

Mesocopic models : from neural circuits to large-scale activity

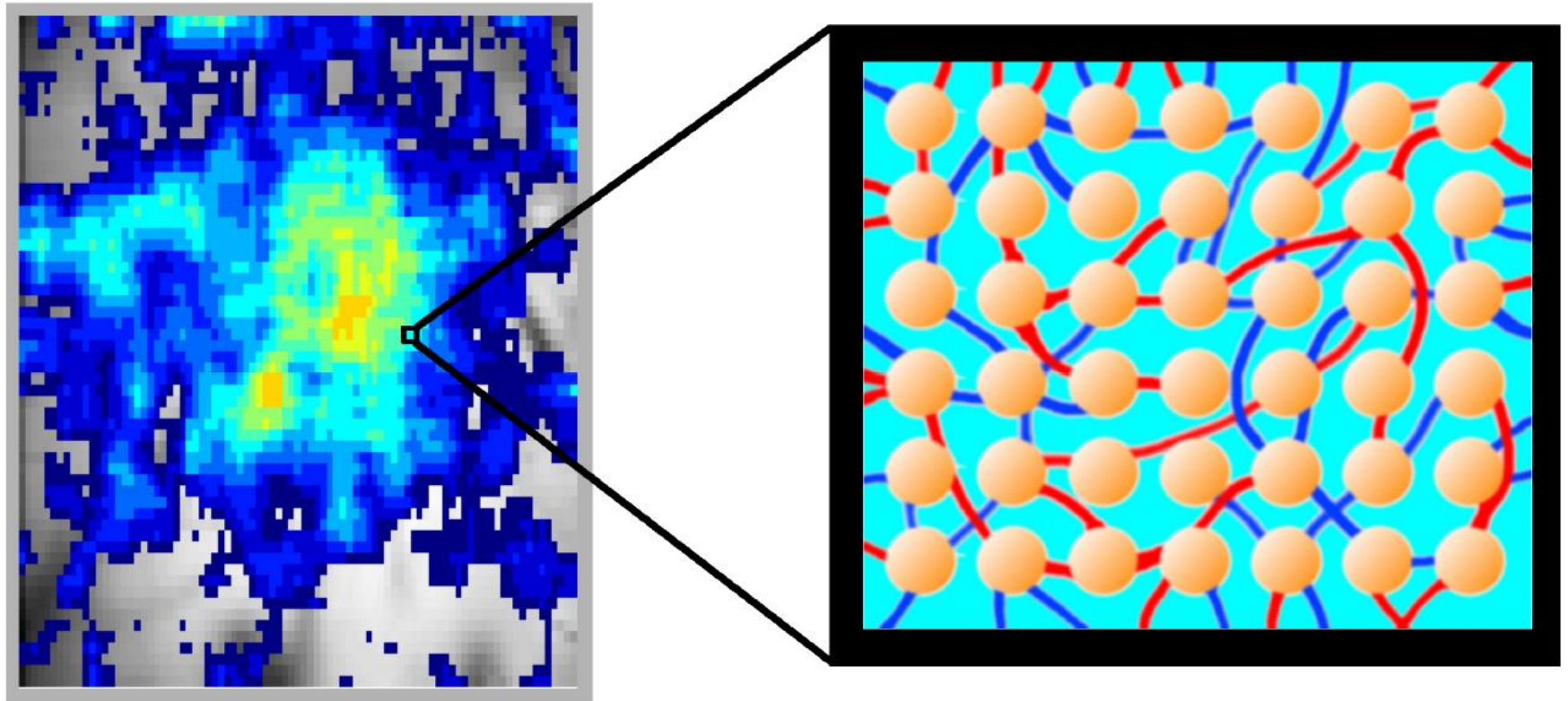
Alain Destexhe (CNRS, NeuroPSI, Paris-Saclay University)
Alain.Destexhe@cnr.fr

November 2023

Mesososcopic modeling of brain activity

Motivation: describing brain activity at large scale

Voltage-sensitive dye (VSD) imaging



1 mm

Classic mean-field models

Wilson-Cowan model

The original Wilson & Cowan (1972) equations:

$$\tau_e \frac{da_e}{dt} = -a_e(t) + [1 - r_e a_e(t)] F_e(w_{ee} a_e(t) - w_{ei} a_i(t) + I_e(t)),$$

$$\tau_i \frac{da_i}{dt} = -a_i(t) + [1 - r_i a_i(t)] F_i(w_{ie} a_e(t) - w_{ii} a_i(t) + I_i(t)).$$

$a(e,i)$ are the activities of excitatory (e) and inhibitory (i) populations, $r(e,i)$ is the refractoriness, $w(e,i)$ are the synaptic weights, I is an external current, and F is a sigmoidal transfer function (of the form $F(x)=1/[1+\exp(a^*(x-b))]$)

Wilson-Cowan model

The “classic” Wilson & Cowan (1972) equations:

$$\tau_e \frac{da_e}{dt} = -a_e(t) + F_e(w_{ee}a_e(t) - w_{ei}a_i(t) + I_e(t)),$$

$$\tau_i \frac{da_i}{dt} = -a_i(t) + F_i(w_{ie}a_e(t) - w_{ii}a_i(t) + I_i(t)).$$

Here, there is no saturation or refractory term. The two models are equivalent, if the transfer function is rescaled appropriately (Pinto et al, JCNS 1996).

This is the **most commonly used form** for mean-field models in neuroscience.

Wilson-Cowan model

Space-continuous Wilson & Cowan equations:

$$\tau_e \frac{\partial a_e(x, t)}{\partial t} = -a_e(x, t) + [1 - r_e a_e(x, t)] F_e(w_{ee} * a_e - w_{ie} * a_i + I_e(x, t))$$

$$\tau_i \frac{\partial a_i(x, t)}{\partial t} = -a_i(x, t) + [1 - r_i a_i(x, t)] F_i(w_{ei} * a_e - w_{ii} * a_i + I_i(x, t))$$

where $w_{jk} * a_k$ is a convolution operator

$$w_{jk} * a_k = \int_{\Omega} w_{jk}(x - y) a_k(y, t) dy$$

Here, the activities are continuous in space, and their connectivities are given by connection kernels $w(x-y)$, typically:

