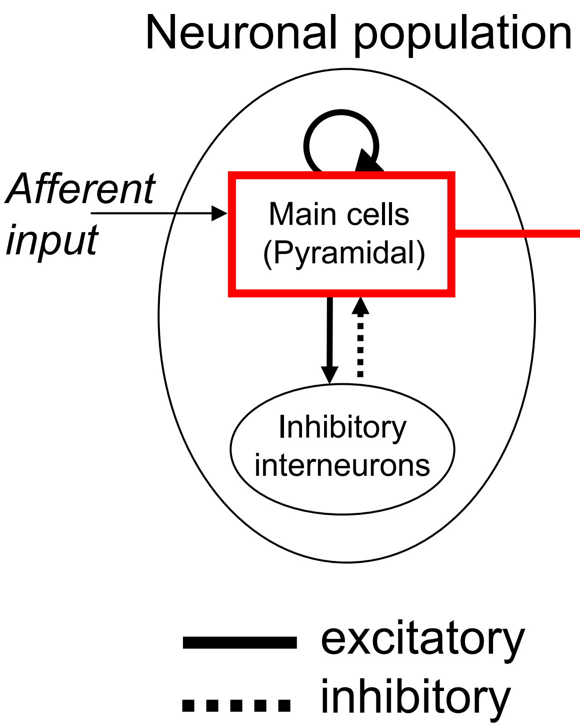
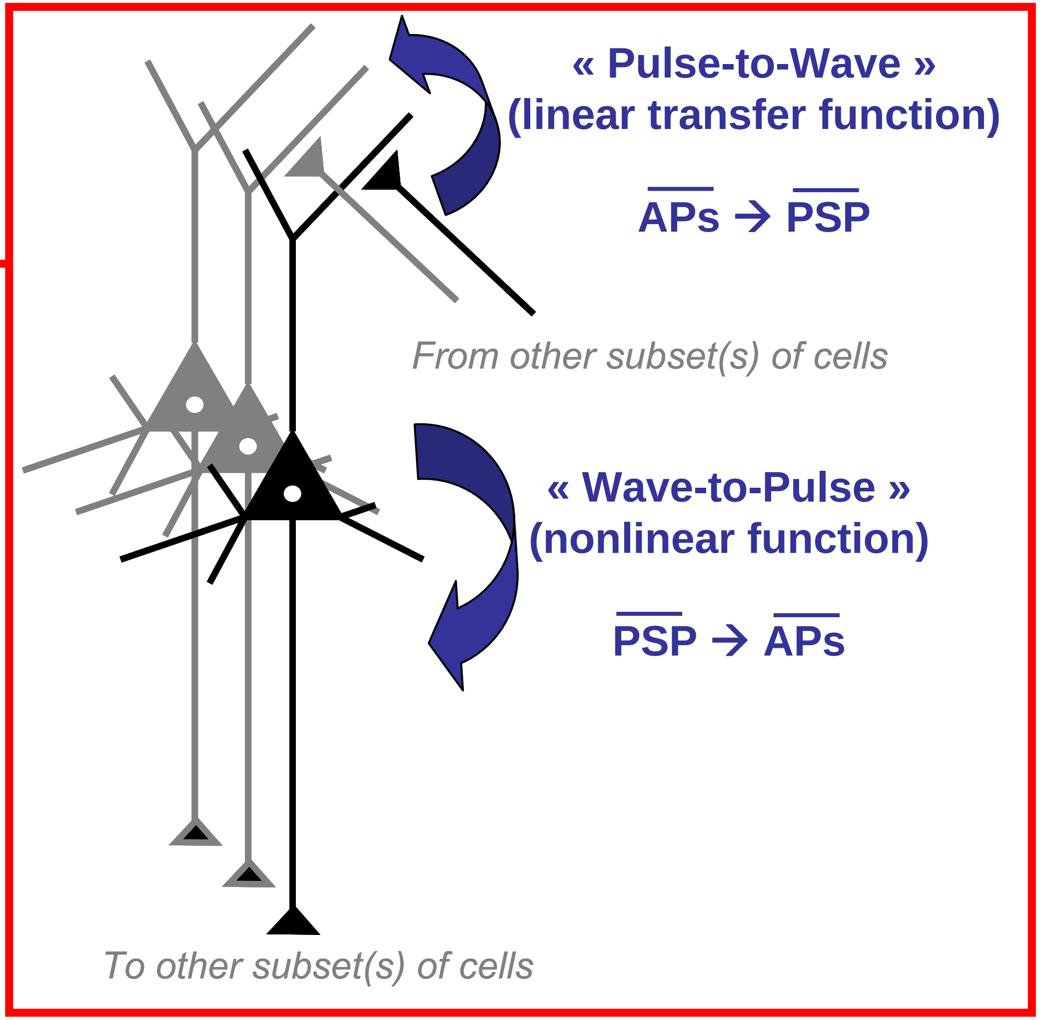


Fig. 9. Comparison of the output of the trace from granule cells (*G*) in the model (*above*) with the OB seizure from a rat (*below*), each plotted against itself lagged 30 ms in time (Ruelle plots). Duration is 1.0 s; rotation is counterclockwise

W.J. Freeman, *Simulation of chaotic EEG patterns with a Dynamic Model of the Olfactory System*, Biol. Cyb., 1987

Neuronal population model : basic principles



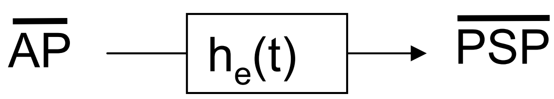


Wendling F, Chauvel P, "Transition to ictal activity in Temporal Lobe Epilepsy: insights from macroscopic models", in Computational Neuroscience in Epilepsy,. I. Soltesz & K. Staley eds., 2008

Pulse-to-wave and wave-to-pulse conversion operations

- **Pulse to wave** : the average membrane potential results from passive integration of PPS's related to afferent AP's (mainly at the dendrites)

  → represented by a second order transfer function of impluse response given by $h_e(t) = u(t).Aate^{-at}$ (excitatory case)

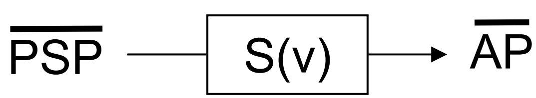


$$\dot{z}(t) = z_1(t)$$

$$\dot{z}_1(t) = Aa\,x(t) - 2a\,z_1(t) - a^2 z(t)$$

- **Wave to pulse** : the average density of action potentials fired by the neurons depends on a nonlinear transform of the average membrane potential (threshold + saturation effect)

→ represented by the sigmoid function



$$S(v) = \frac{2e_0}{1 + e^{r(v_0 - v)}}$$

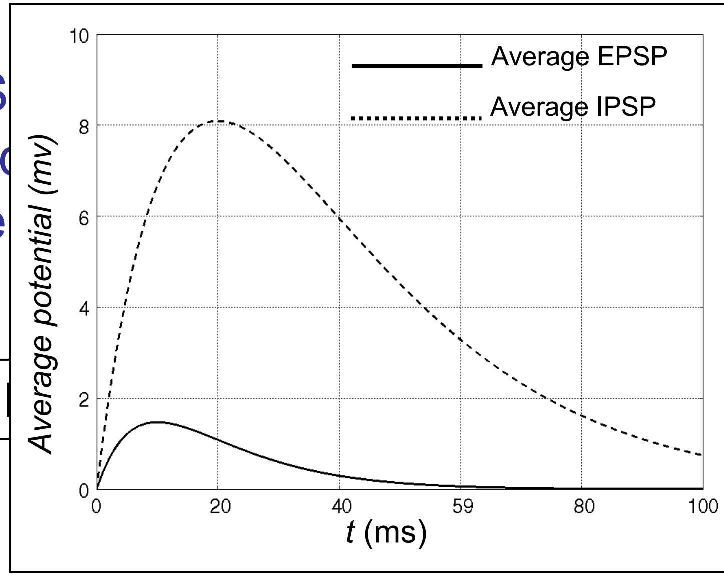
Pulse-to-wave and wave-to-pulse conversion operations

- **Pulse to wave** : ... al results from passive integration of PPS ... nly at the dendrites)

  → represente ... nction of impluse response give ... tory case)

⇨ $\overline{\text{AP}}$ — ... $t)$

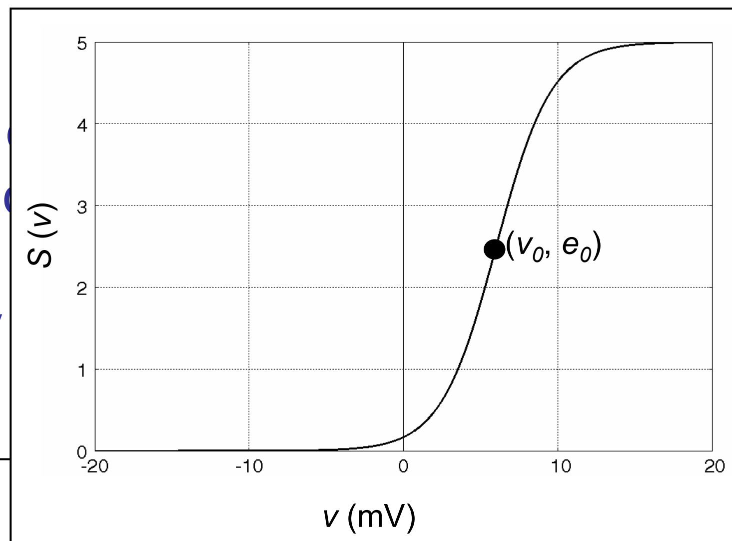
... $x(t) - 2a\,z_1(t) - a^2 z(t)$



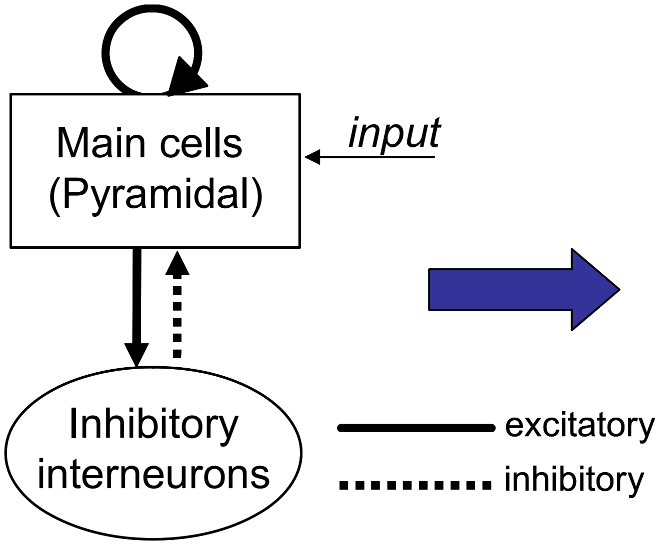
- **Wave to pulse** : ... otentials fired by the neurons depends ... average membrane potential (threshol ...

→ represented by ...

⇨ $\overline{\text{PSP}}$ — ... $\dfrac{2e_0}{1+e^{r(v_0-v)}}$



Block diagram, equations and generated signals



Nonlinear dynamical system (ODEs)

$$\dot{y}_0(t) = y_3(t)$$

$$\dot{y}_3(t) = AaS(y_1 - y_2) - 2ay_3(t) - a^2 y_0(t)$$

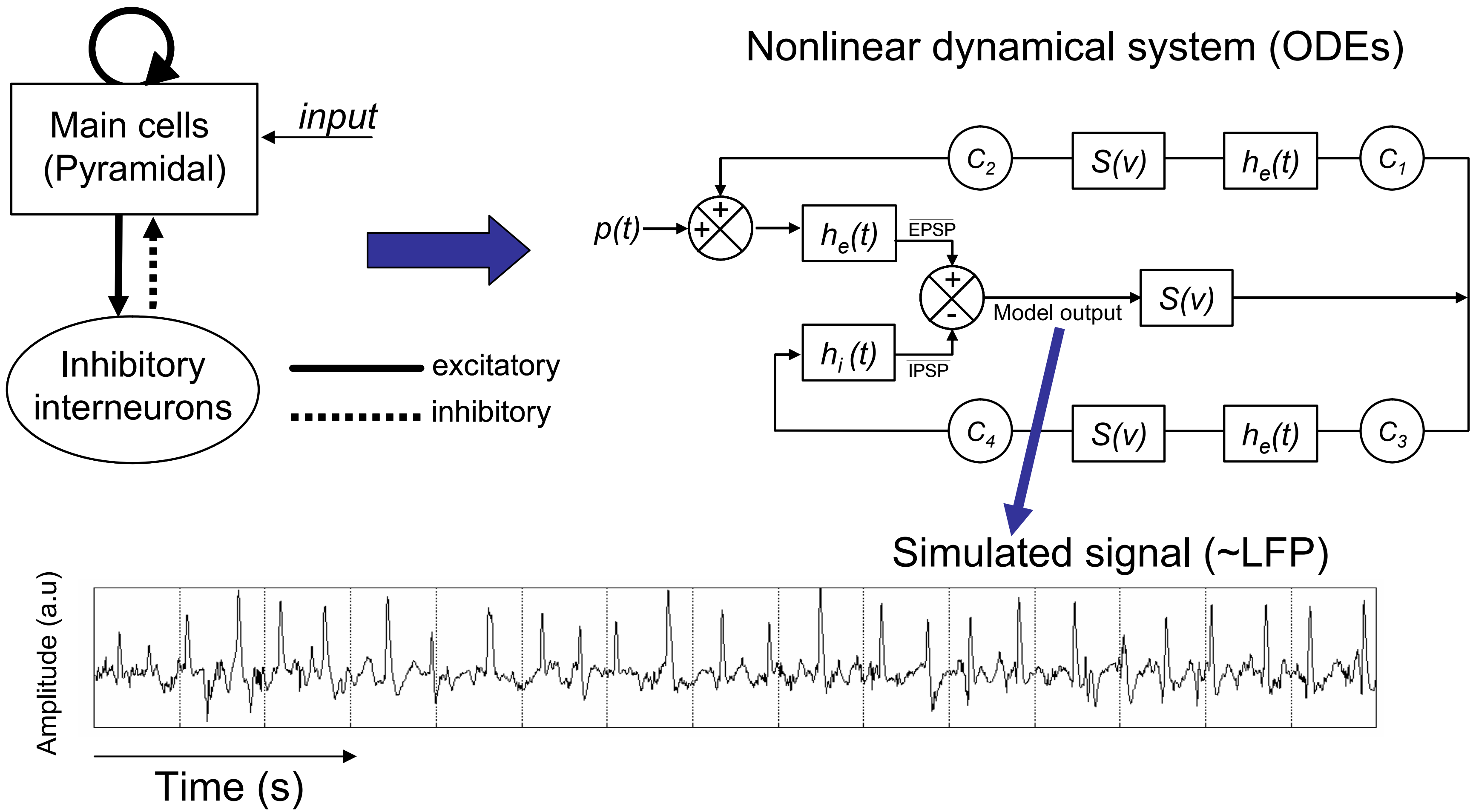
$$\dot{y}_1(t) = y_4(t)$$

$$\dot{y}_4(t) = Aa\{p(t) + C_2 S[C_1 y_0(t)]\} - 2ay_4(t) - a^2 y_1(t)$$

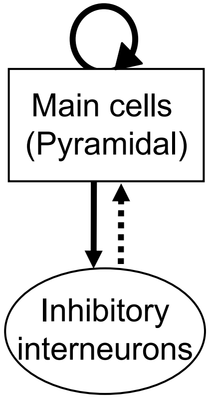
$$\dot{y}_2(t) = y_5(t)$$

$$\dot{y}_5(t) = Bb\{C_4 S(C_3 y_0(t)\} - 2by_5(t) - b^2 y_2(t)$$

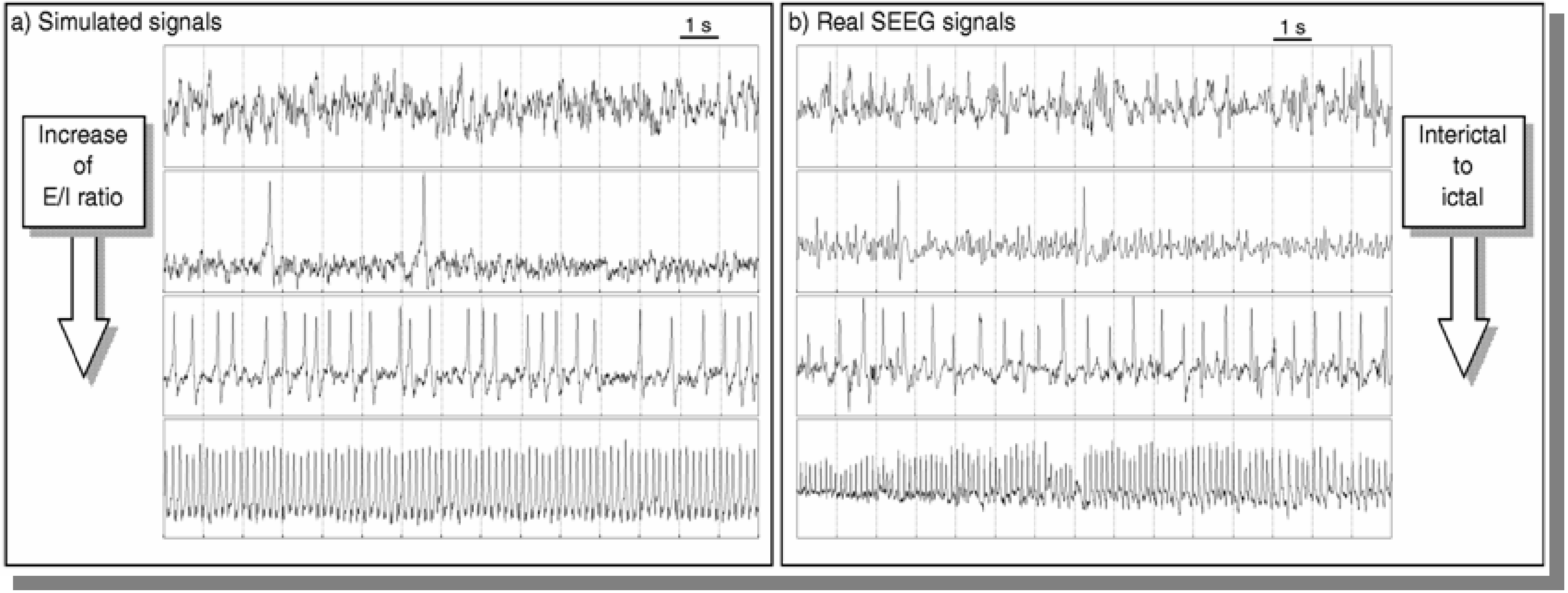
Block diagram, equations and generated signals