$$w_{jk}(x - y) = k_{jk} e^{-(x-y)^2 / \sigma_k^2}$$

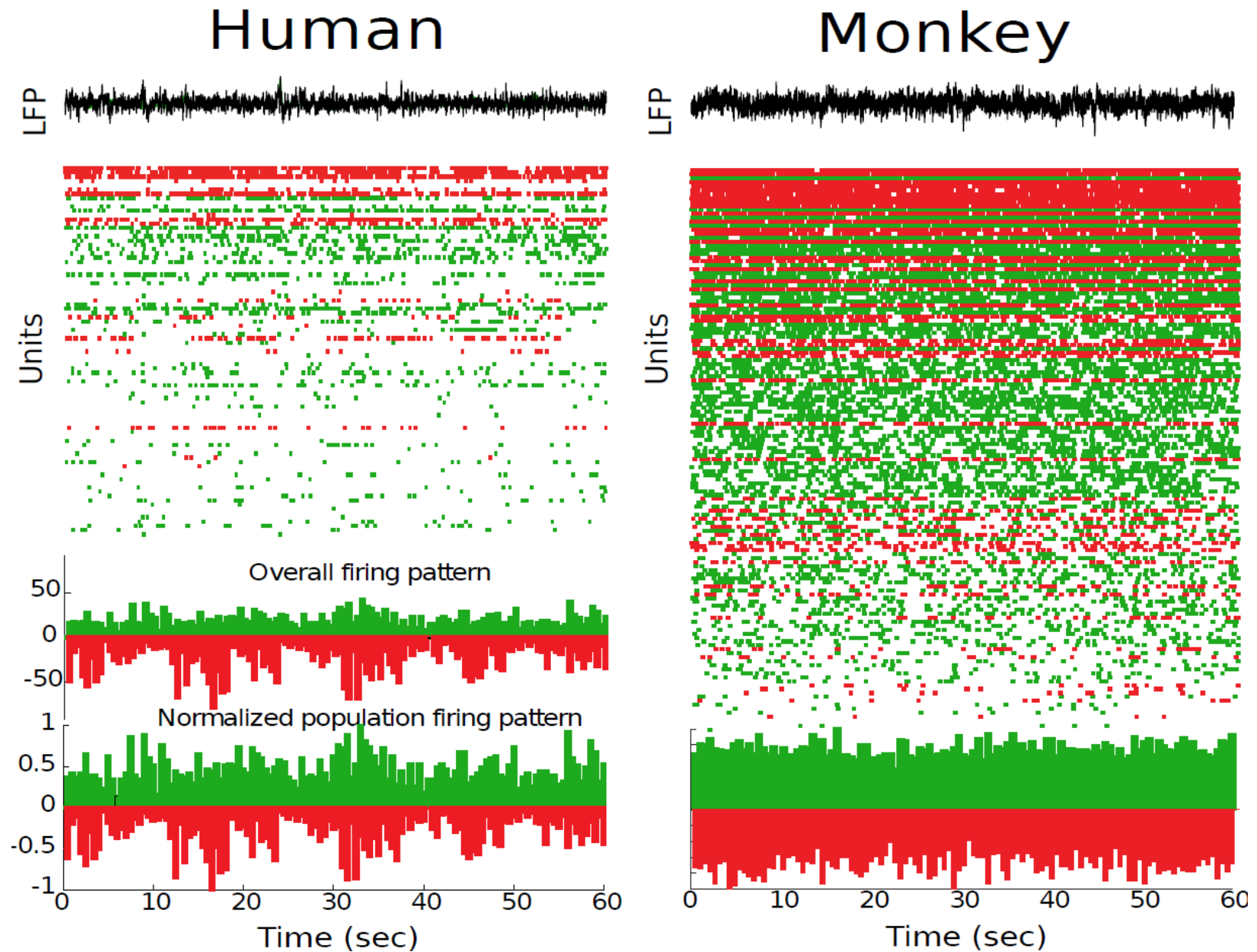
Mean-field models of spiking neurons

Mesoscopic modeling of brain activity

A long (but recent) history of mean-field approaches to spiking networks

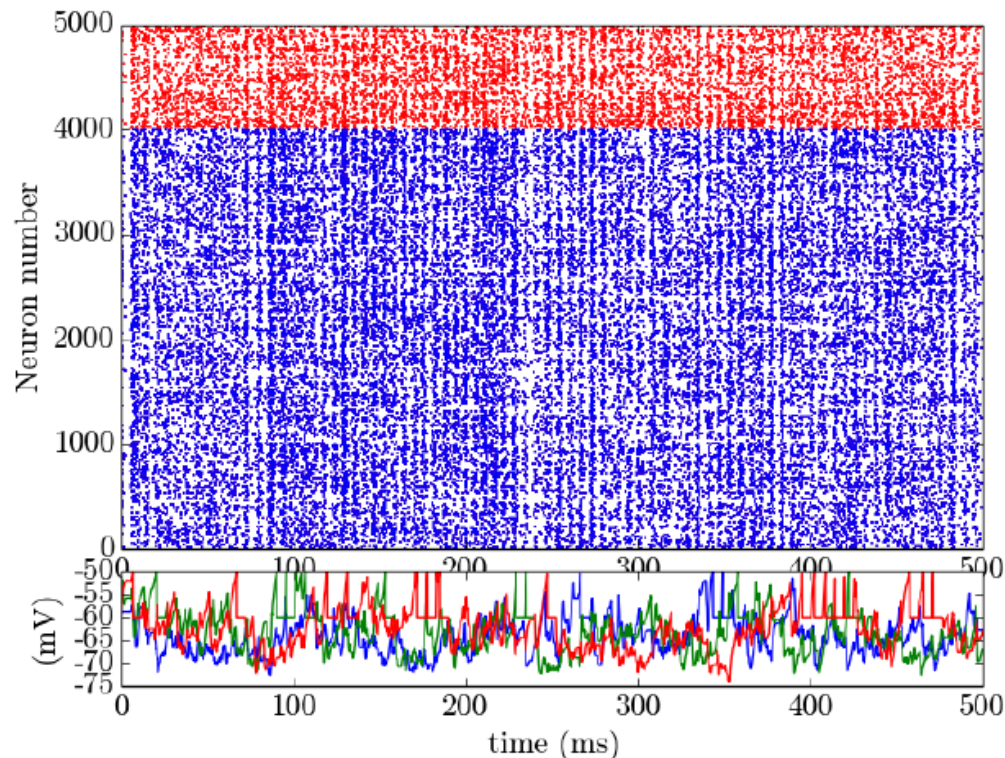
- MF model of IF neurons (Amit and Brunel, 1997)
- oscillatory regimes (Brunel and Hakim, 1999, Brunel, 2000)
- applied to other spiking models (Fusi and Mattia, 1999, Hansel and Mato, 2001, Gerstner, 2000)
- irregular activity (Renart et al., 2007, Mattia and Giudice, 2002).
- discrete Markovian model (Soula and Chow, 2007)
- continuous models based on diffusion approx. (Ricciardi, 1977, Tuckwell, 1988, Brunel and Sergi, 1998, Fourcaud and Brunel, 2002, Moreno-Bote et al., 2008).
- Master Equation formalism (Ohira and Cowan, 1993, Ginzburg and Sompolinsky, 1994, ElBoustani and Destexhe, 2009; Buice et al., 2010).
- Semi-analytic mean-field (Zerlaut et al., 2018); general and can be applied to any neuron type

AI states

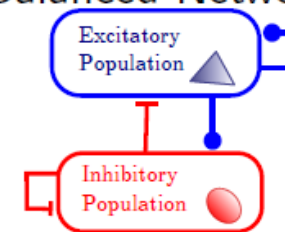


Networks of spiking neurons

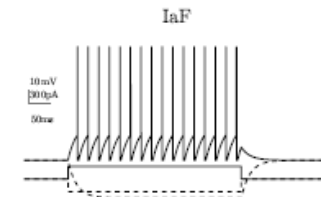
$$C_m \frac{dV_i}{dt} = -g_L(V_i - E_L) + S(t) - \sum_j g_{ji}(t)(V_i - E_j)$$



Sparse-Recurrent-Random-Balanced Network

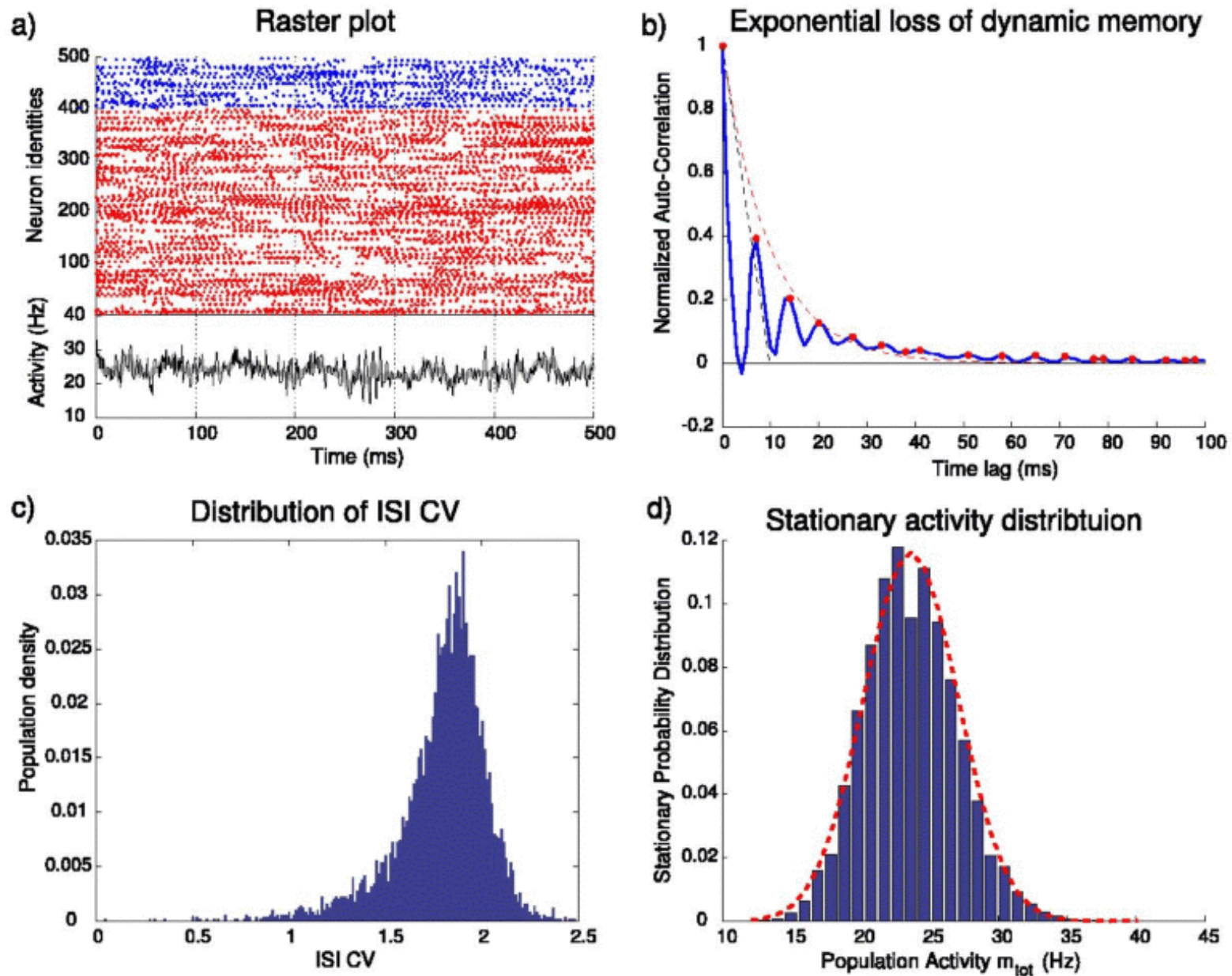


Integrate-and-Fire Neurons



The population activity in the network is the result of the recurrent and afferent activity on the cells.

Networks of spiking neurons



Mean-field model of spiking neurons

Master Equation formalism

Network activity variables:

the network contains K homogeneous populations of neurons, denoted by $1, 2, \dots, K$. We define $m_\gamma(t)$ as the network activity at time t ,

$$m_\gamma(t) = \lim_{\Delta t \rightarrow 0} \frac{n_\gamma(t - \Delta t, t)}{\Delta t N_\gamma}, \quad (3.1)$$

where $n_\gamma(t - \Delta t, t)$ is the number of spikes emitted by population γ during the time interval $[t - \Delta t, t]$ and N_γ is the population size for $\gamma = 1, \dots, K$.

Mean-field model of spiking neurons

Master Equation formalism

Time evolution of the probability density (Master Equation, *assumes the dynamics is Markovian*):

$$\begin{aligned} \partial_t P_t(\{m_\gamma\}) = & \prod_{\alpha=1,\dots,K} \int_0^{1/T} dm'_\alpha (P_t(\{m'_\gamma\}) W(\{m_\gamma\} \mid \{m'_\gamma\}) \\ & - P_t(\{m_\gamma\}) W(\{m'_\gamma\} \mid \{m_\gamma\})), \end{aligned}$$

W are transition probabilities between the different states of the system

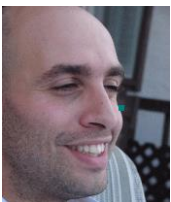
Mean-field model of spiking neurons

Master Equation formalism

If we close the statistical moments hierarchy to 2nd order, after adiabatic approximation (the system reaches a quasi steady-state within period T), we obtain the closed form:

$$T \partial_t \langle m_\mu \rangle = (v_\mu - \langle m_\mu \rangle) + \frac{1}{2} \partial_\lambda \partial_\eta v_\mu c_{\lambda\eta}$$

$$T \partial_t c_{\mu\nu} = \delta_{\mu\nu} A_{\mu\mu}^{-1} + (v_\mu - \langle m_\mu \rangle)(v_\nu - \langle m_\nu \rangle) \\ + \partial_\lambda v_\mu c_{\nu\lambda} + \partial_\lambda v_\nu c_{\mu\lambda} - 2c_{\mu\nu}$$

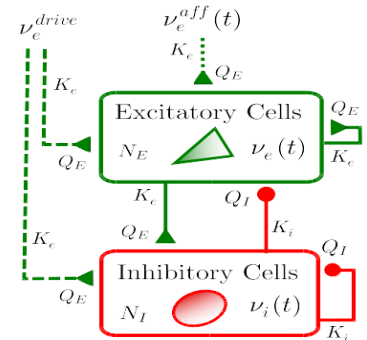


Mean-field model of spiking neurons

Master Equation formalism

In conclusion, the ME formalism is based on 2 assumptions:

- 1) The macroscopic dynamics is Markovian
- 2) The transfer function captures cellular responses



Second-order description:

$$\begin{cases} T \frac{\partial \nu_\mu}{\partial t} = (\mathcal{F}_\mu - \nu_\mu) + \frac{1}{2} c_{\lambda\eta} \frac{\partial^2 \mathcal{F}_\mu}{\partial \nu_\lambda \partial \nu_\eta} \\ T \frac{\partial c_{\lambda\eta}}{\partial t} = A_{\lambda\eta} + (\mathcal{F}_\lambda - \nu_\lambda) (\mathcal{F}_\eta - \nu_\eta) + \\ \quad c_{\lambda\mu} \frac{\partial \mathcal{F}_\mu}{\partial \nu_\lambda} + c_{\mu\eta} \frac{\partial \mathcal{F}_\mu}{\partial \nu_\eta} - 2c_{\lambda\eta} \end{cases}$$

Transfer functions $\mathcal{F}_\mu$

$$\mathcal{F}_\mu(\nu_e, \nu_i), \forall \mu \in \{e, i\}.$$

At first-order :

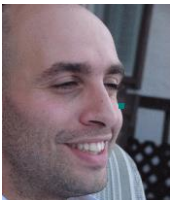
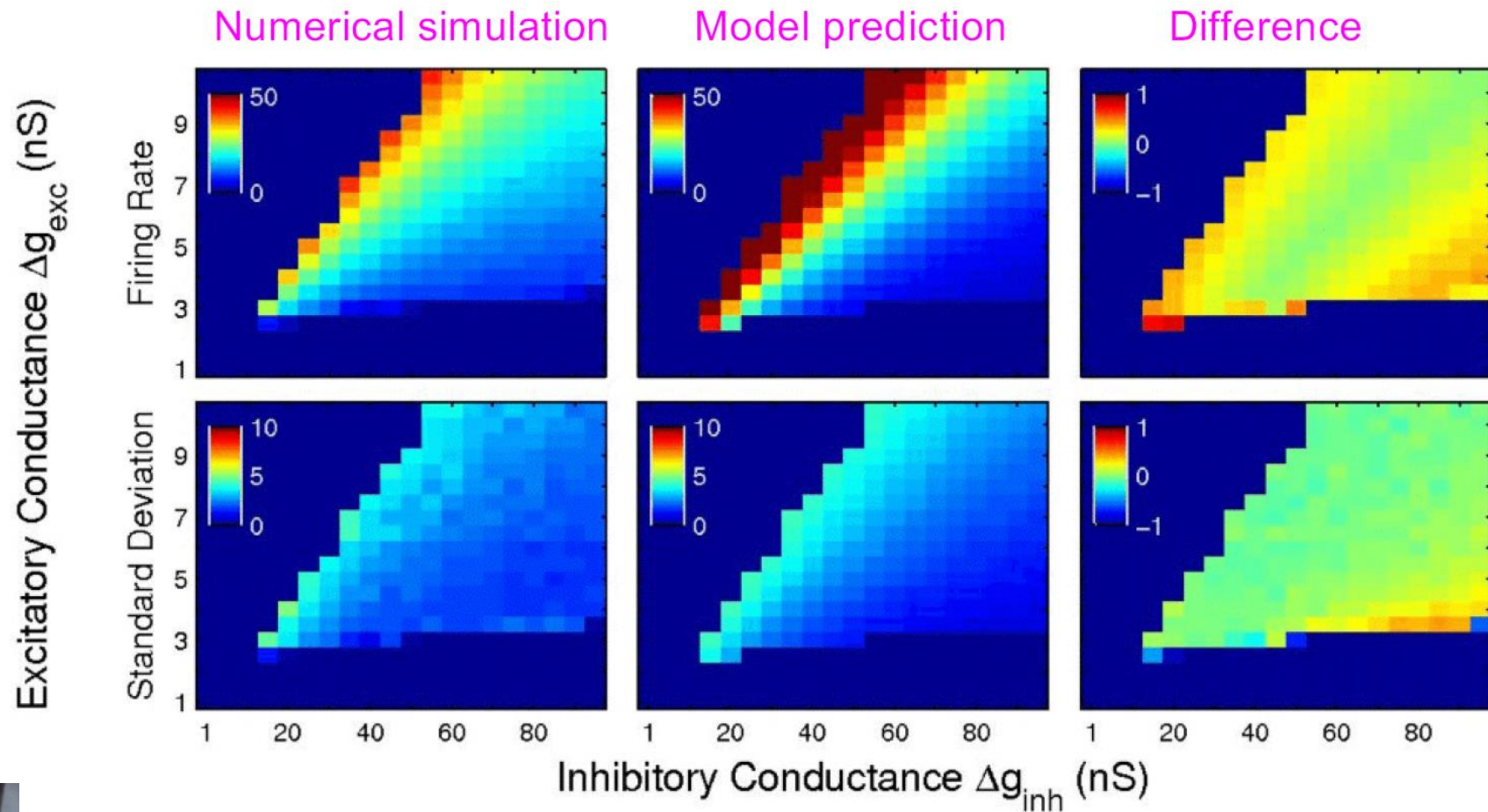
$$T \frac{\partial \nu_\mu}{\partial t} = \mathcal{F}_\mu - \nu_\mu$$