Single population model



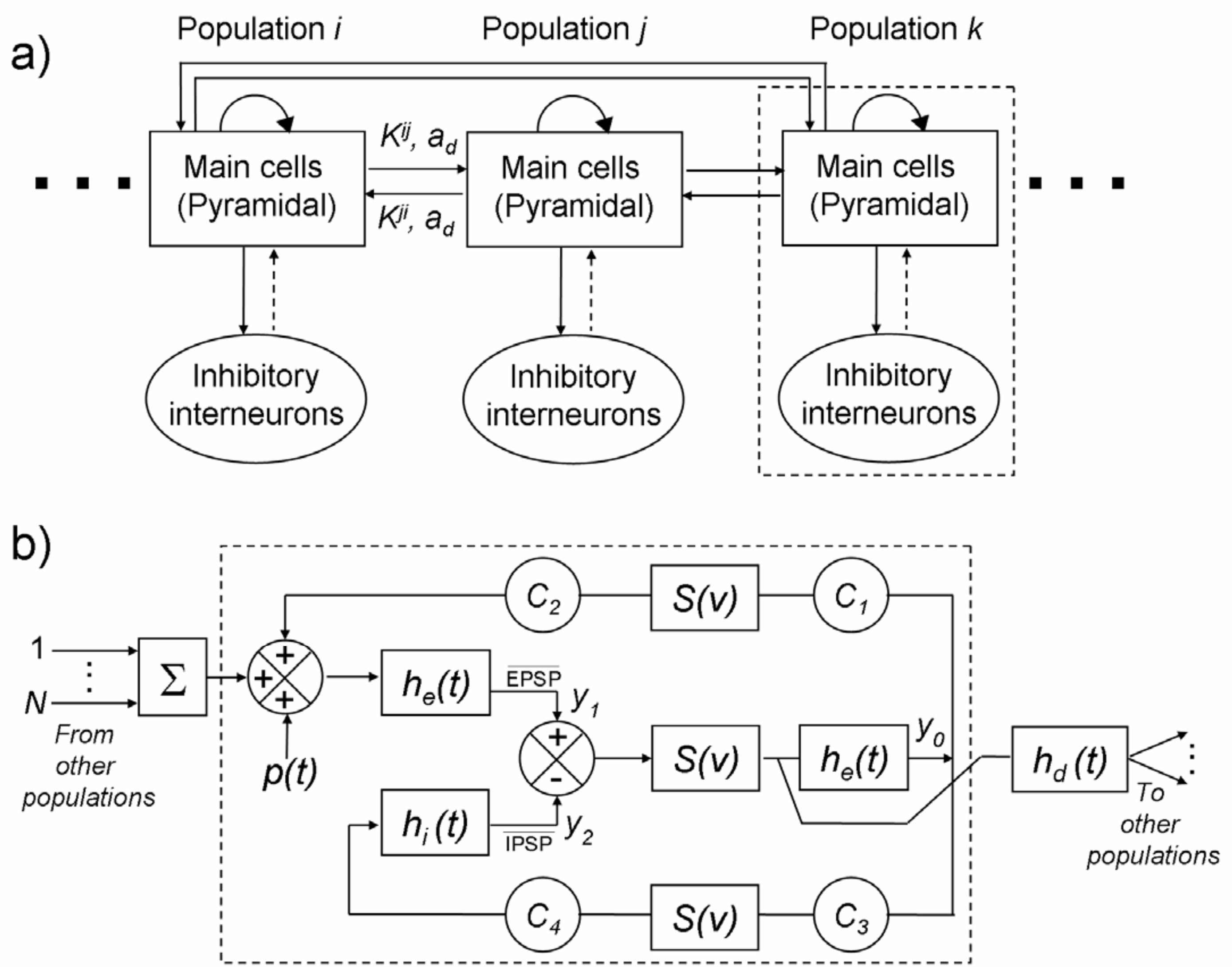
- Model configuration :
  Single population + progressive increase of the E/I ratio (excitation/inhibition)



- Similarity with real intracerebral EEG signals

Wendling et al., Biol. Cyb., 2000

Model of multiple coupled populations



Influence of couplings

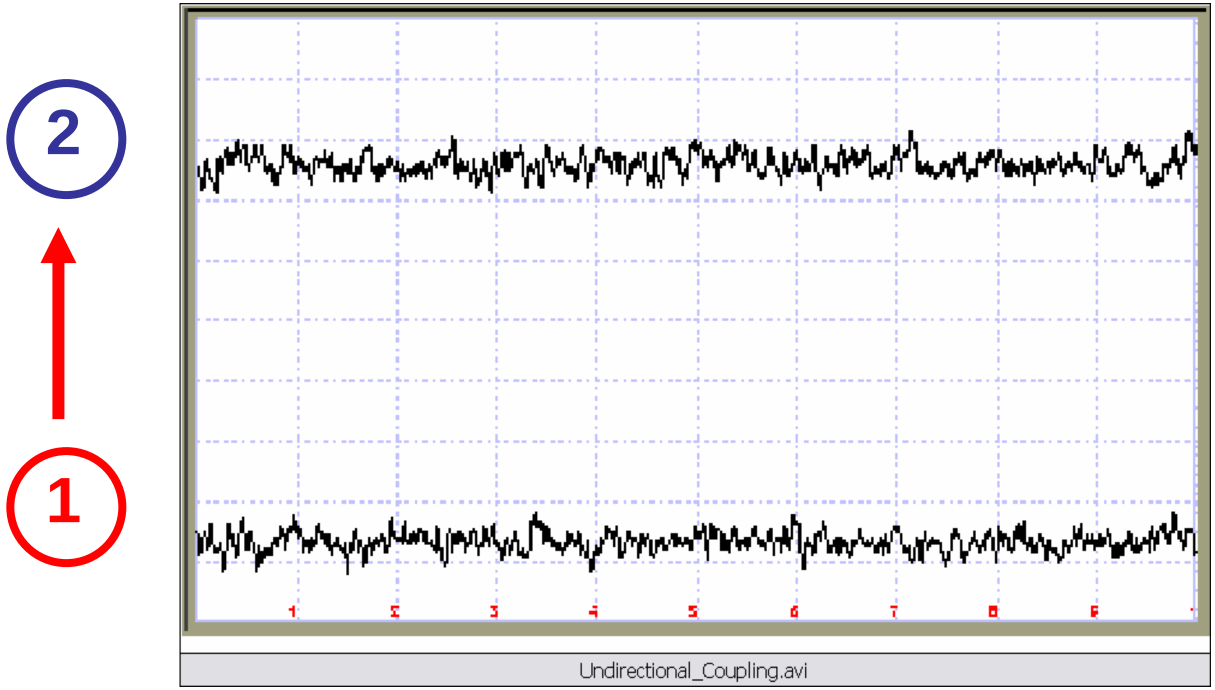
- Model configuration :
  3 populations, unidirectional couplings: *isolated spikes propagate from P1 to P3*

- Introduction of a recurrent connection:
  isolated spikes ⇨ *sustained discharges of spikes*

- Real intracerebral EEG signals recorded during seizure (TLE)

Wendling et al., Biol. Cyb., 2000

Exemple of model simulation

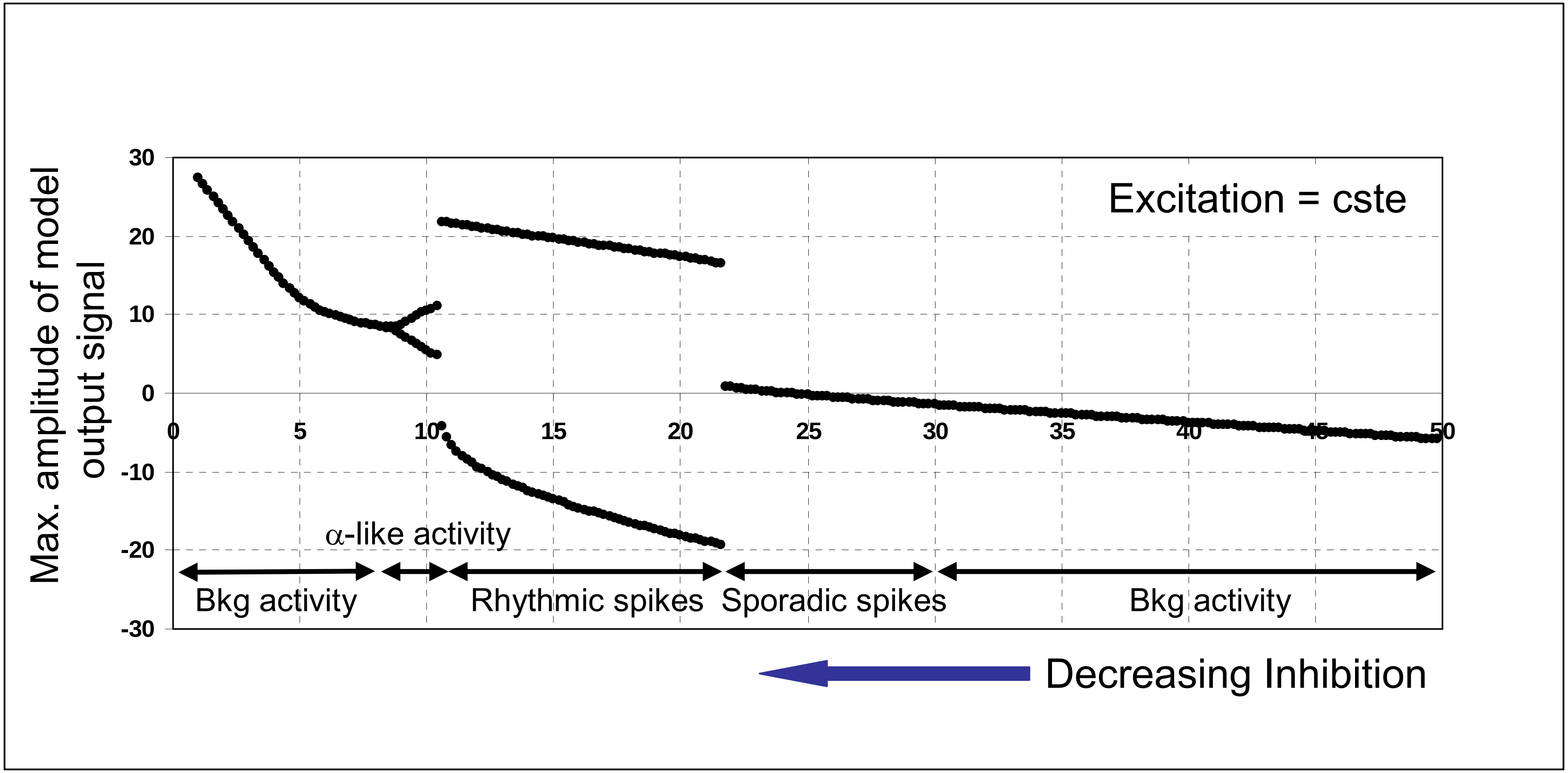


Legends

E/I + : increase of the Excitation/Inhibition ratio

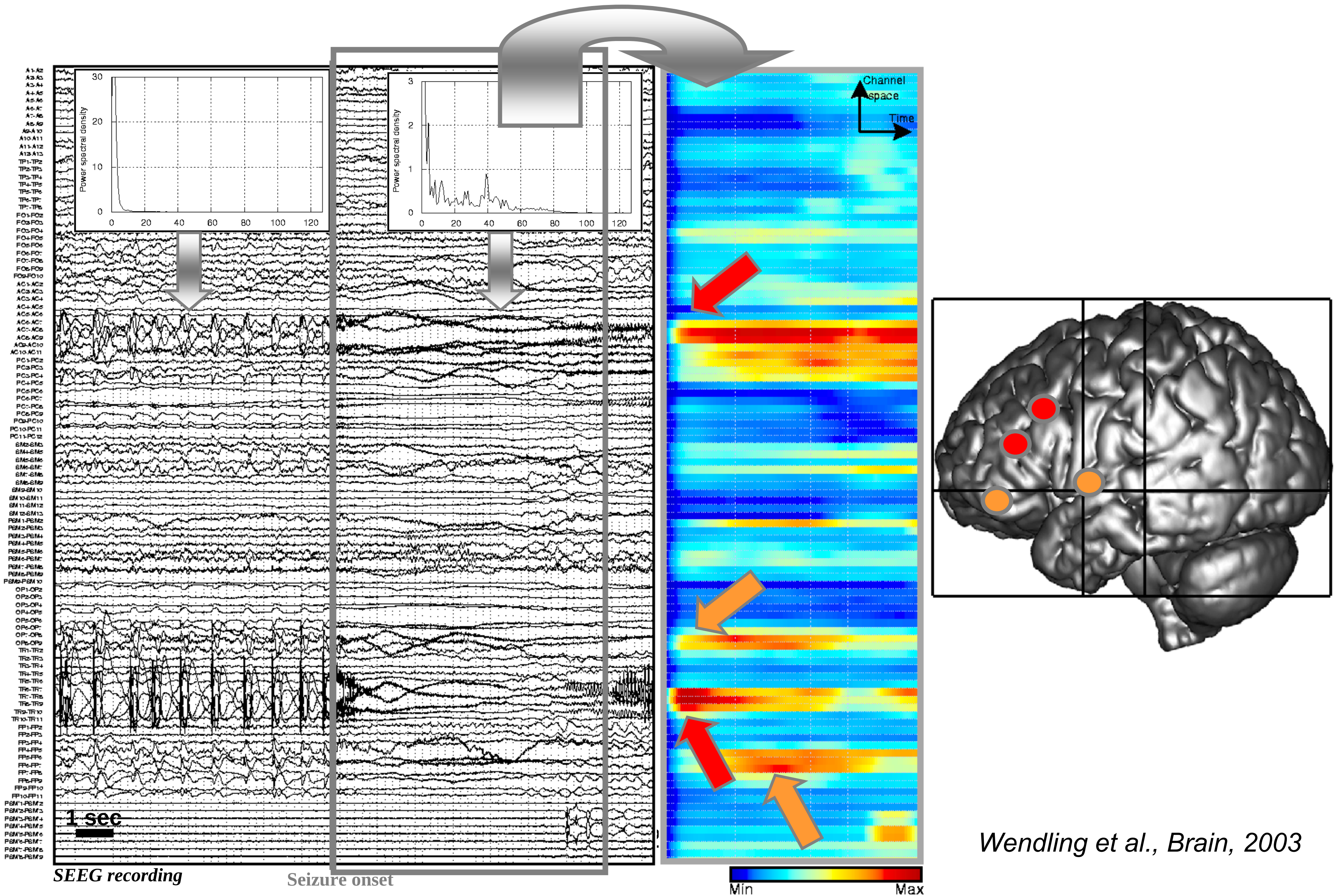
↑ **C+** : increase of the coupling from P1 to P2