Equivalent to Wilson & Cowan! ,
but with different transfer functions



Mean-field model of spiking neurons

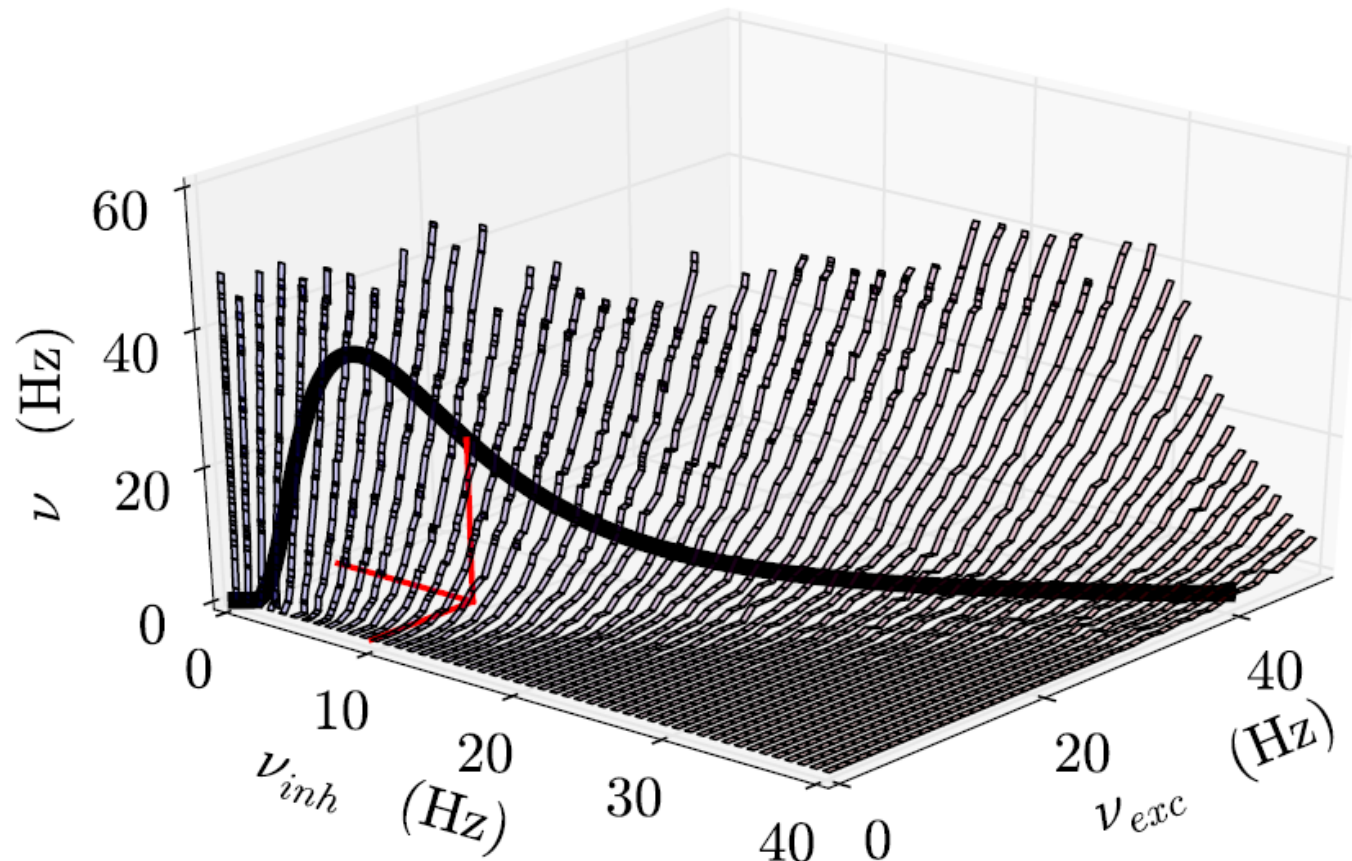
Application to conductance-based IF models:



Transfer function

For a neuron embedded in the previous network

Output firing rate as a function of the presynaptic stimulation rates



Semi-analytic approach

To obtain the transfer function: $\mathcal{F}_\mu$

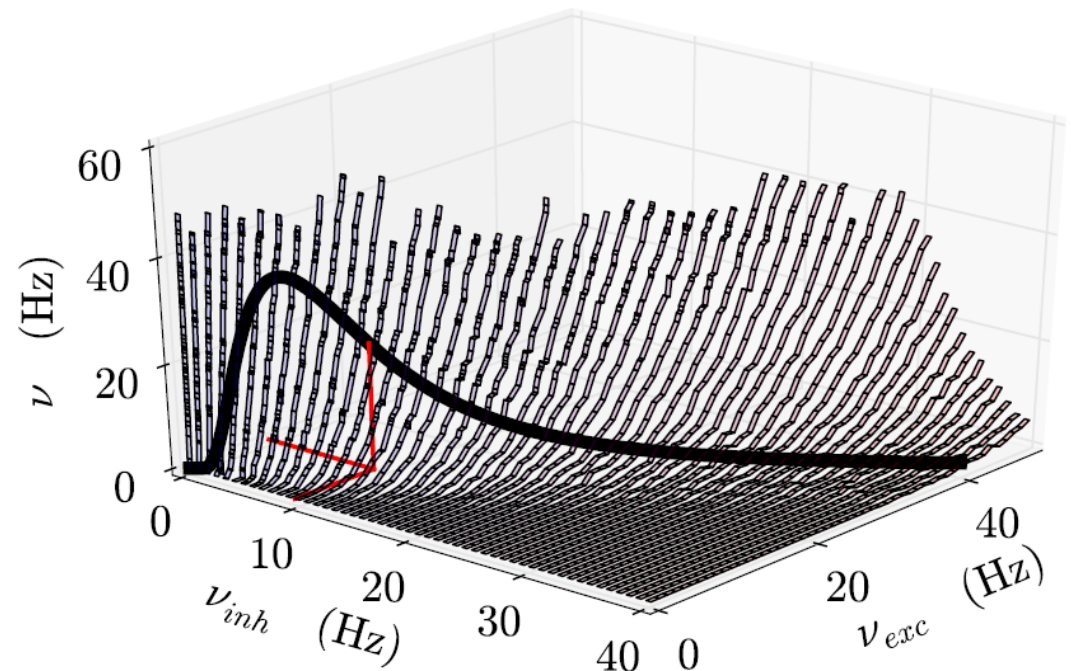
- 1) Analytically => possible only in very simple models
- 2) Numerically => table of values
- 3) Semi-analytic => fit of a template to numerical data:

Template from the IF model
(Amit & Brunel, 1997)

$$\nu_{\text{out}}(\mu_V, \sigma_V, \tau_V^N) = \frac{\Pr(V \geq V_{\text{thre}})}{\tau_V}$$

$$= \frac{1}{2 \tau_V^N \tau_m^0} \text{Erfc} \left(\frac{V_{\text{thre}} - \mu_V}{\sqrt{2} \sigma_V} \right).$$

Fitting the template to simulations



Calculation of the transfer function

If the membrane fluctuations are Gaussian-distributed, with a fixed threshold, the firing rate is given by:

$$\nu_{out} = \mathcal{F}(\nu_e, \nu_i) = \frac{1}{2\tau_V} \cdot \text{Erfc}\left(\frac{V_{thre}^{eff} - \mu_V}{\sqrt{2}\sigma_V}\right)$$

Where $(\mu_V, \sigma_V, \tau_V)$ are the mean, standard deviation and autocorrelation time constant of the membrane potential fluctuations.



Calculation of the transfer function

From Campbell's theorem (Papoulis 1991), we first get the mean (μ_{Ge}, μ_{Gi}) and standard deviation (σ_{Ge}, σ_{Gi}) of the excitatory and inhibitory conductance:

$$\mu_{Ge}(v_e, v_i) = v_e K_e \tau_e Q_e$$

$$\sigma_{Ge}(v_e, v_i) = \sqrt{\frac{v_e K_e \tau_e}{2}} Q_e$$

$$\mu_{Gi}(v_e, v_i) = v_i K_i \tau_i Q_i$$

$$\sigma_{Gi}(v_e, v_i) = \sqrt{\frac{v_i K_i \tau_i}{2}} Q_i$$



Calculation of the transfer function

It is straightforward to calculate the mean V_m :

$$\mu_V(v_e, v_i) = \frac{\mu_{Ge} E_e + \mu_{Gi} E_i + g_L E_L}{\mu_{Ge} + \mu_{Gi} + g_L}$$



Calculation of the transfer function

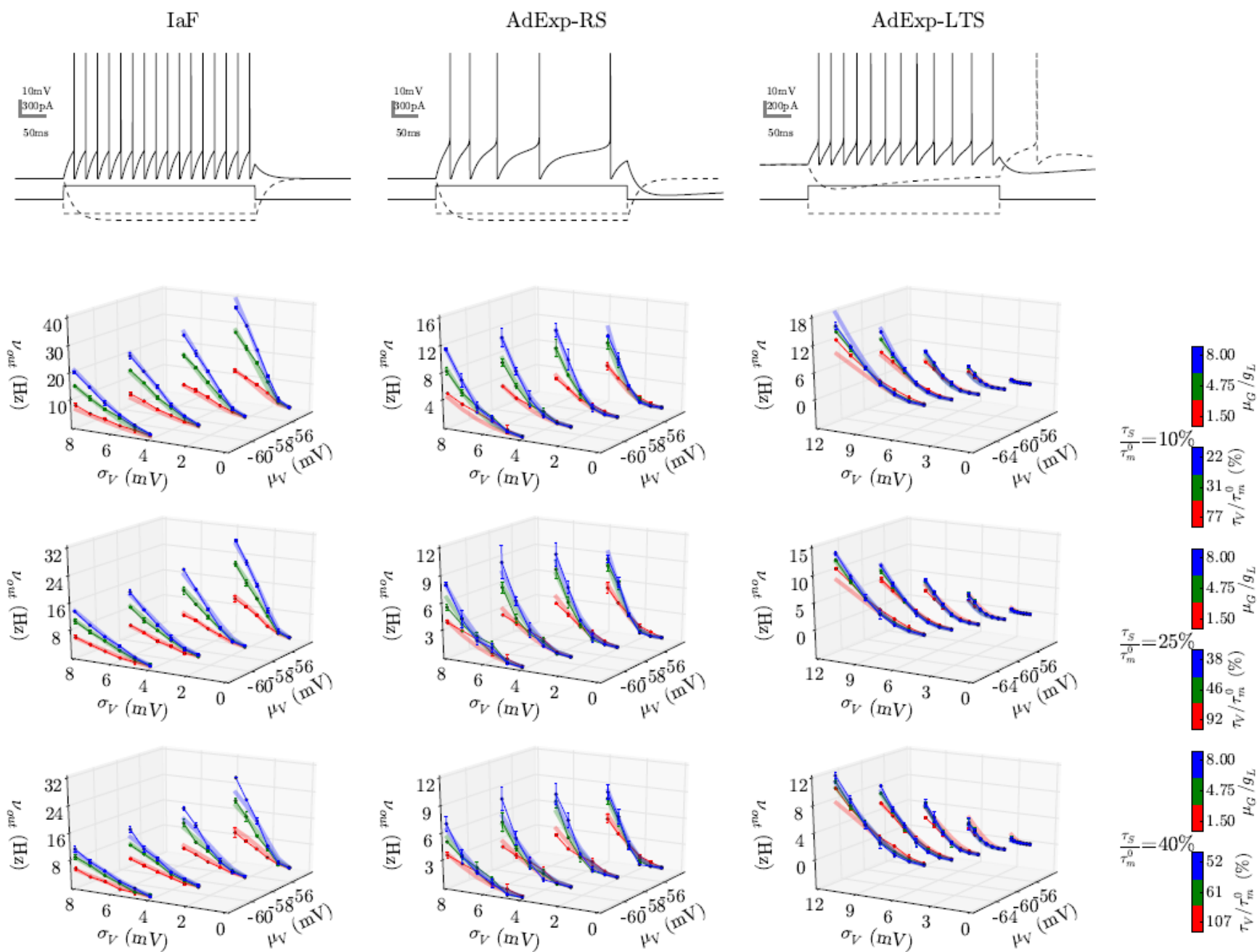
The standard deviation and autocorrelation time of the Vm can be obtained by Fourier transforms, leading to:

$$\sigma_V(\nu_e, \nu_i) = \sqrt{\sum_s K_s \nu_s \frac{(U_s \cdot \tau_s)^2}{2(\tau_m^{\text{eff}} + \tau_s)}}$$

$$\tau_V(\nu_e, \nu_i) = \left(\frac{\sum_s (K_s \nu_s (U_s \cdot \tau_s)^2)}{\sum_s (K_s \nu_s (U_s \cdot \tau_s)^2 / (\tau_m^{\text{eff}} + \tau_s))} \right)$$