Bifurcation diagram



- Simulated signals exhibit properties similar to those of real signals
- **However** some activities are not represented in the model (fast onset activity)

Fast onset activity



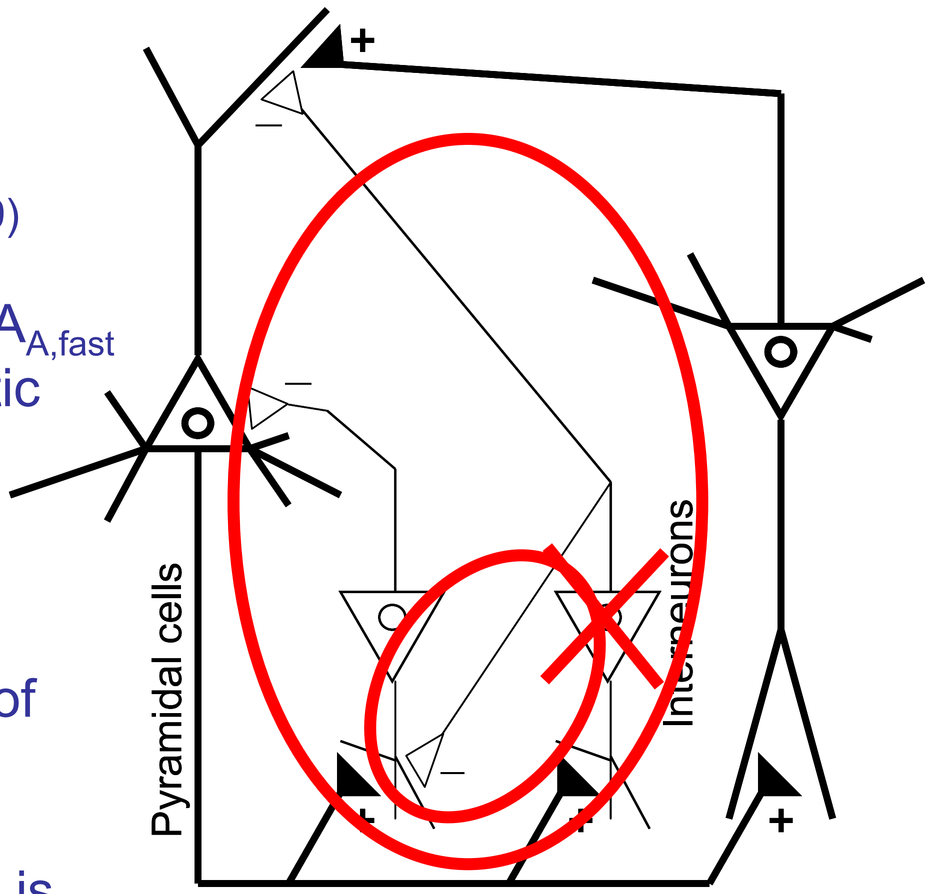
Wendling et al., Brain, 2003

Data related to the topic

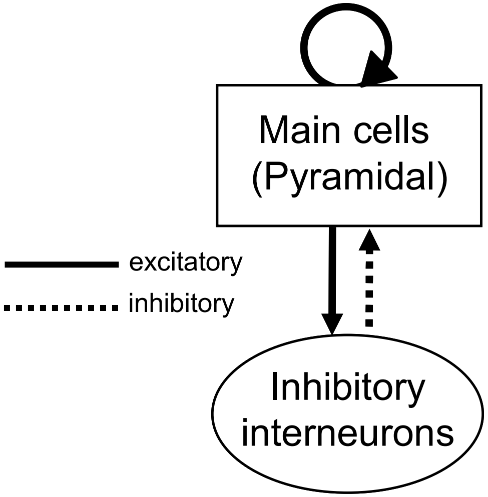
1) The generation of gamma-band activities is probably linked to the behavior of interneurons (« inhibition-based rhythms ») (*Traub*, *Jefferys*, …, 1999)

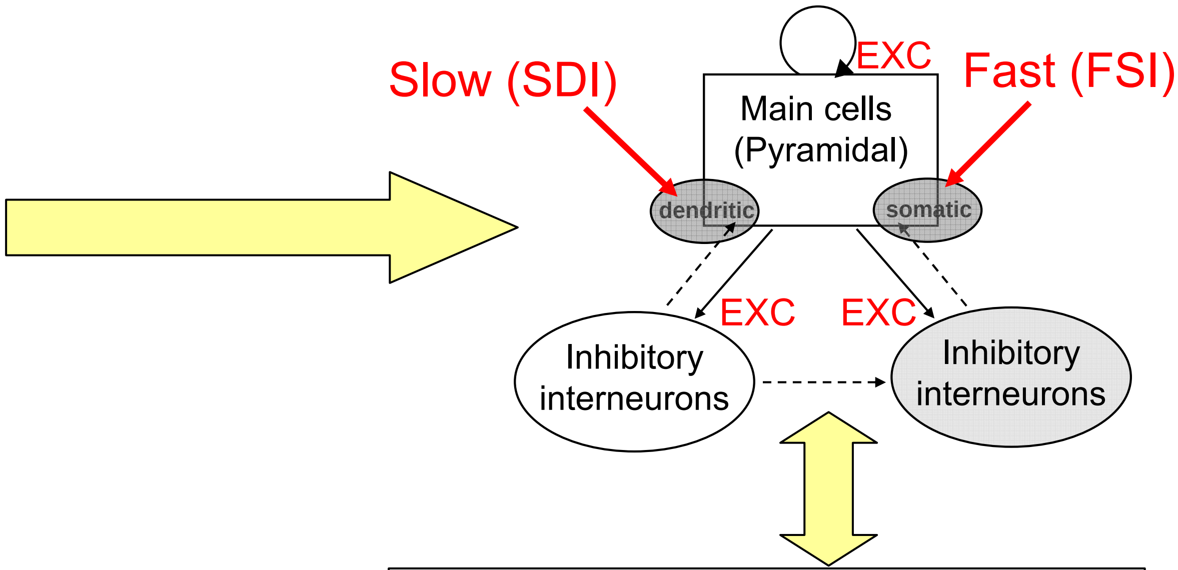
2) Somatic interneurons activity ($GABA_{A,fast}$ circuit) is depressed by that of dendritic interneurons ($GABA_{A,slow}$) → nested rhythms (*Banks*, Neuron 2000)

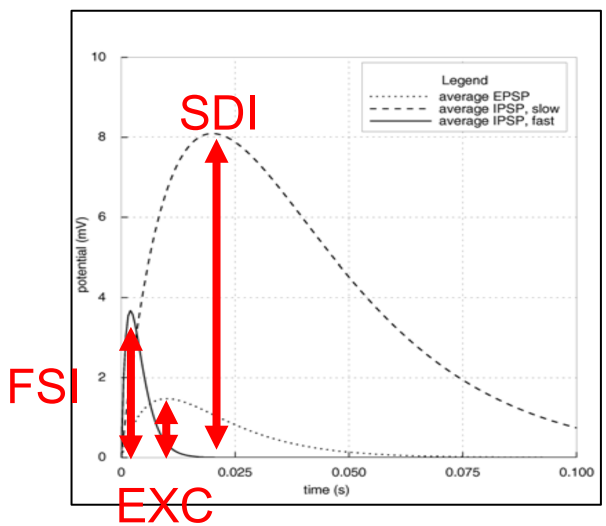
3) In the experimental model of focal epilepsy (kainate acid), the alteration of GABAergic inhibition is not uniform: dendritic-projecting interneurons are altered whereas perisomatic inhibition is preserved
(*Cossart et al.*, Nature Neurosc. 2001)