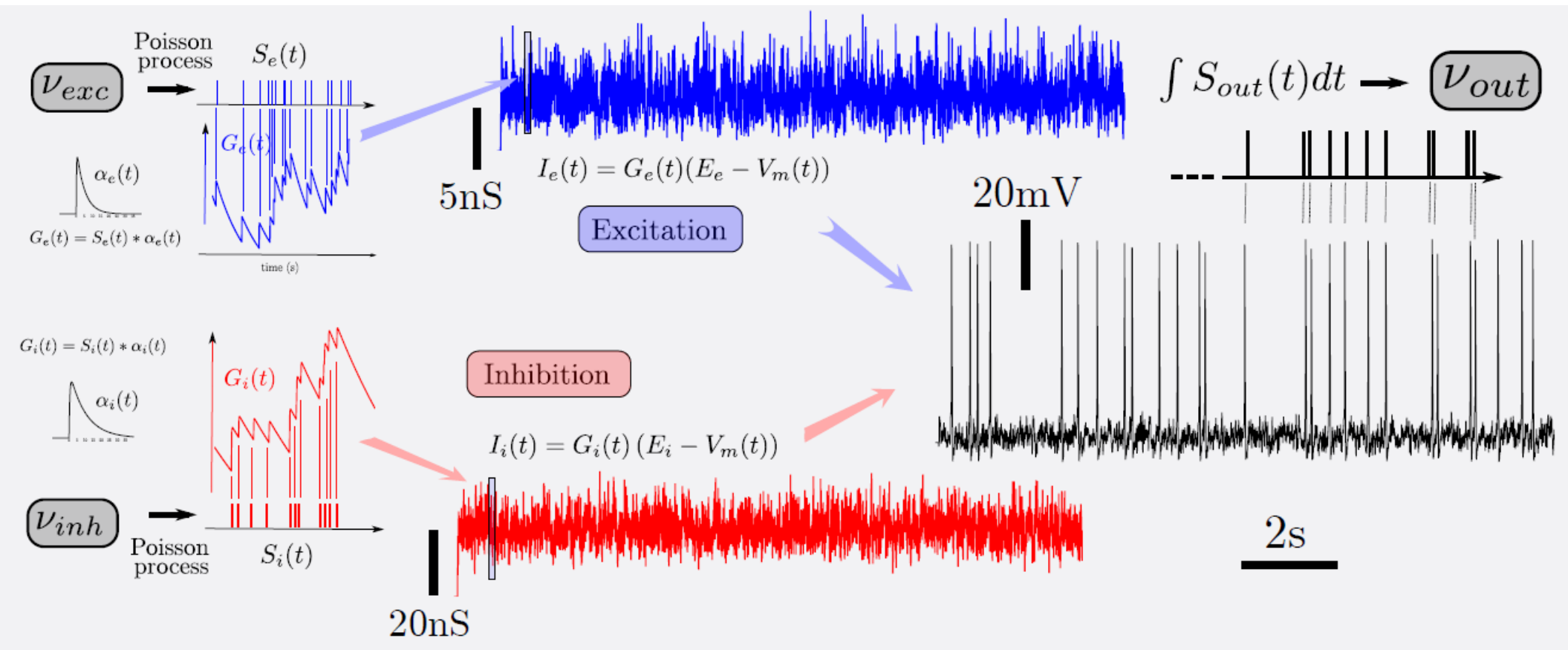


Transfer function of models of various complexity



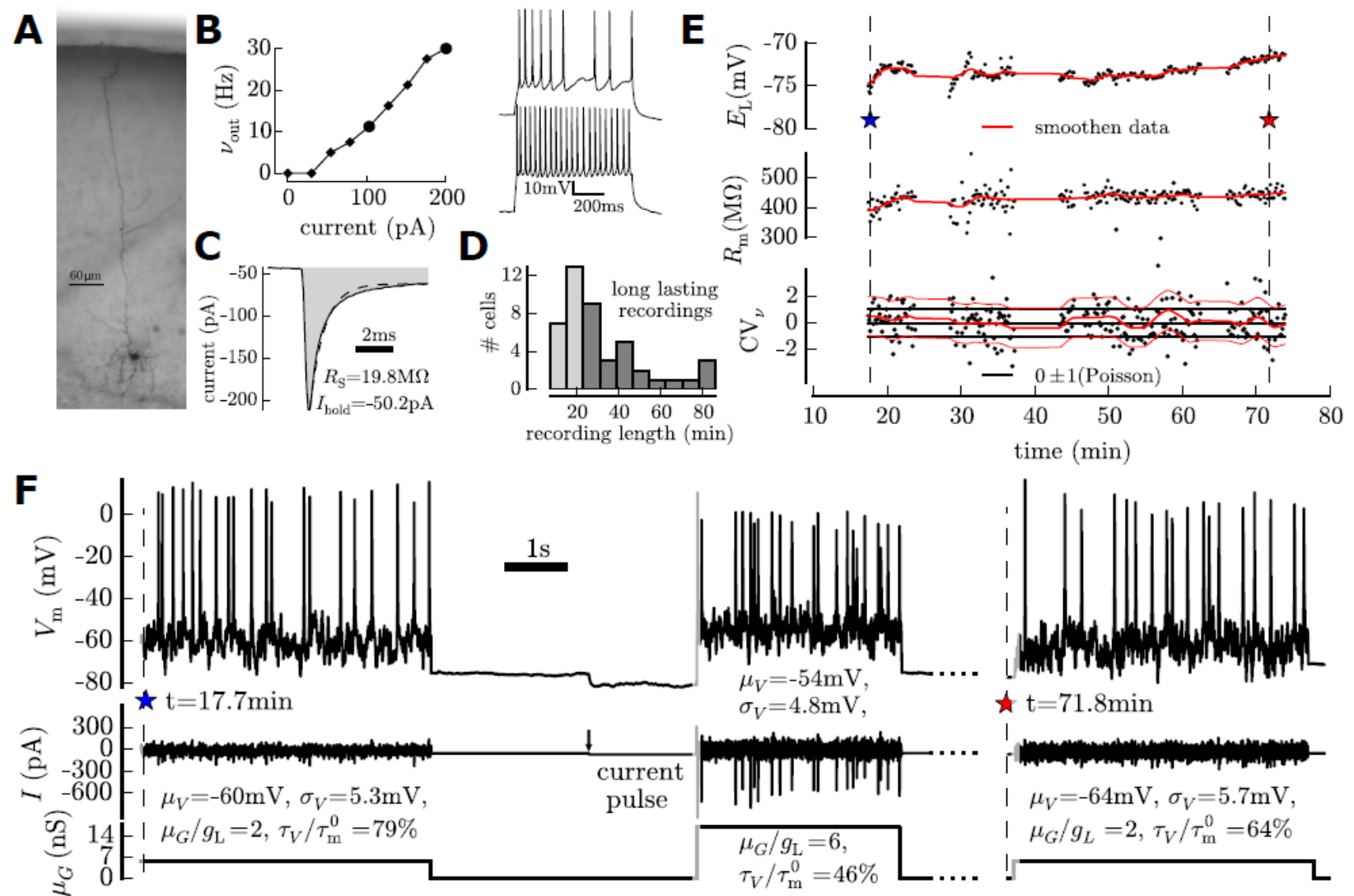
Transfer function from real neurons

How to calculate the transfer function from real neurons



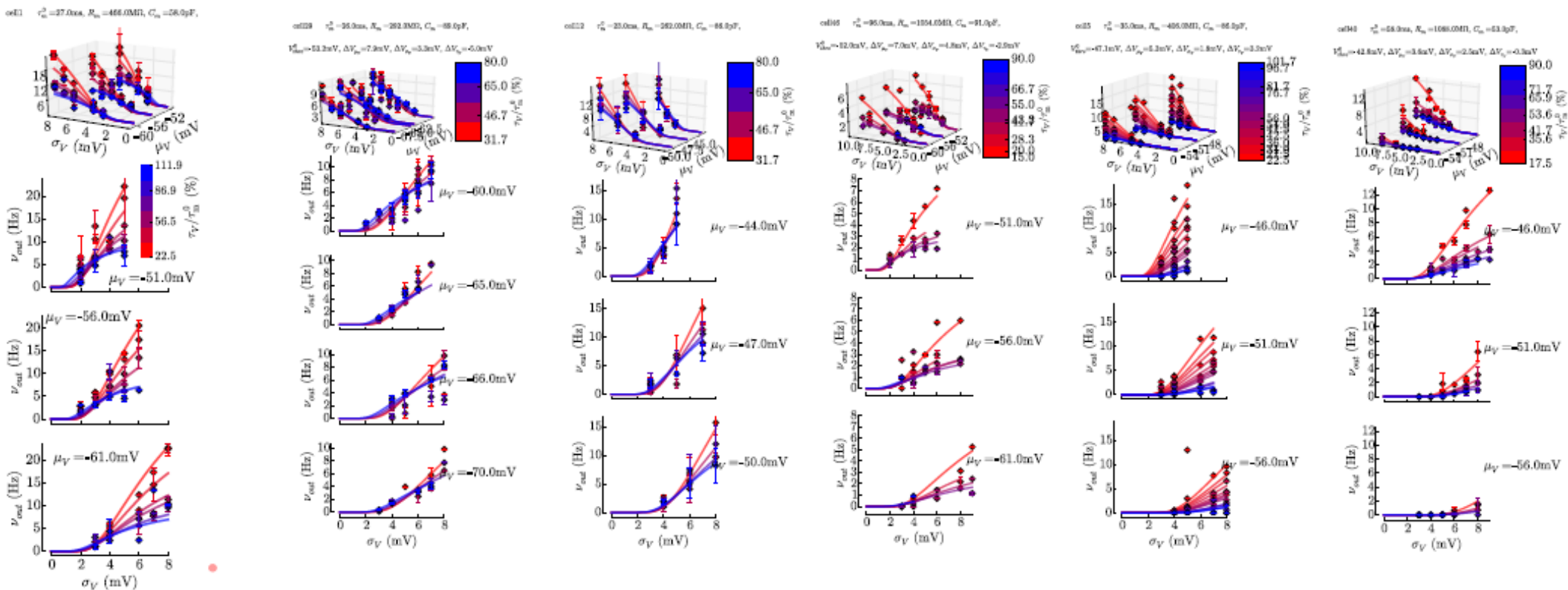
Transfer function from real neurons

Intracellular perforated patch recordings on pyramidal neurons in the visual cortex of juvenile mice in vitro using the dynamic clamp technique



Transfer function from real neurons

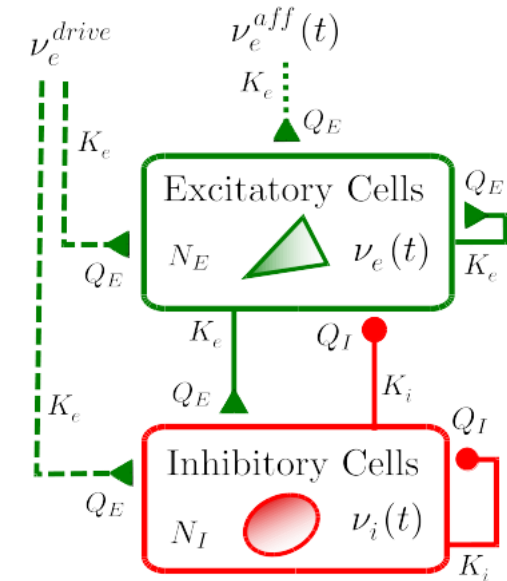
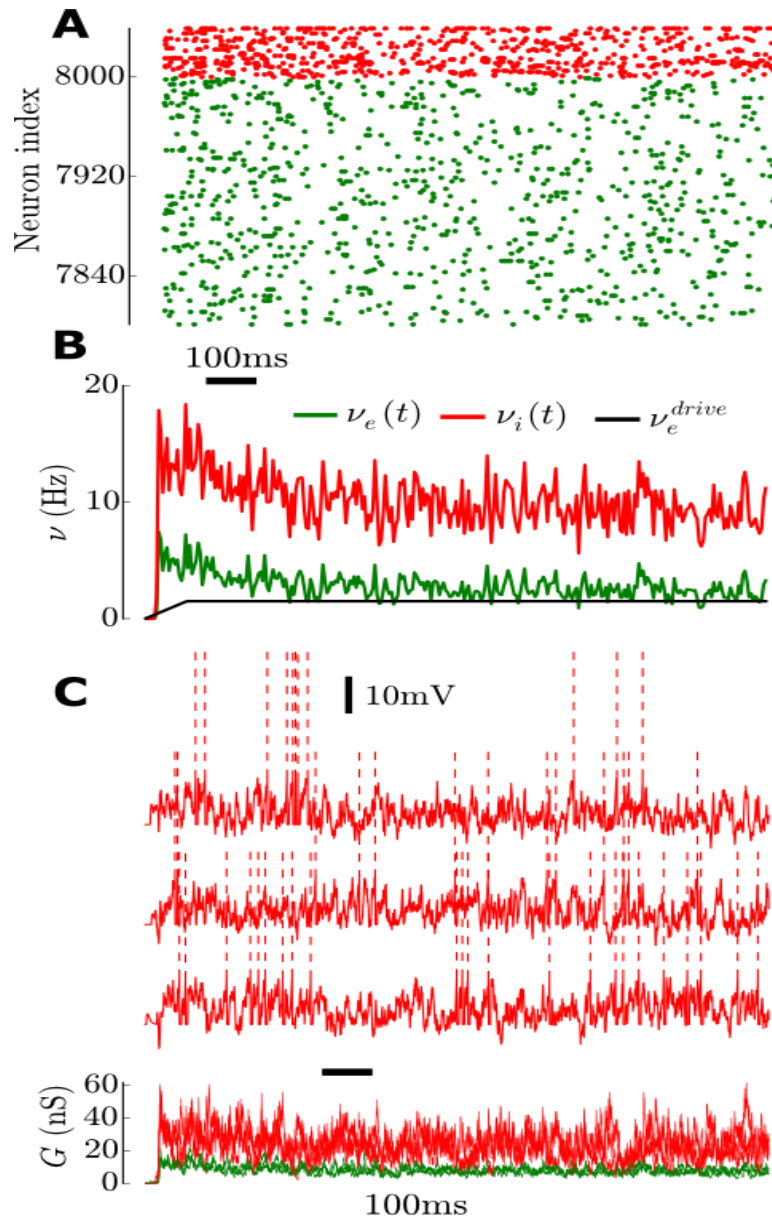
Examples of transfer functions from mouse V1 neurons



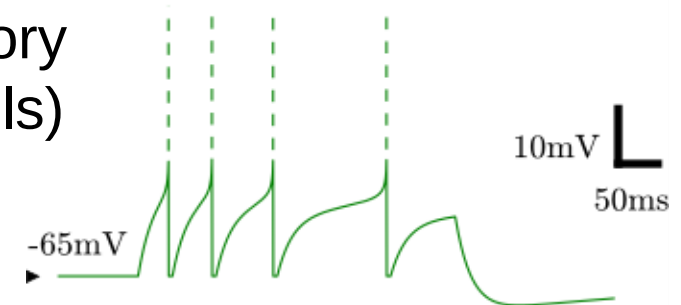
Mean-field model of a local neural population

Networks of nonlinear IF neurons

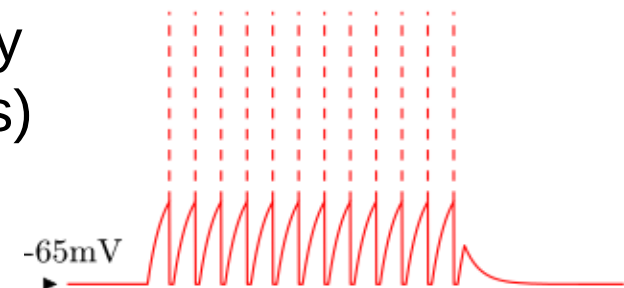
Biophysical model of AI states :



Excitatory
(RS cells)



Inhibitory
(FS cells)

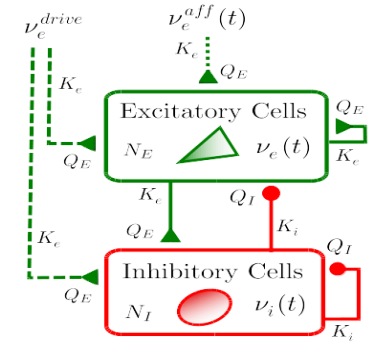


Mean-field model of AdEx networks

Master Equation formalism with 2 populations

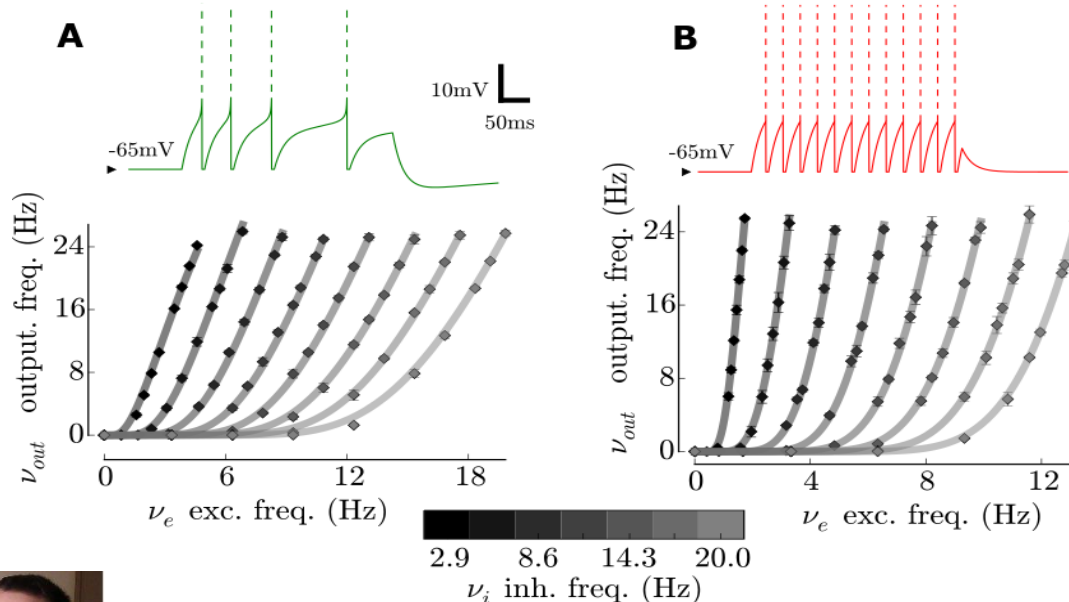
Transfer functions $\mathcal{F}_\mu$

$$\mathcal{F}_\mu(\nu_e, \nu_i), \forall \mu \in \{e, i\}.$$



Excitatory cells

Inhibitory cells



Second-order description:

$$\begin{cases} T \frac{\partial \nu_\mu}{\partial t} = (\mathcal{F}_\mu - \nu_\mu) + \frac{1}{2} c_{\lambda\eta} \frac{\partial^2 \mathcal{F}_\mu}{\partial \nu_\lambda \partial \nu_\eta} \\ T \frac{\partial c_{\lambda\eta}}{\partial t} = A_{\lambda\eta} + (\mathcal{F}_\lambda - \nu_\lambda) (\mathcal{F}_\eta - \nu_\eta) + c_{\lambda\mu} \frac{\partial \mathcal{F}_\mu}{\partial \nu_\lambda} + c_{\mu\eta} \frac{\partial \mathcal{F}_\mu}{\partial \nu_\eta} - 2c_{\lambda\eta} \end{cases}$$