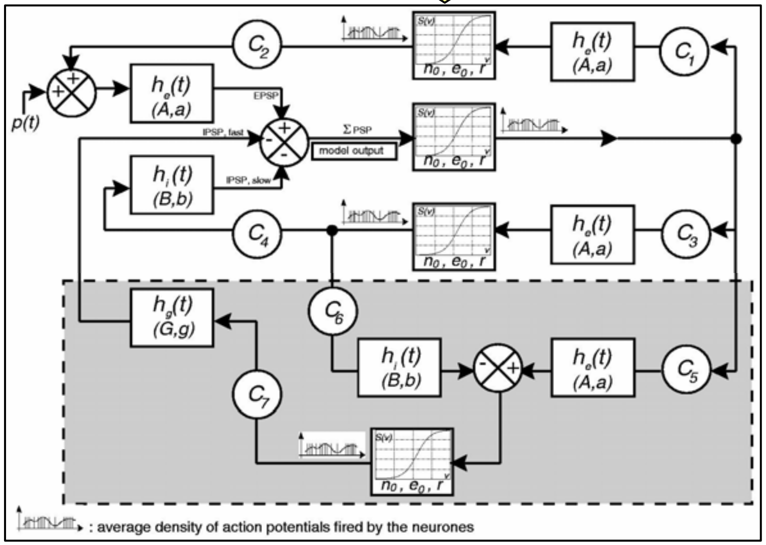


From generic to specific model



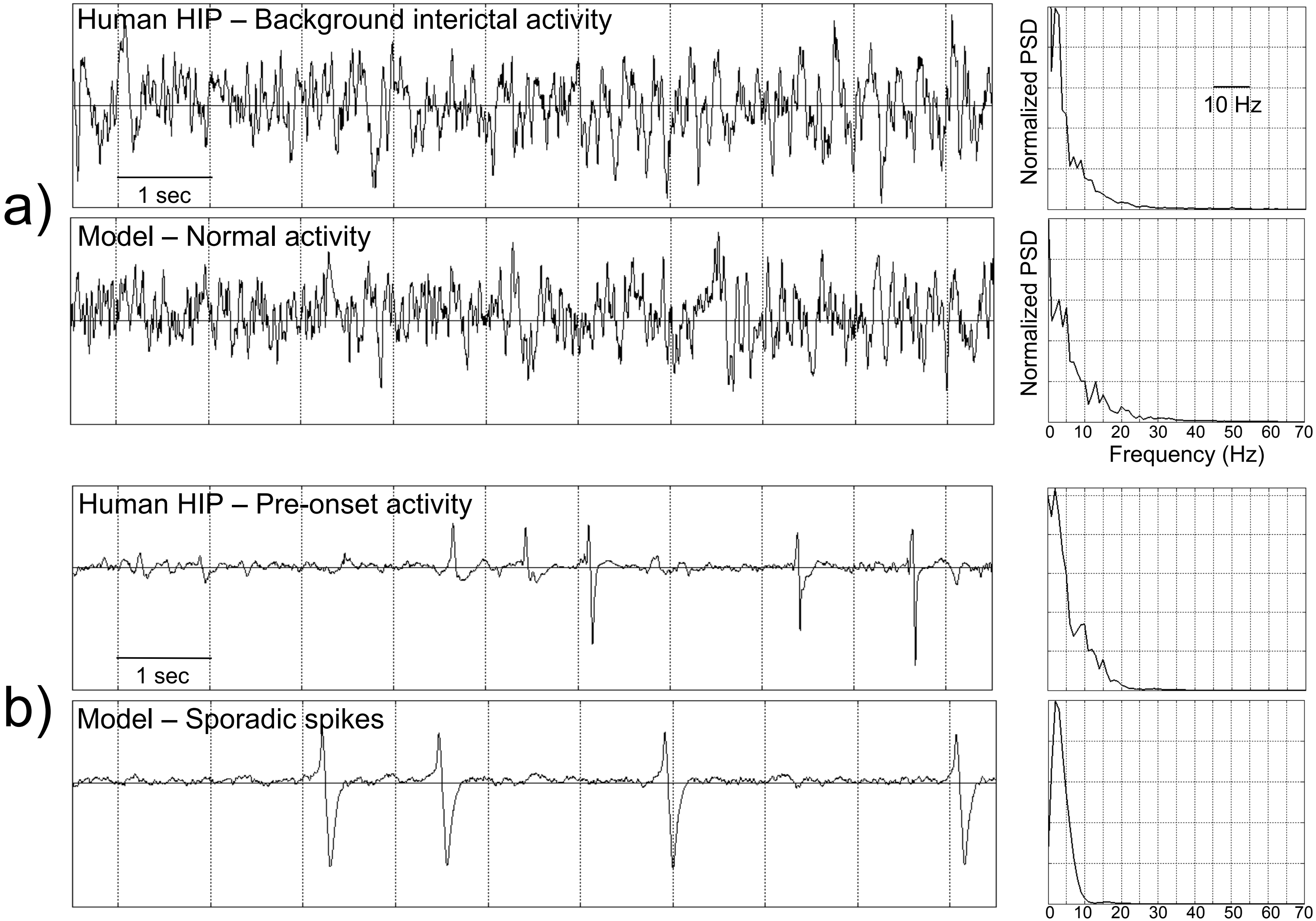




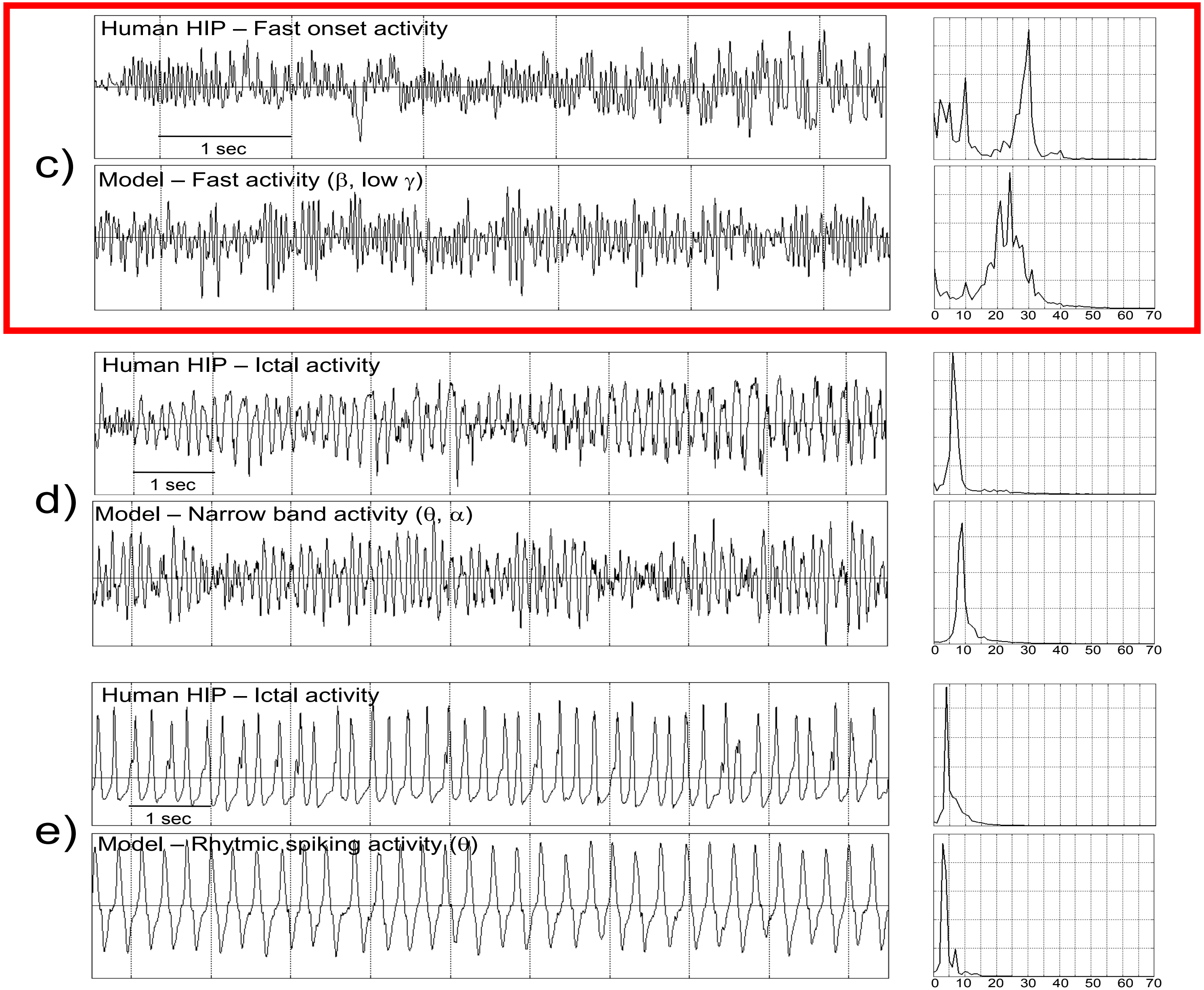


Wendling et al., European J. Neurosc., 2002, J. Clin Neurophysiol. 2005

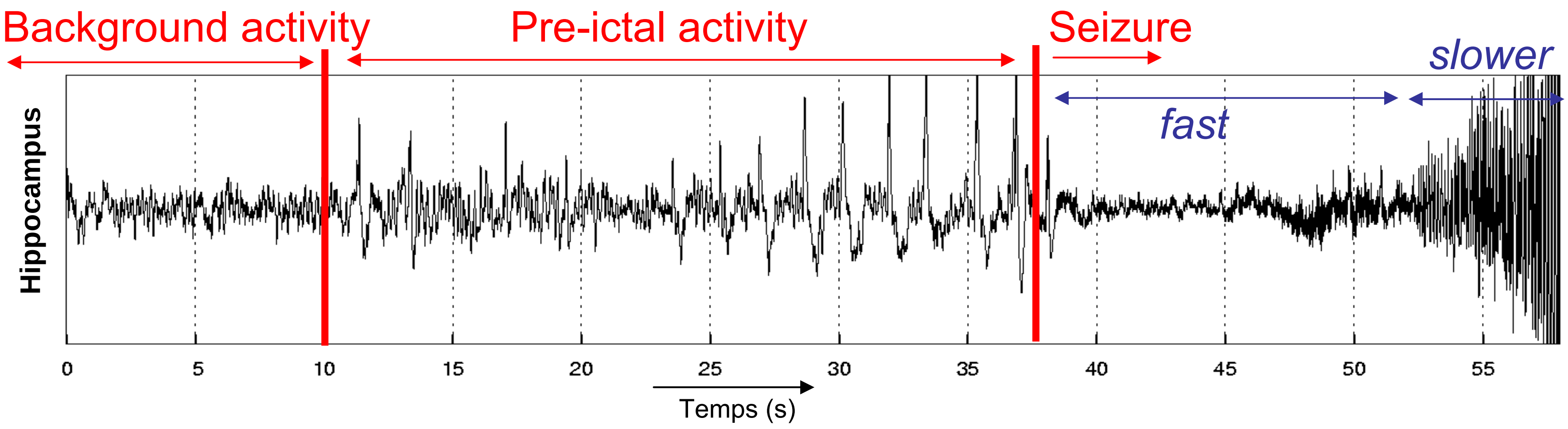
Simulated activity vs Real activity (interictal)



Simulated activity vs Real activity (ictal)



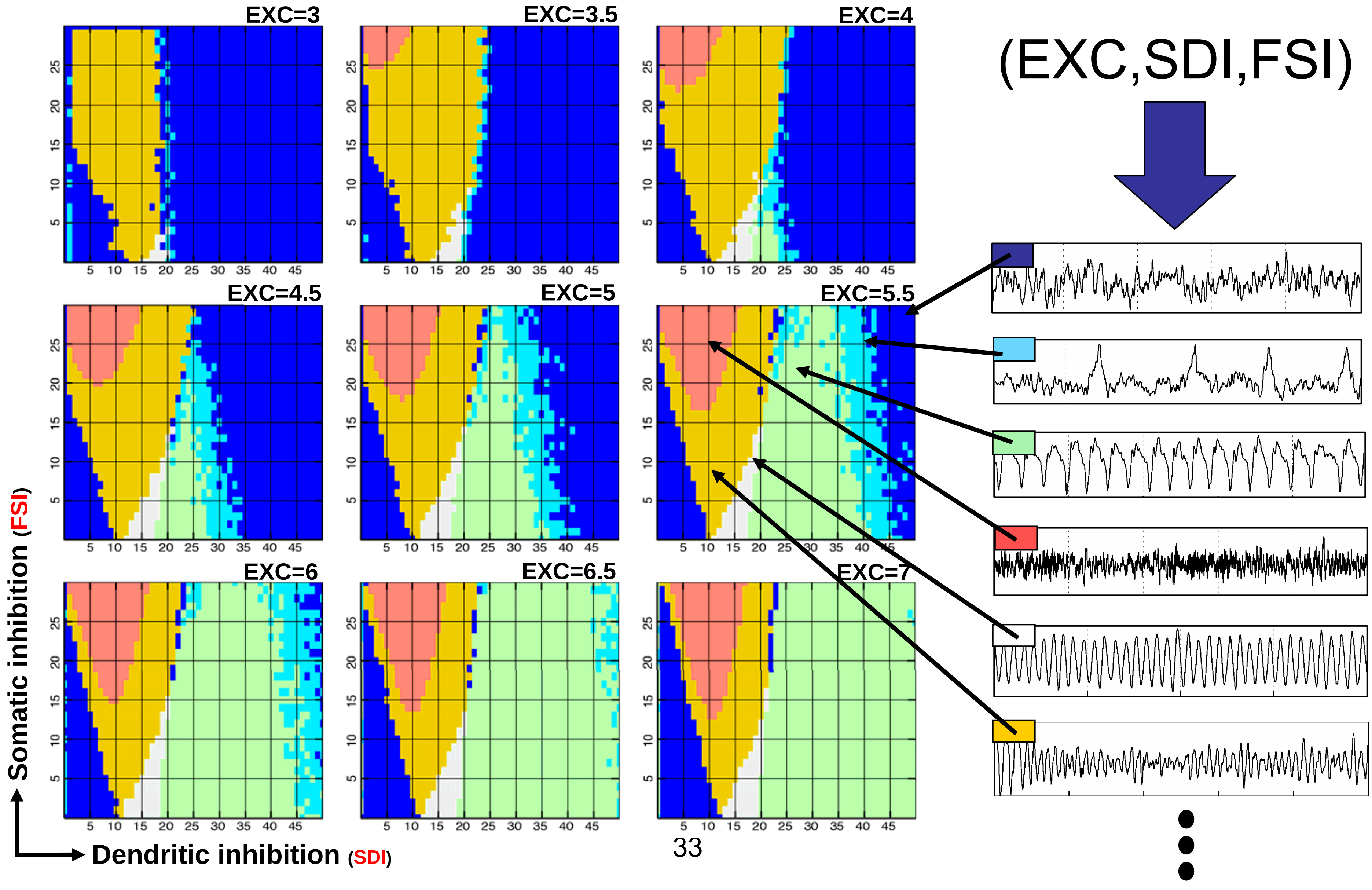
Transitions of dynamics



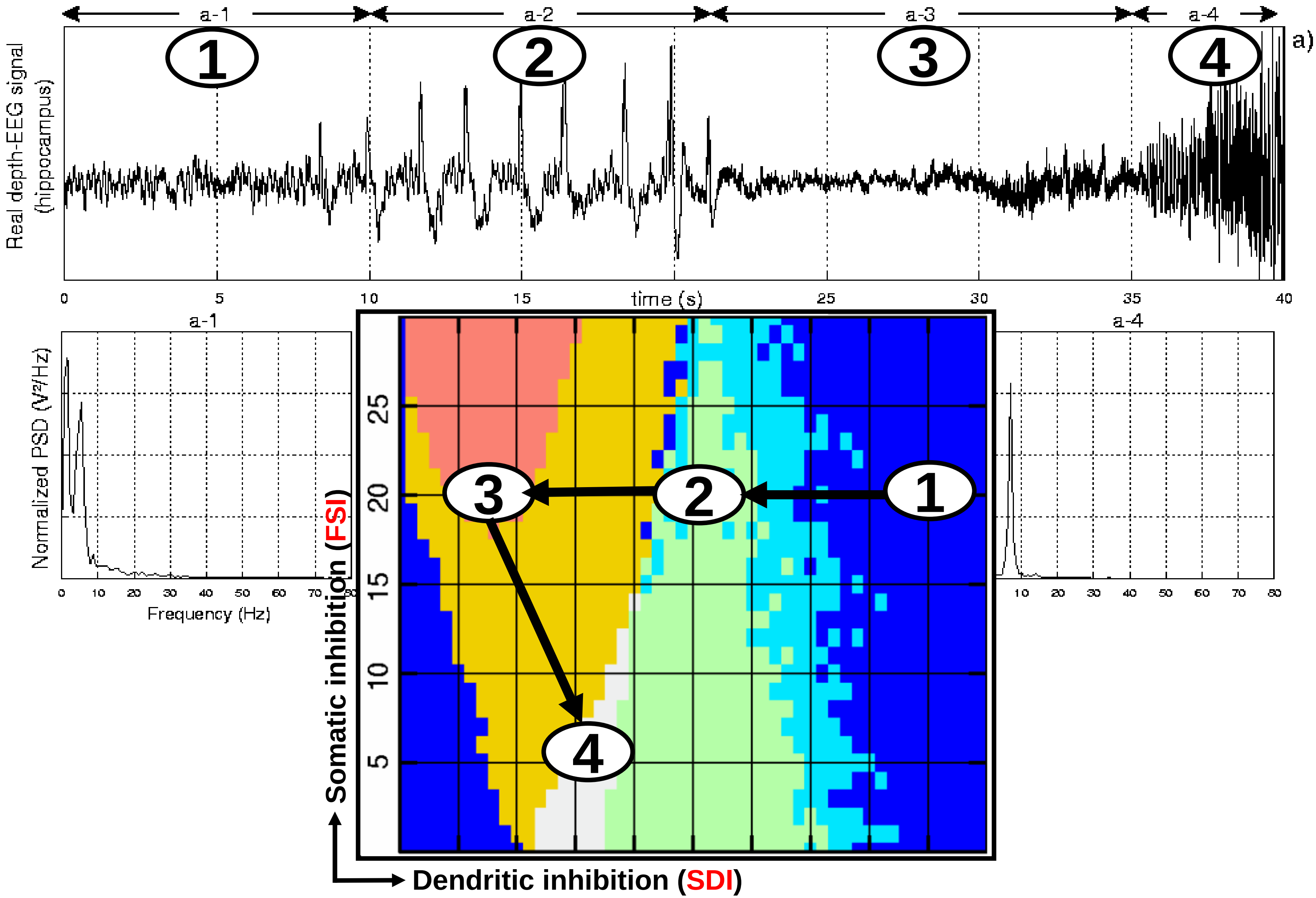
Goal: interpret, using the model, observed transitions as a function excitation- and inhibition-related parameters (**EXC**, **SDI**, **FSI**)

➡ **Parameter sensitivity analysis**

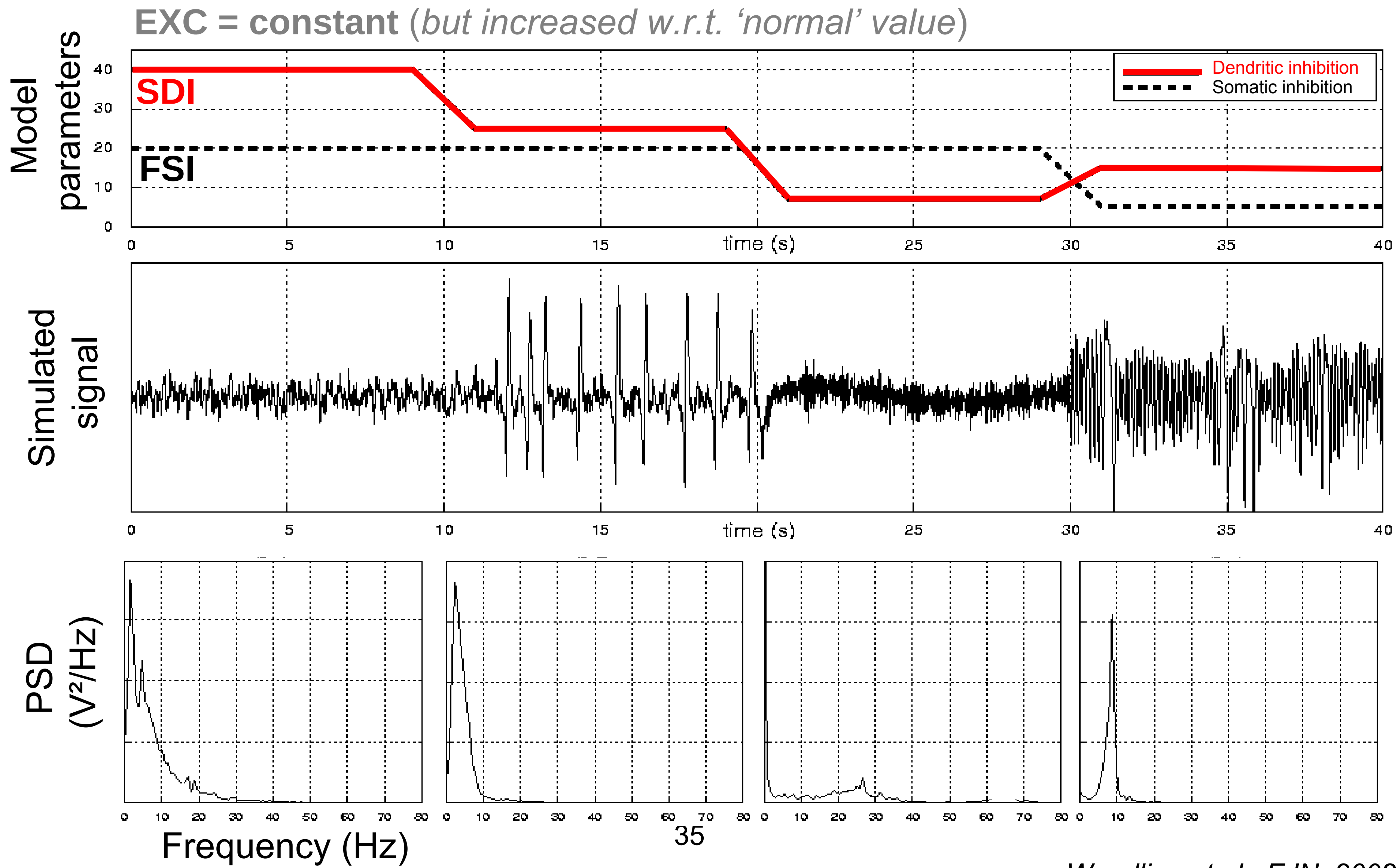
Parameter space and classes of simulated signals



Interictal → ictal transition: model-based interpretation

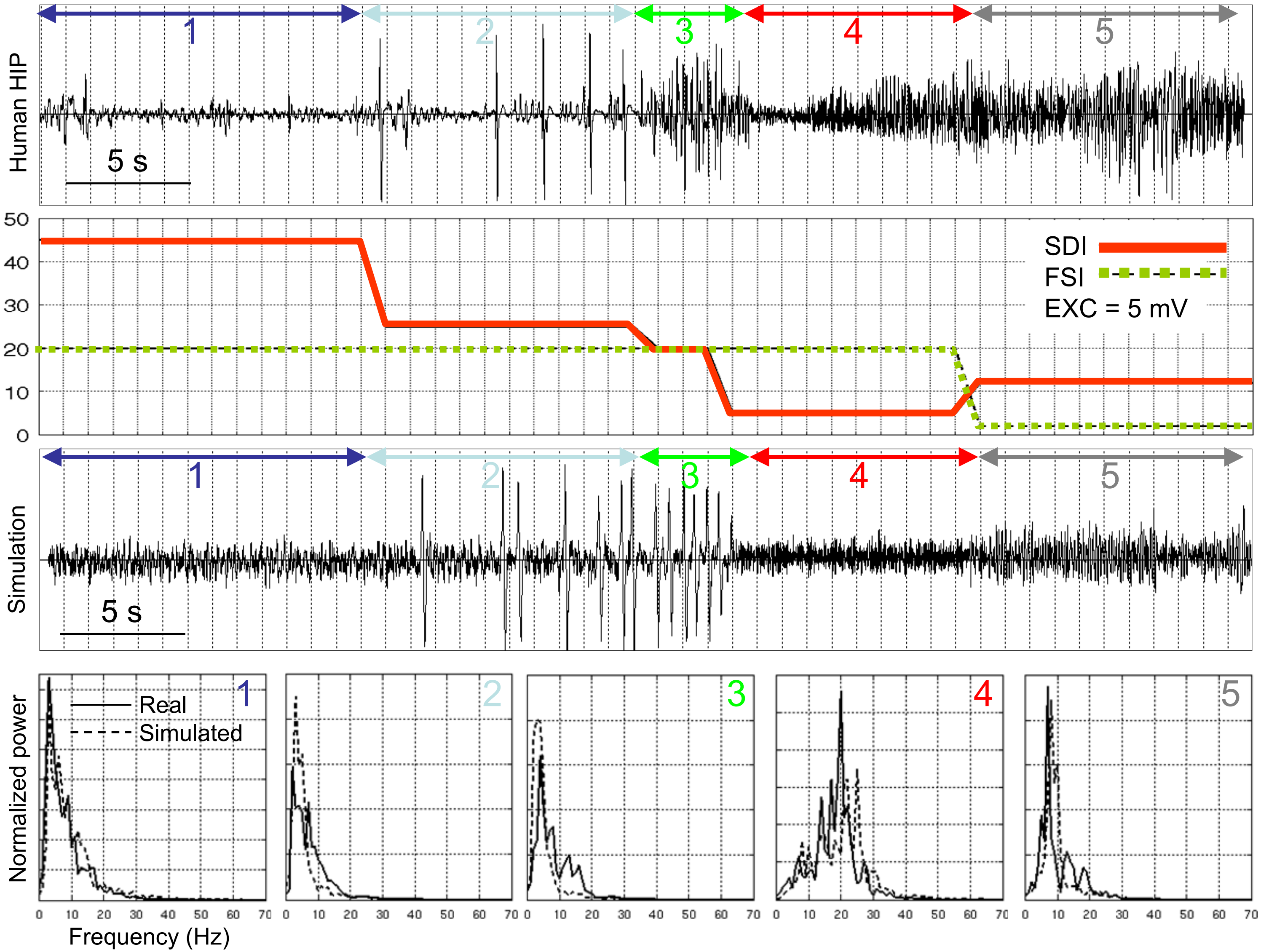


Simulation of the 'interictal to ictal' transition



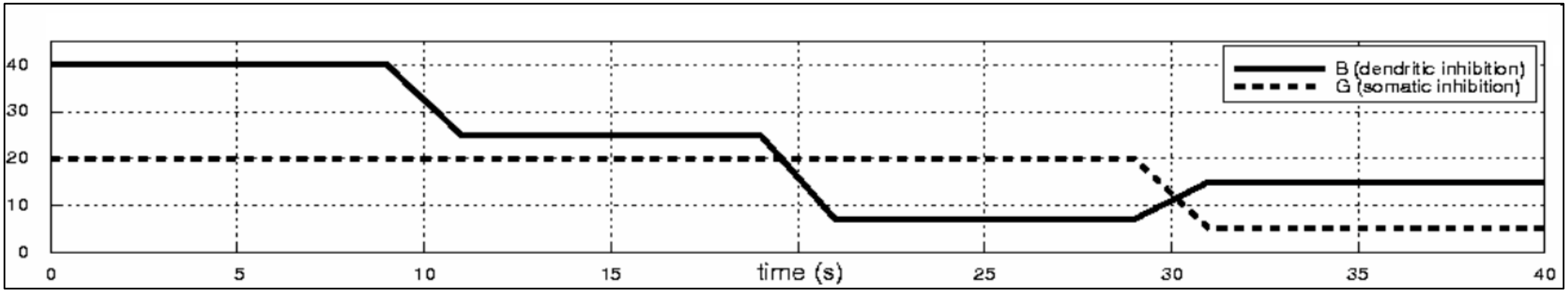
Wendling et al., EJN, 2002

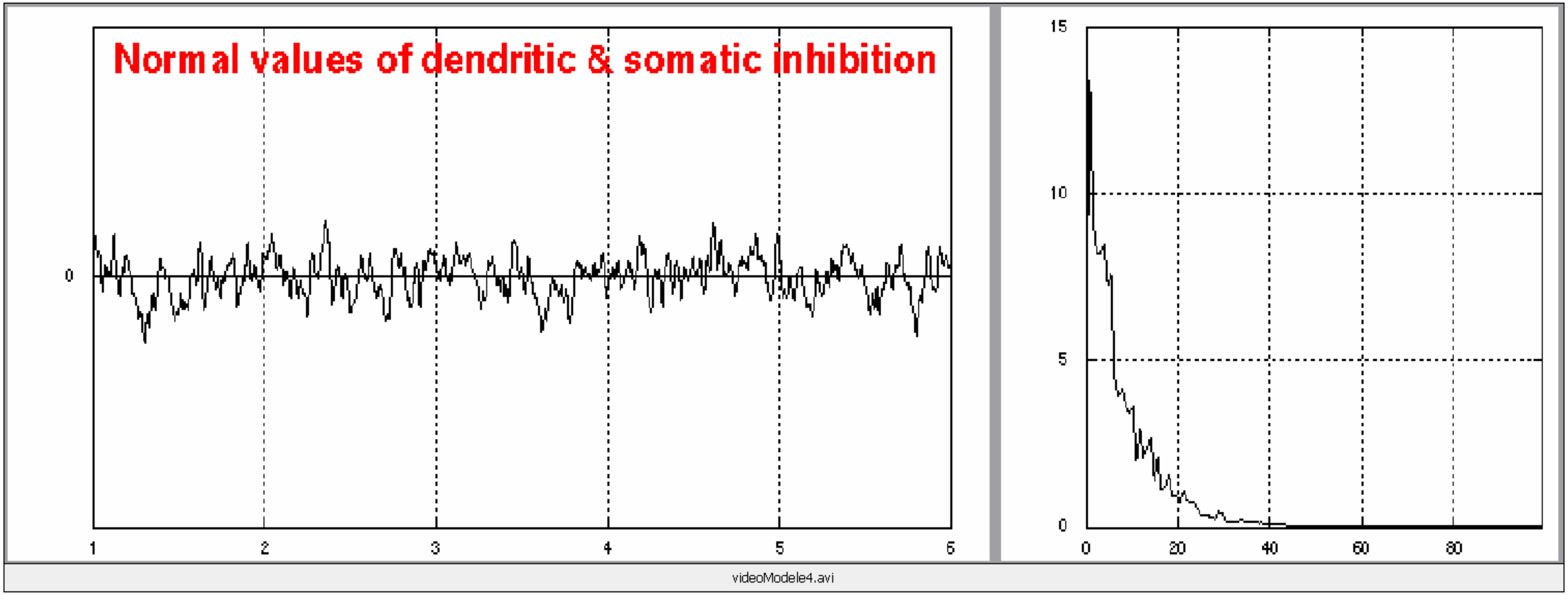
Real vs simulated signals



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 EEG for the identified scenario





Insights from the « hippocampus » model

- The transition from interictal to ictal activity is explained by a “gradual” decrase of inhibition at the level of PYR cell dendrites

- The model reproduces a sequence of “classical” electrophysiological patterns observed in MTLE:

  Bkg activity → spiking activity → fast onset activity → ictal activity

- Necessary conditions to generate fast onset activity:

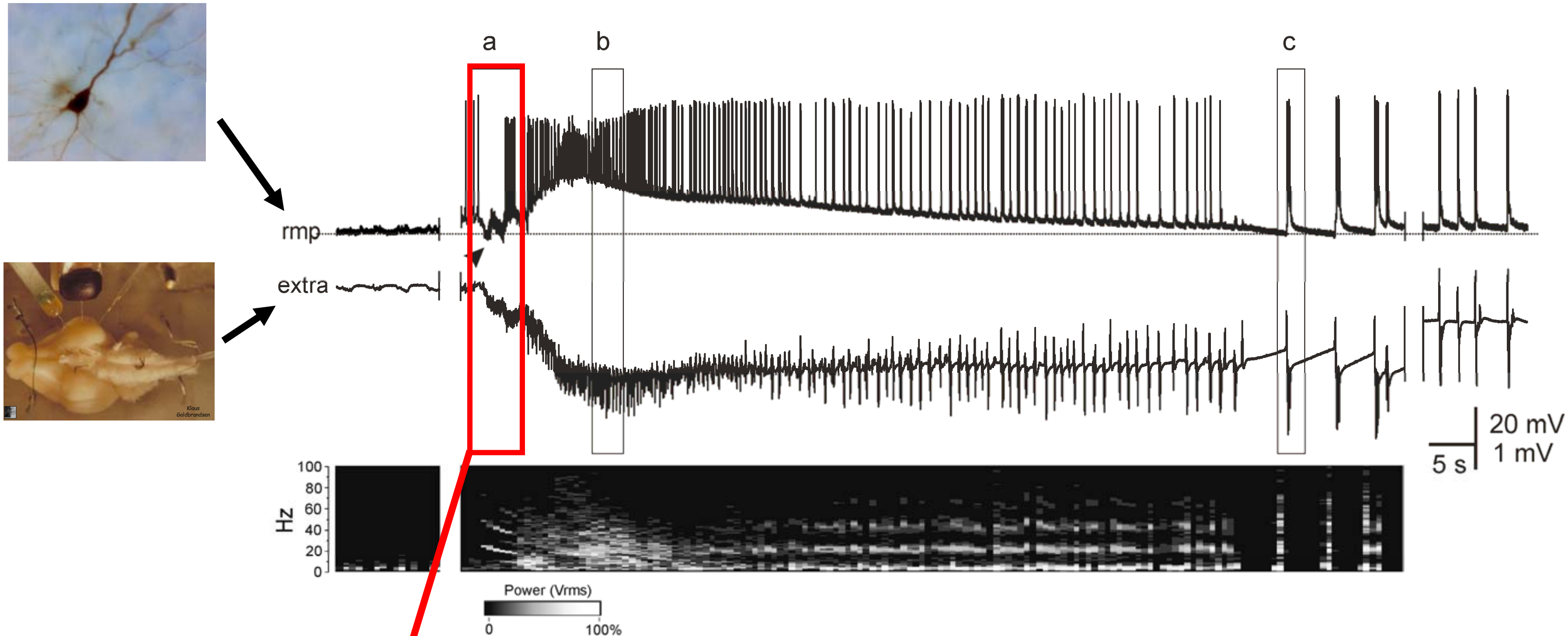
  1. Increased excitatory drive (PYR→PYR & PYR→IN)
  2. Decreased inhibitory drive on the dendrites of PYR cells
  3. Preserved inhibitory drive on the perisomatic region of PYR cells

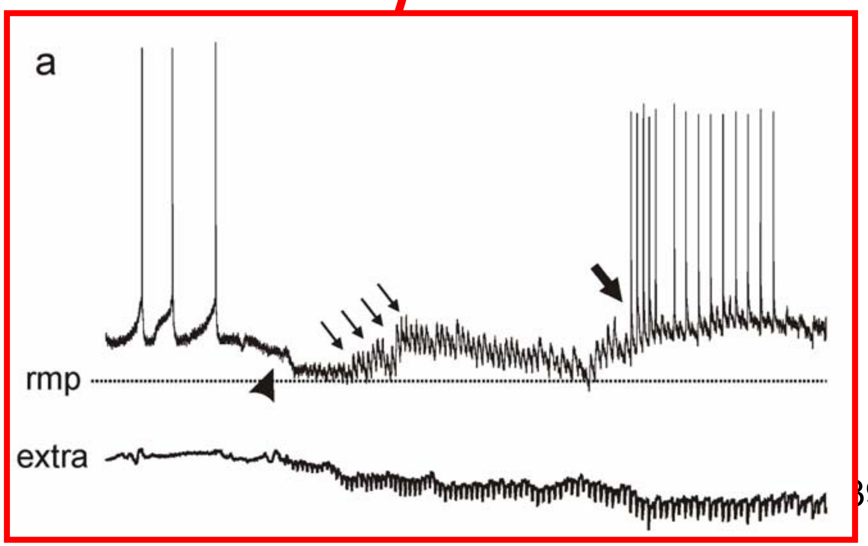
  ➔ Fast onset activity = reflection of fast IPSPs on PYR cells represented by the fast feedback inhibitory loop

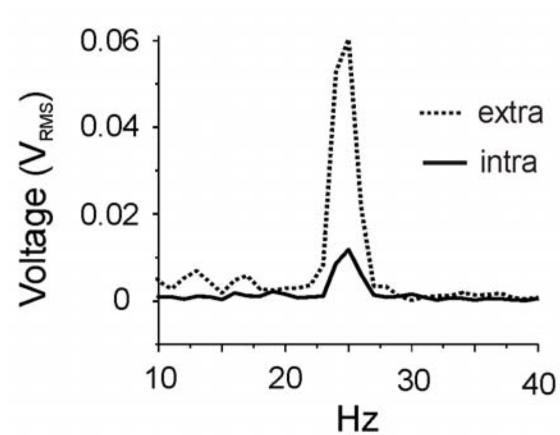
- An experimental validation was reported recently by M. de Curtis’ team (Ann. Neurol. 2008)

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







Gnatkovsky et al., Ann. Neurol. 2008

Discussion about the « macroscopic approach »

- Confirmation of particular experimental results
    - *alteration of interneurons (targeting the dendrites of Pyr cells)*
    - *role of inhibitory interneurons (targeting the soma of Pyr cells) in the generation of fast oscillations*

- Macroscopic level of the model (population) ⇨ nature of real EEG signals (intracerebral macroelectrodes).

- Class of models can be specifically adapted to explored brain structures (ex: hippocampus) or macrocircuits (thalamo-cortical loop, olfactory system)

However

- Several structures are often involved simultaneously (hippocampus-entorhinal cortex system in MTLE)
- Identified parameters remain « macroscopic » (excitation, inhibition)
- Non-invasive data (scalp EEG, MEG) also contain relevant information

→ **Work in progress**

Work in progress

- Several structures are often involved simultaneously (hippocampus-entorhinal cortex system in MTLE)

  ➔ 1) Towards « larger scale models »

- Identified parameters remain « macroscopic » (excitation, inhibition)

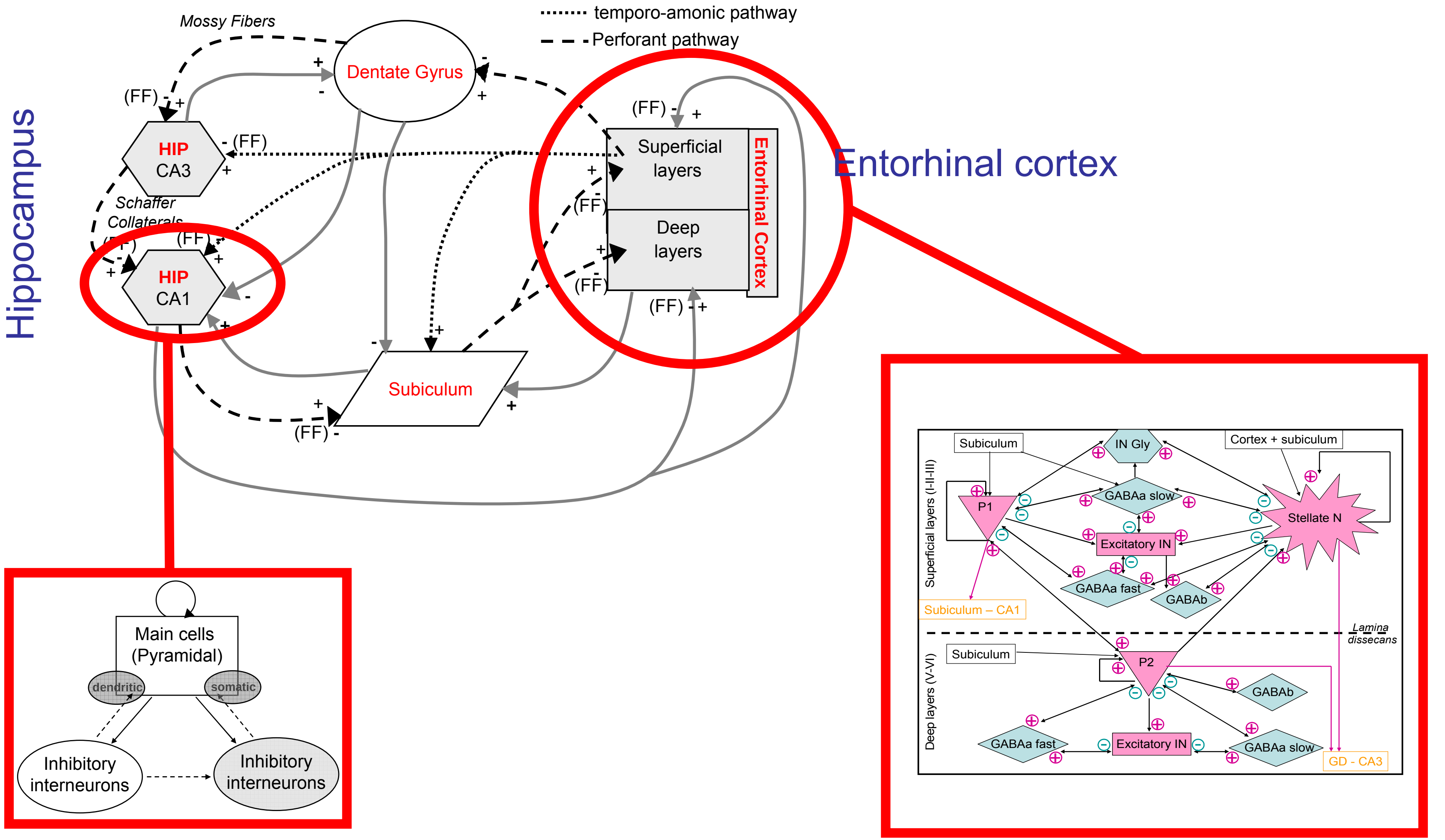
  ➔ 2) From « population » models to « detailed » models

- Non-invasive data (scalp EEG, MEG) also contain relevant information

  ➔ 3) Relationships between scalp and intracerebral data

1) Towards « larger scale models » (brain region)

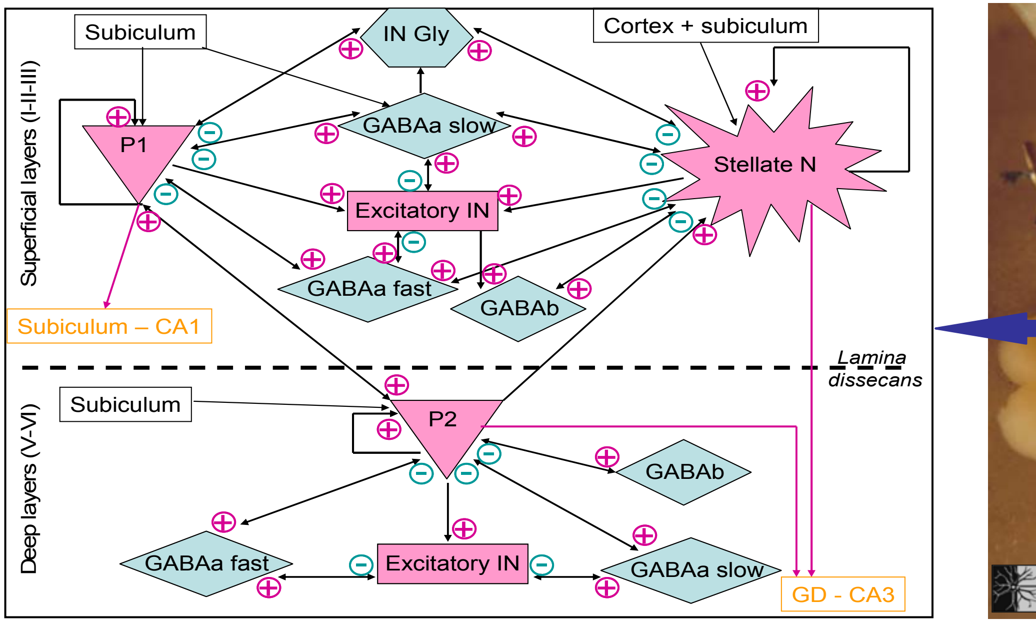
Objective: To study the role of the HIP-EC « closed-loop » system in MTLE



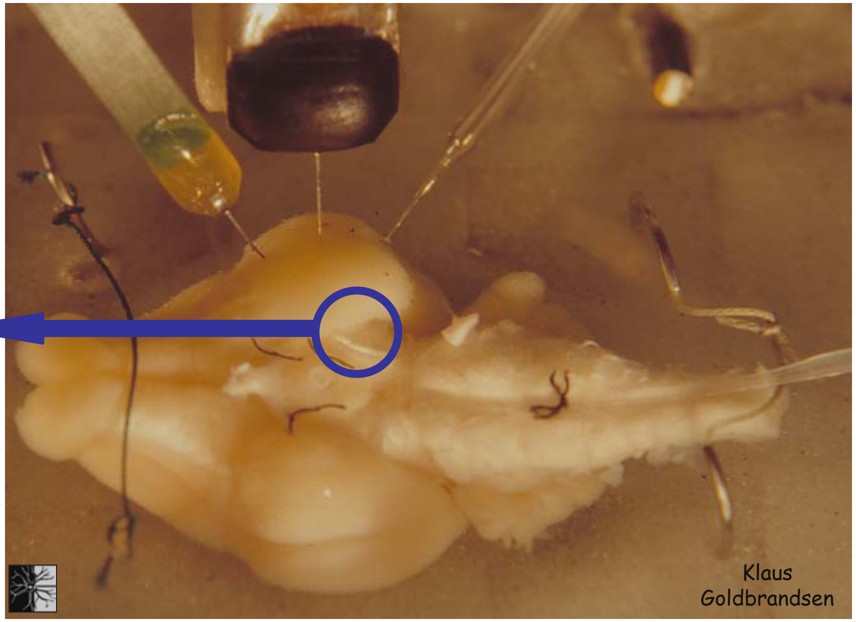
Lopes da Silva FH, Witter MP, Boeijinga PH, and Lohman AH. Anatomic organization and physiology of the limbic cortex. *Physiol Rev* 70: 453-511, 1990.
Witter MP. Organization of the entorhinal-hippocampal system: a review of current anatomical data. *Hippocampus* 3 Spec No: 33-44, 1993.

1) Entorhinal cortex model and evaluation on experimental data

COMPUTATIONAL MODEL



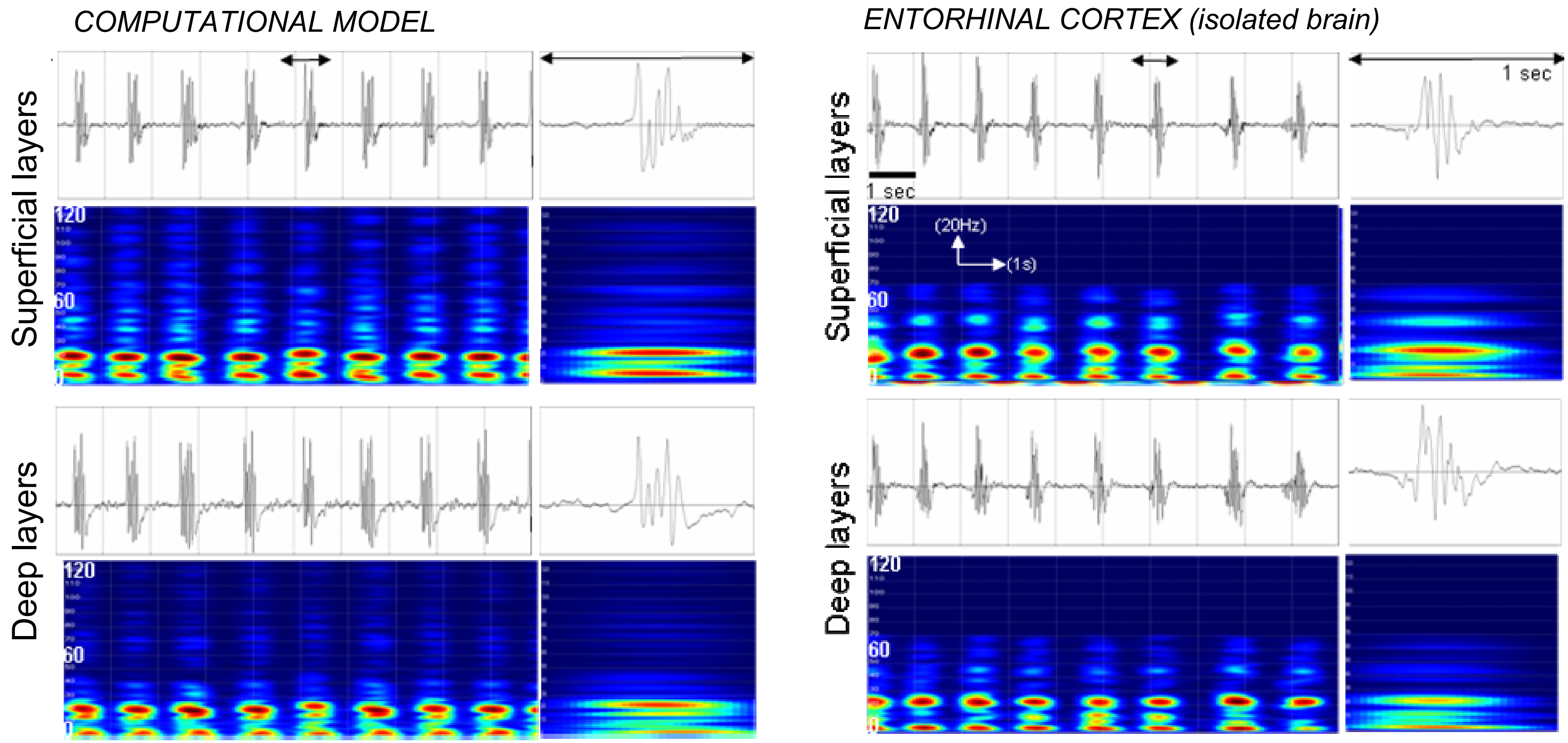
ENTORHINAL CORTEX (isolated brain)



Collaboration Institut C. Besta, Milan

Labyt et al., J. Neurophysiol, 2006, IEEE TITB 2007

1) Entorhinal cortex model and evaluation on experimental data



→ Role of inhibition (GABAa receptors) // experimental protocol (bicuculline)

Labyt et al., J. Neurophysiol, 2006, IEEE TITB 2007

Work in progress

- Several structures are often involved simultaneously (hippocampus-entorhinal cortex system in MTLE)

  ➔ 1) Towards « larger scale models »

- Identified parameters remain « macroscopic » (excitation, inhibition)

  ➔ 2) From « population » models to « detailed » models

- Non-invasive data (scalp EEG, MEG) also contain relevant information

  ➔ 3) Relationships between scalp and intracerebral data

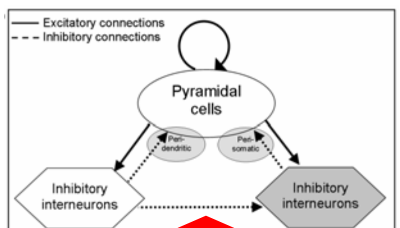
2) From « population » models to « detailed » models

Objective : to interpret observations as a function of cellular parameters (epilepsy and « channelopathy »)

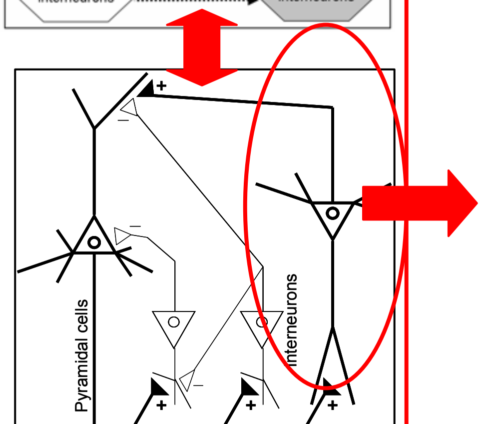
Methods:

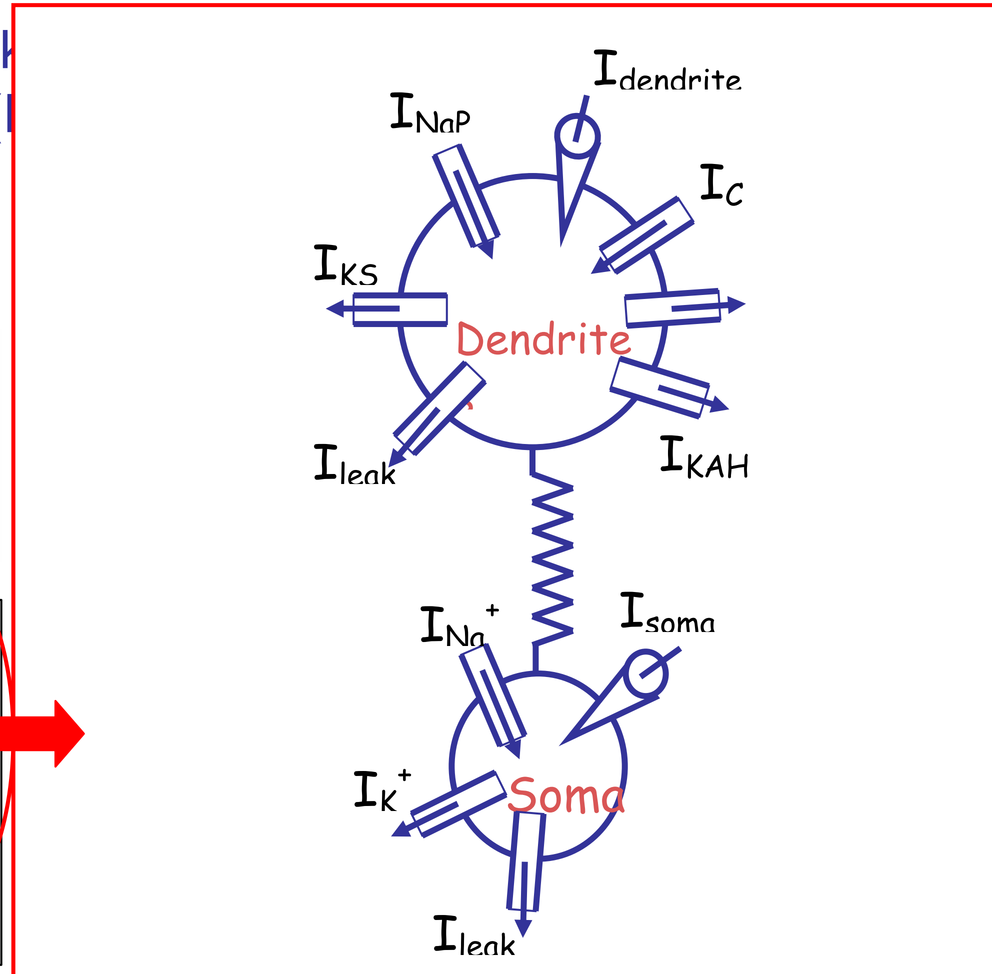
- Detailed models (network
- Cell level: ion channels (I

Neuronal population



Neuronal networks (~ 10^4 Cell.)





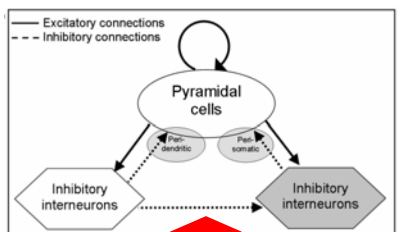
2) From « population » models to « detailed » models

Objective : to interpret observations as a function of cellular parameters (epilepsy and « channelopathy »)

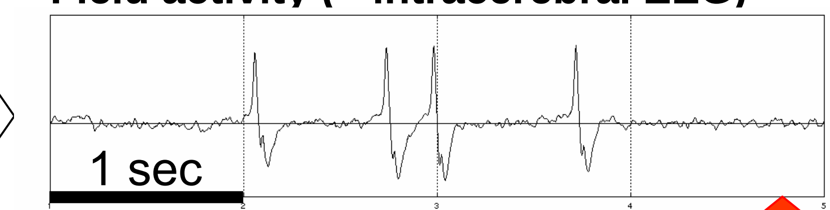
Methods:

- Detailed models (networks) // population models
- Cell level: ion channels (Hodgkin & Huxley), membrane receptors

Neuronal population



Field activity (~ intracerebral EEG)



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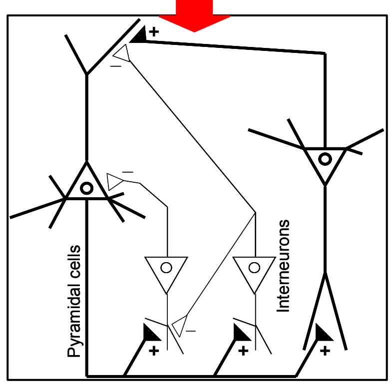
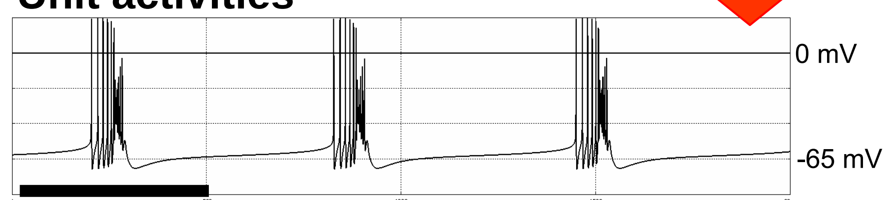


?

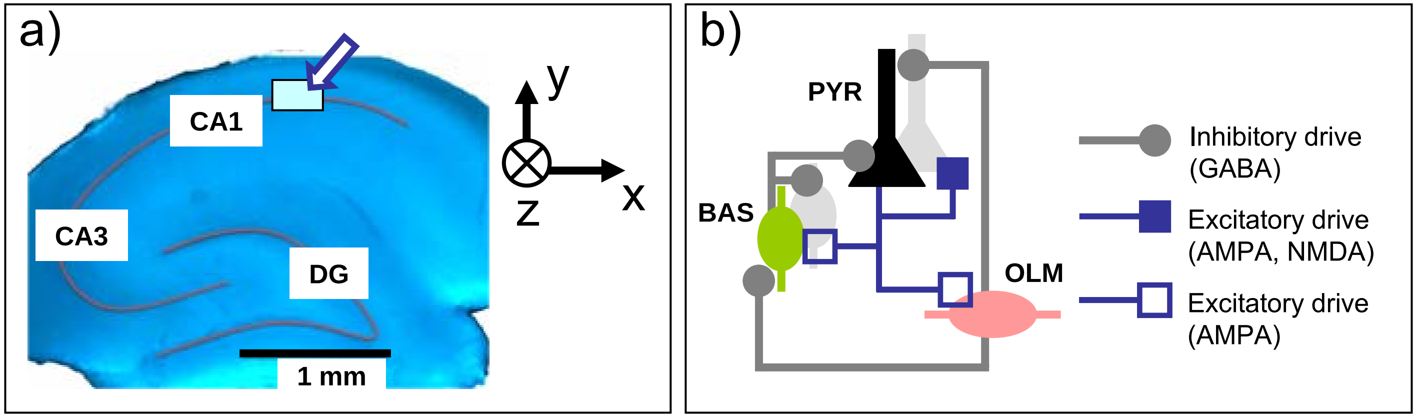
Unit activities



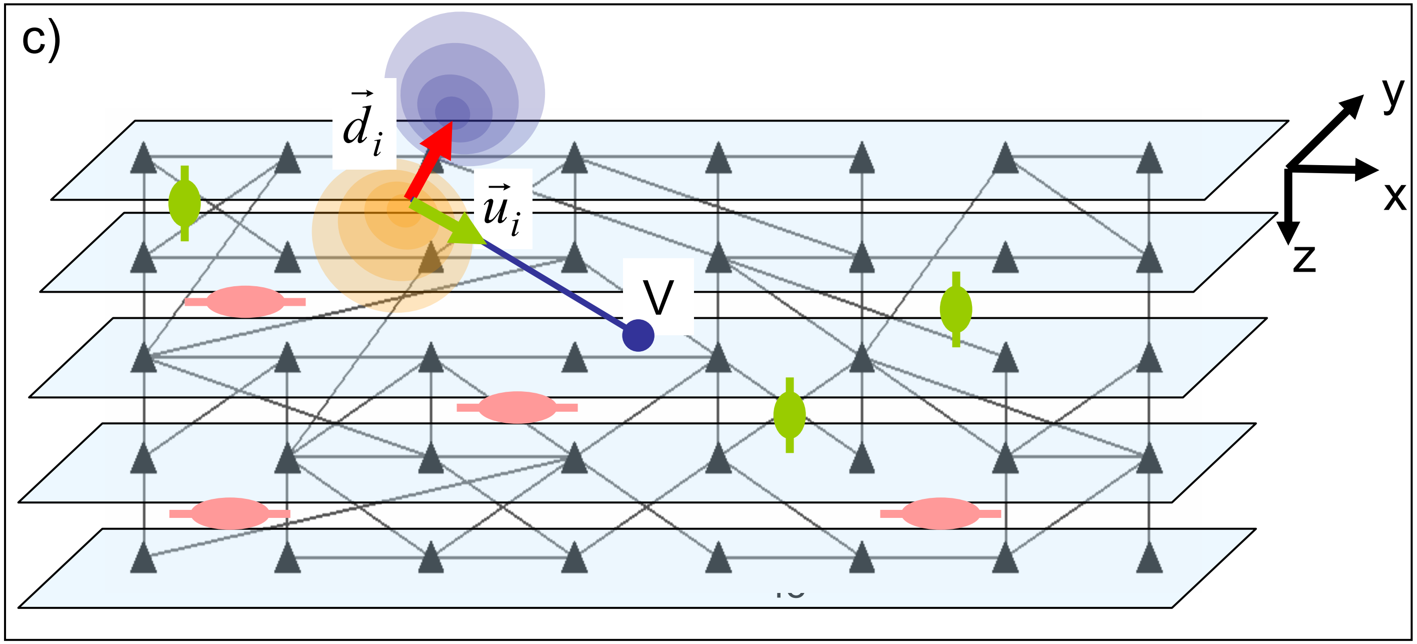
500 msec

2) Neural network model: main features

- Hippocampus, CA1 subfield, PYR, OLM & basket cells

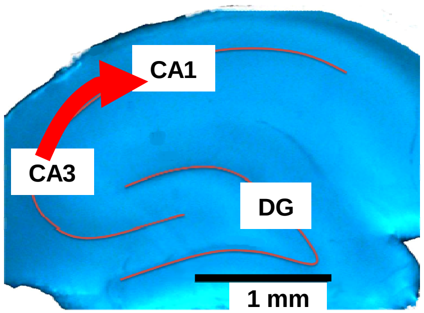


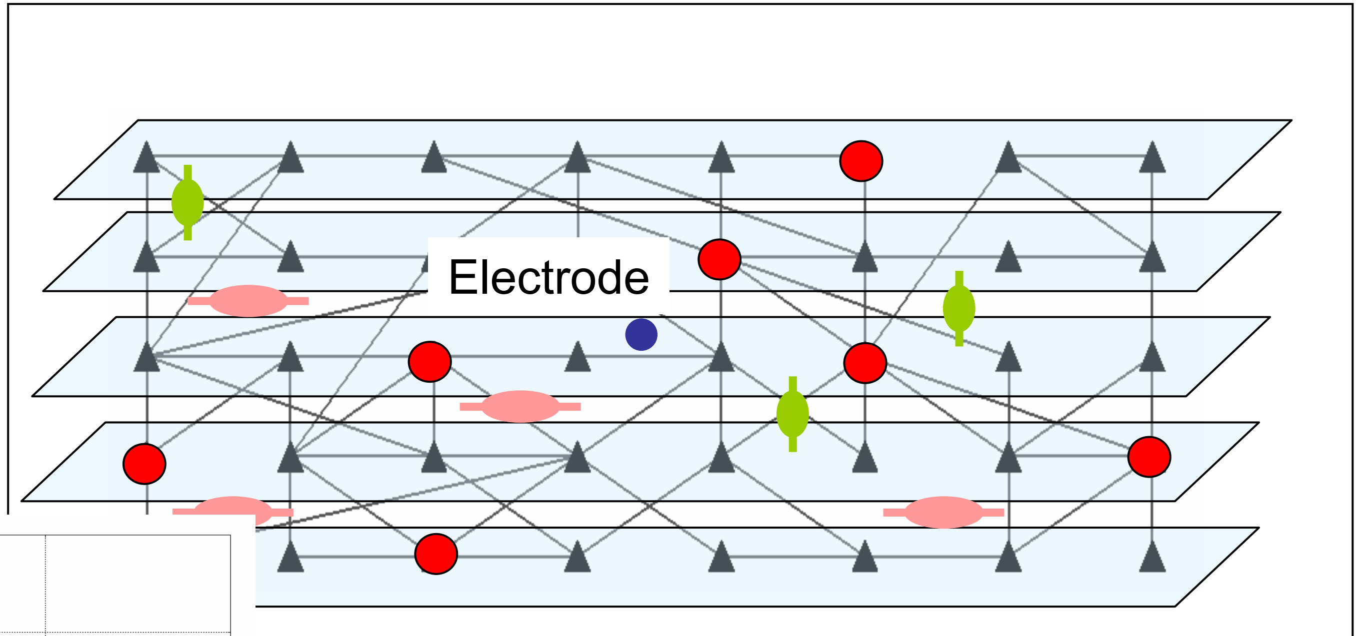
- Reconstruction of the field activity (forward problem, dipole theory)

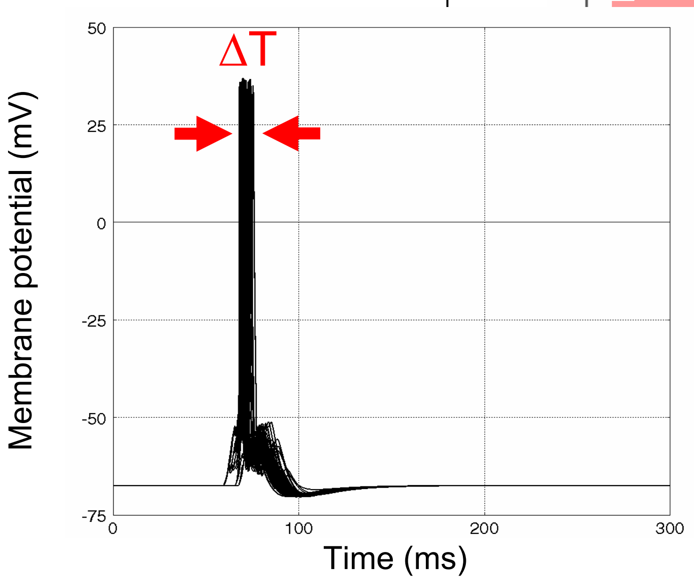


Stimulation of the network

- Simulation of volley of afferent APs on randomly-selected cells (from CA3)







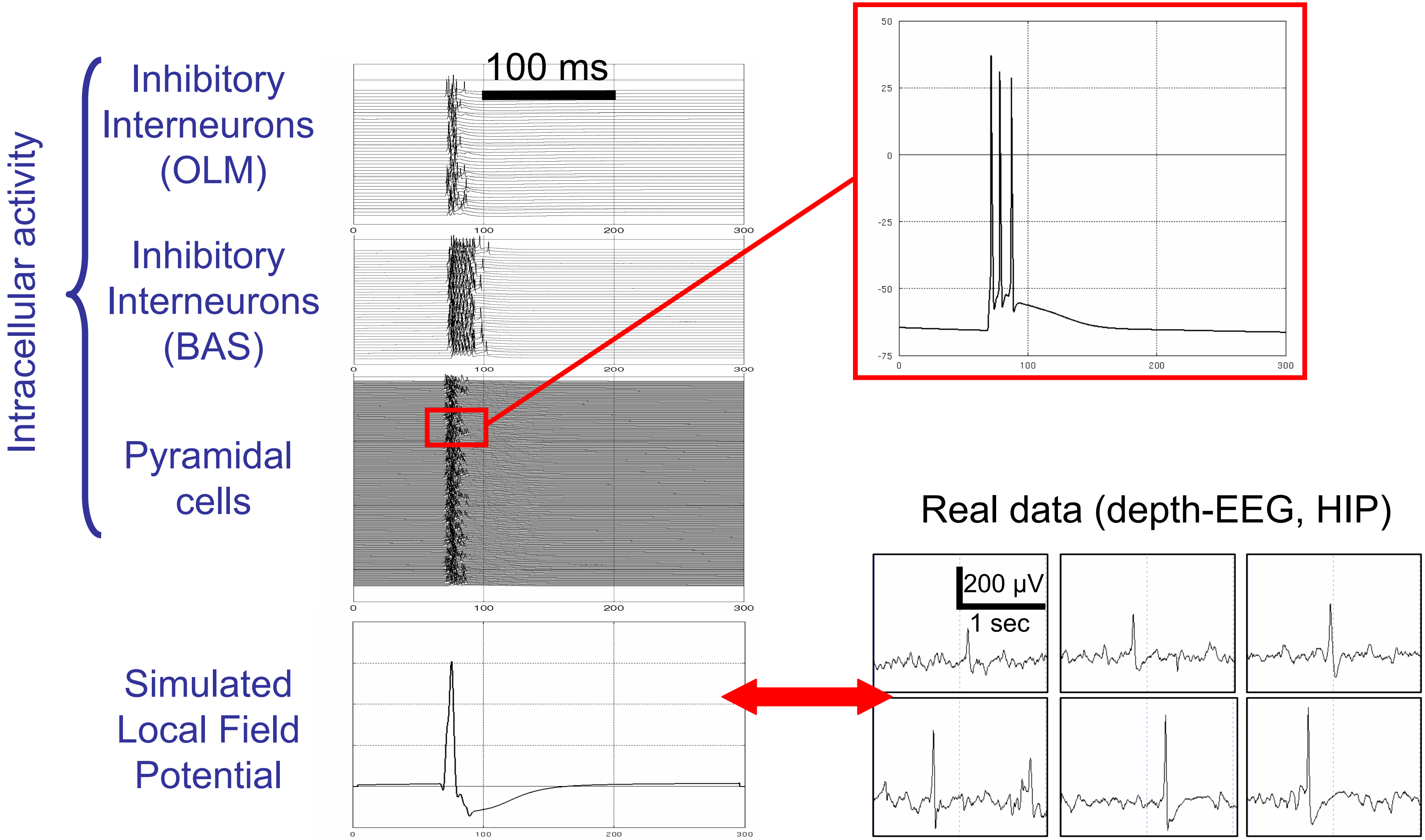
Stimulation parameters:

- Number of stimulated cells in the network
- Variance of the delay between afferent APs

Demont-Guignard et al., IEEE Conf. Neural Engineering, 2009

2) Simulated activity in « hyperexcitable » networks

For **ALL** pyramidal cells
- Increased conductances NMDA- and AMPA-mediated synaptic currents
- increased reversal potential of GABA-mediated synaptic currents (-70 to -50 mV)



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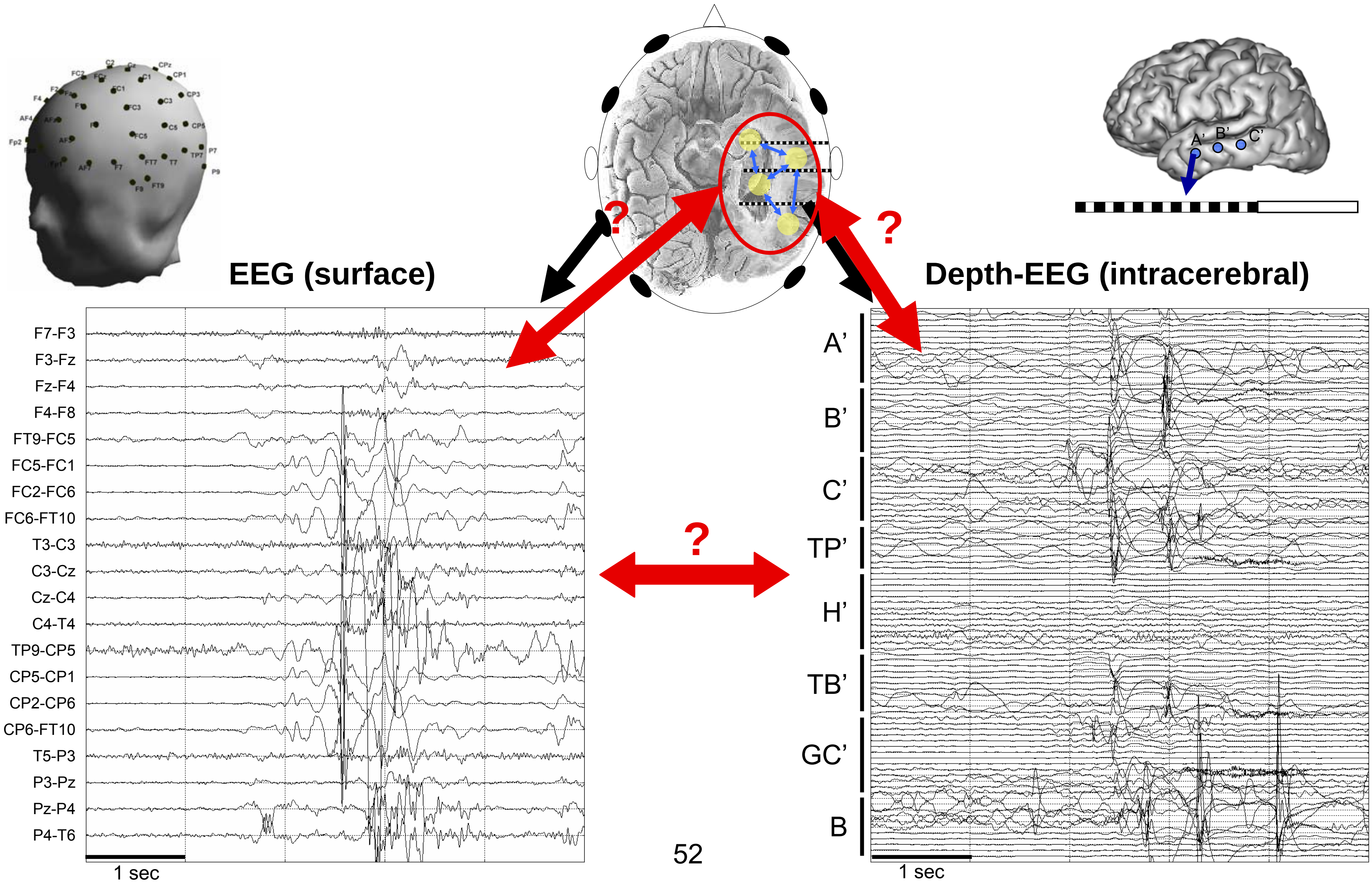
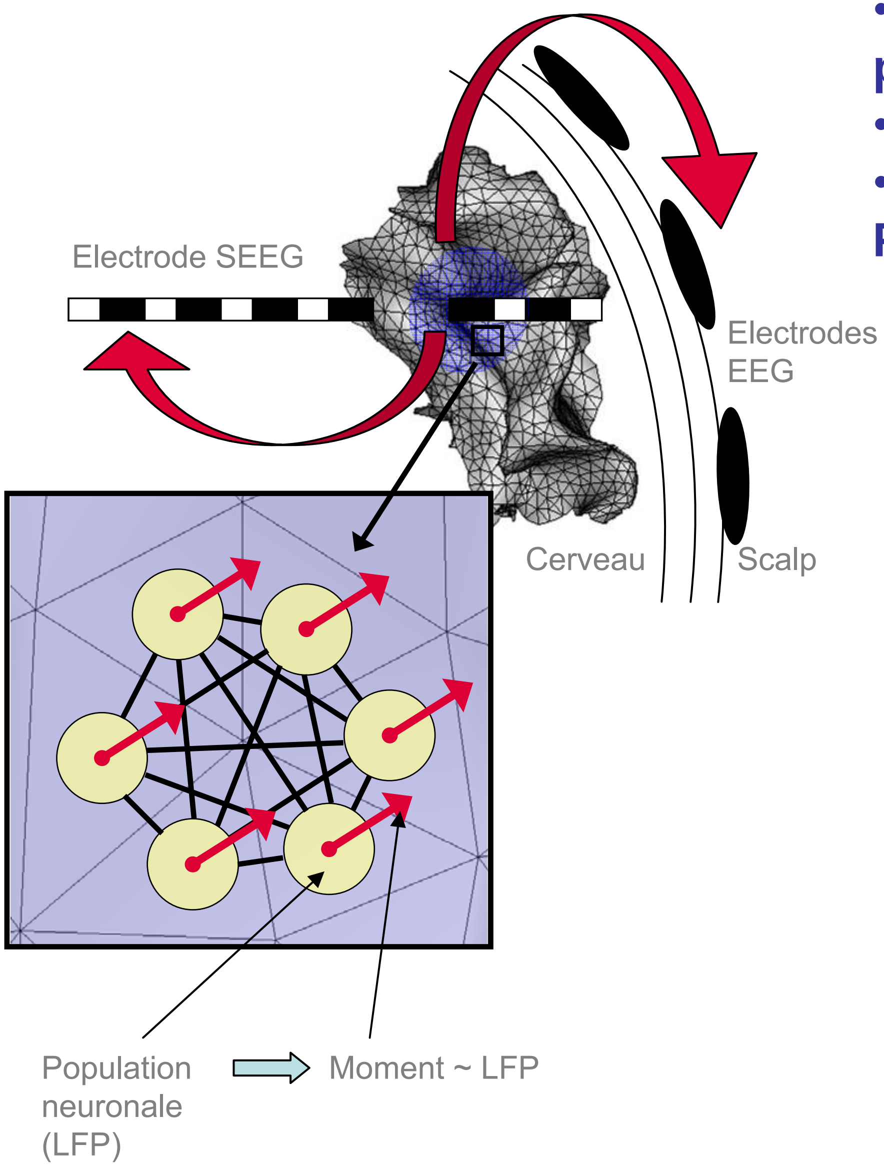
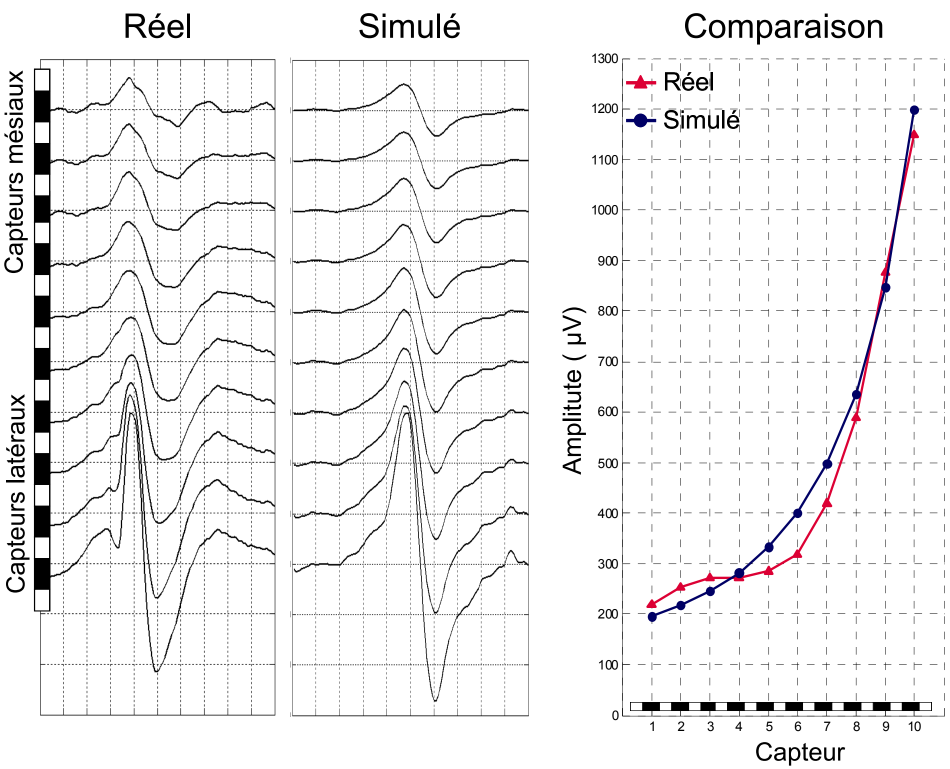


3) Modeling of scalp and intracerebral EEG



- Extended source: **dipole layer + neuronal population model**
- Realistic head model (IRM)
- Electrical potentials :

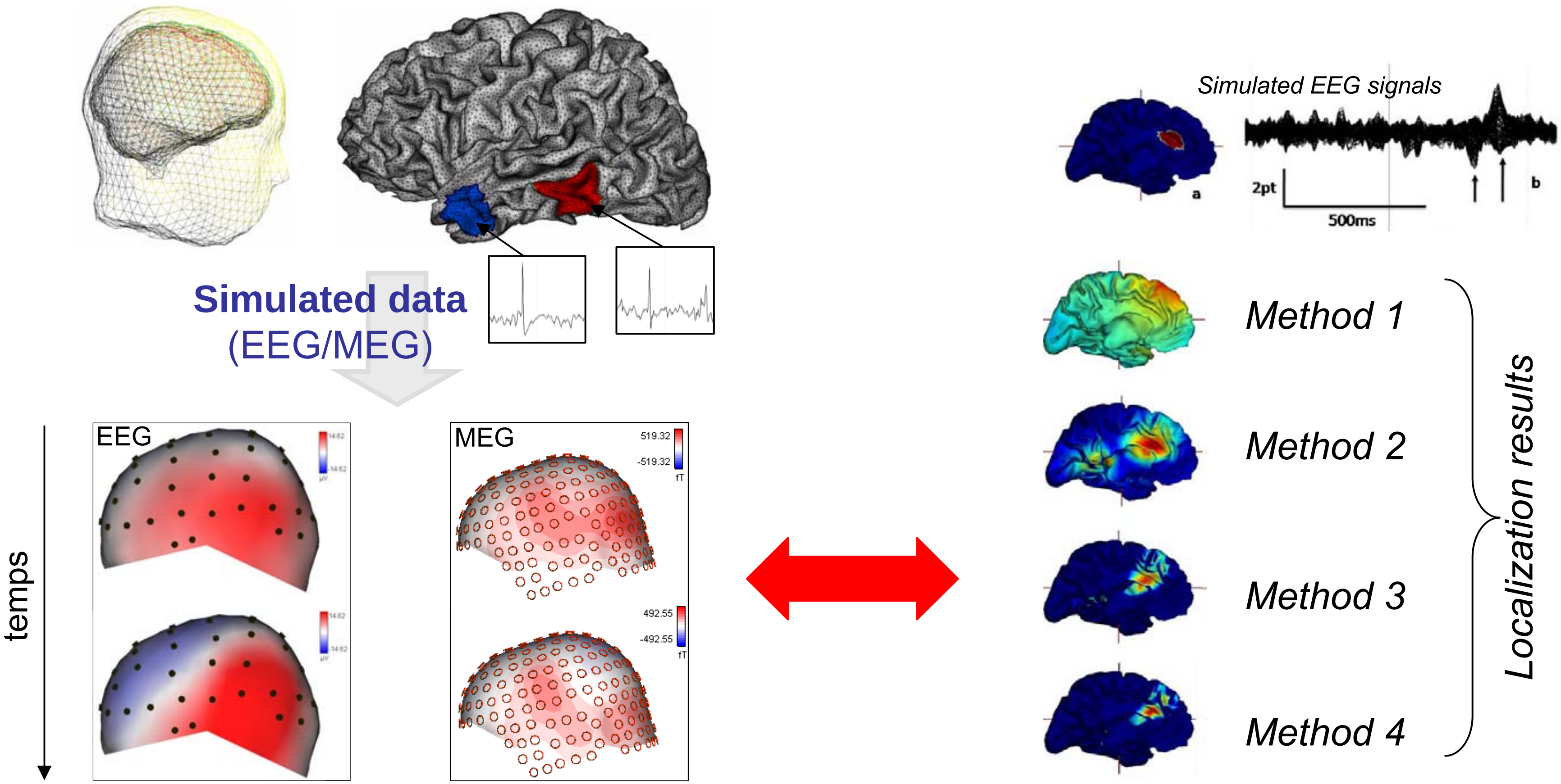
Forward problem (sources→sensors)



Cosandier-Rimélé et al., IEEE TBME 2007

3) Model-based evaluation of localization methods

- **Parametric study of the model :** influence of source parameters related to **space** and **time** (extension of sources, position, synchronisation degree)



Cosandier-Rimélé et al., Neuroimage 2008

Albera et al., TBME, 2008

General conclusion

- “**Epilepsy** is a **complex dynamical** disease” (F. Lopes da Silva)

- **Approach** combining **signal processing** and **modeling** in order to interprete the observations and to identify some pathological mechanisms

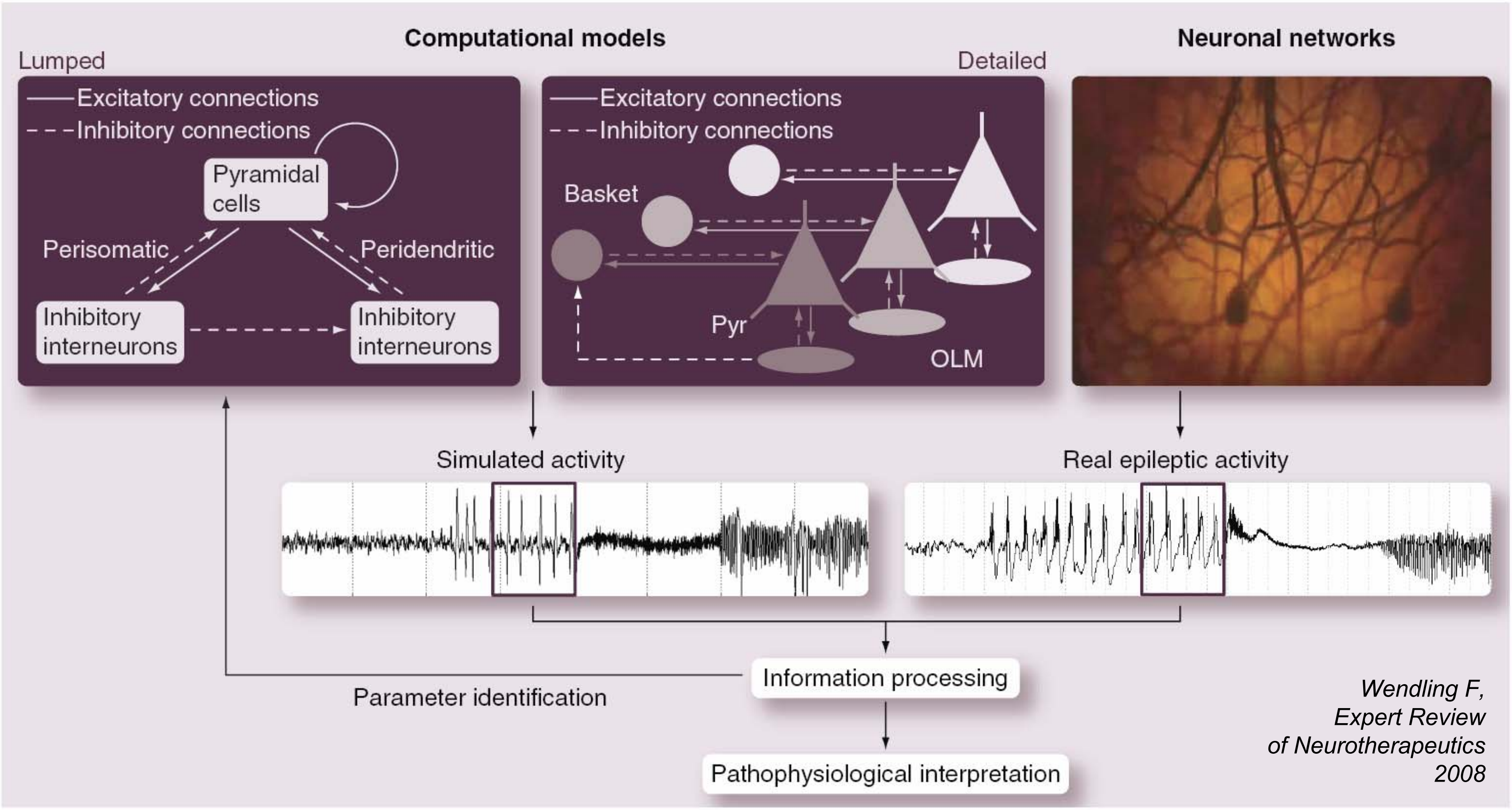
- **Intervalidation** with experimental models is required (intimate link between models and experiments)

- **Open questions**

  ☑ Development of « multi-level » approaches

  ☑ Relationship between the sources of activity and the signals that are collected on sensors (forward problem, biophysics)

  ☑ The use of multimodal data (fMRI, EEG, MEG, depth-EEG) in epilepsy



Thank you for your attention