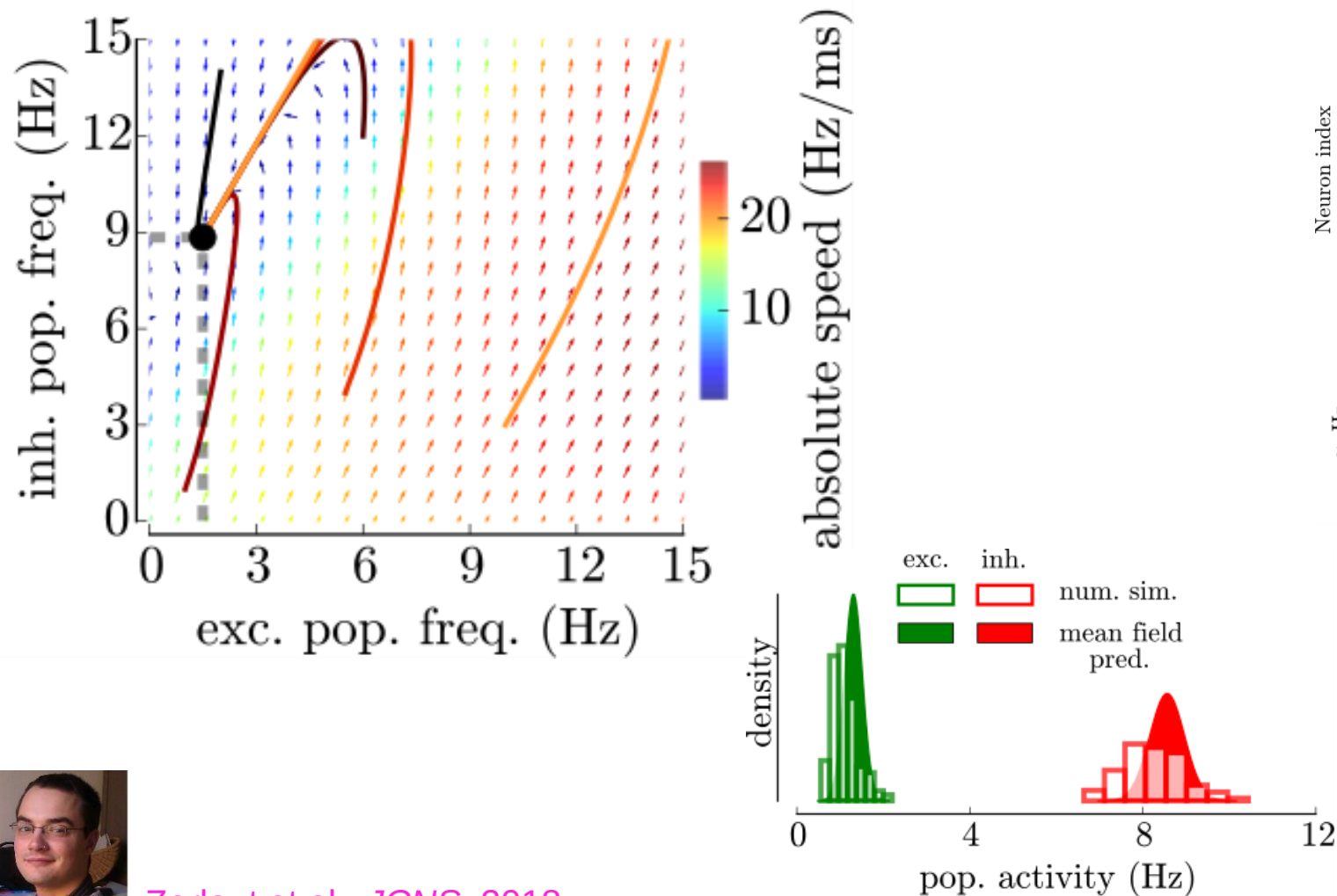
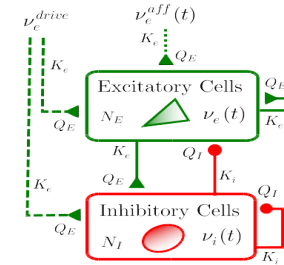
At first-order :

$$T \frac{\partial \nu_\mu}{\partial t} = \mathcal{F}_\mu - \nu_\mu$$



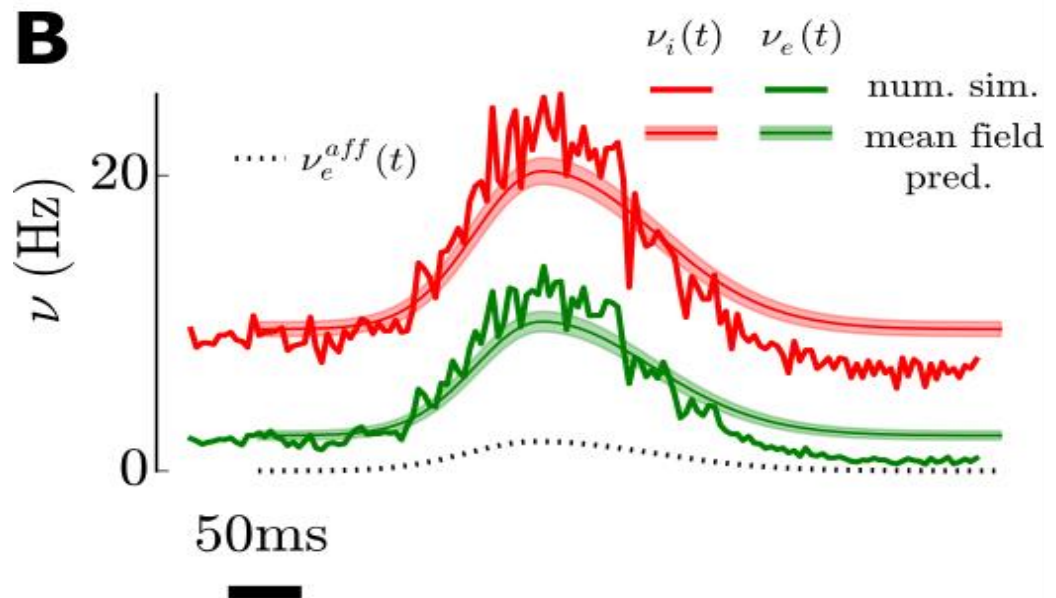
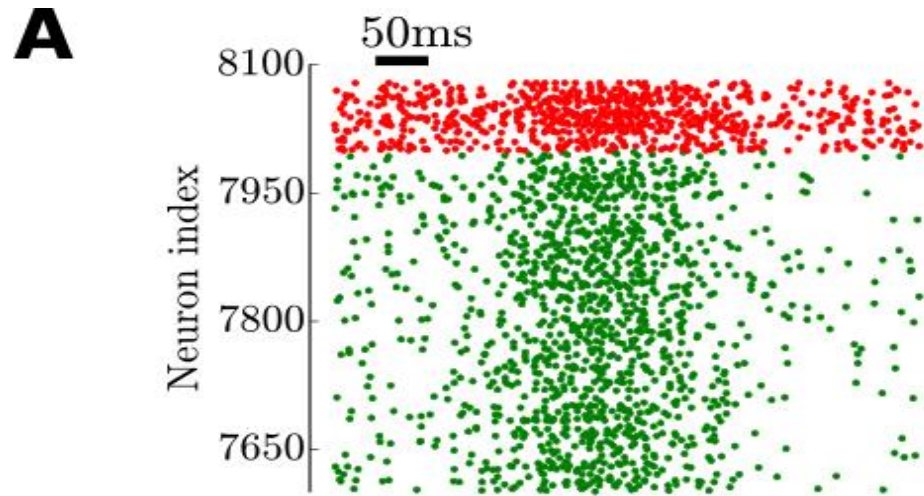
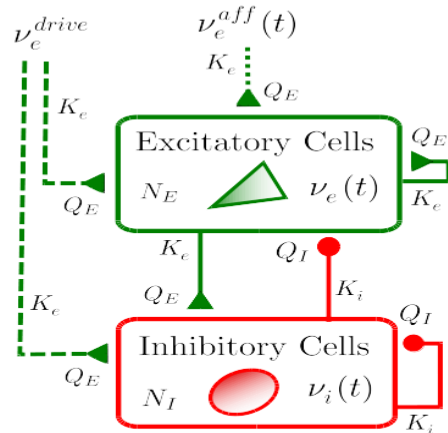
Prediction of spontaneous activity

Mean field (1st-order) prediction of RS and FS stationary firing rates during AI activity states

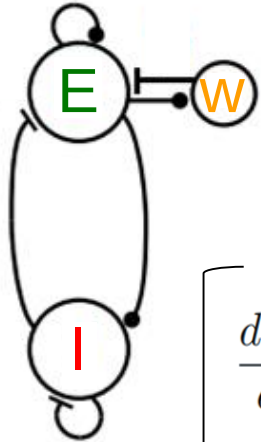


Time-dependent responses

Mean field (2nd-order) prediction of the population response of RS and FS cells following excitatory input

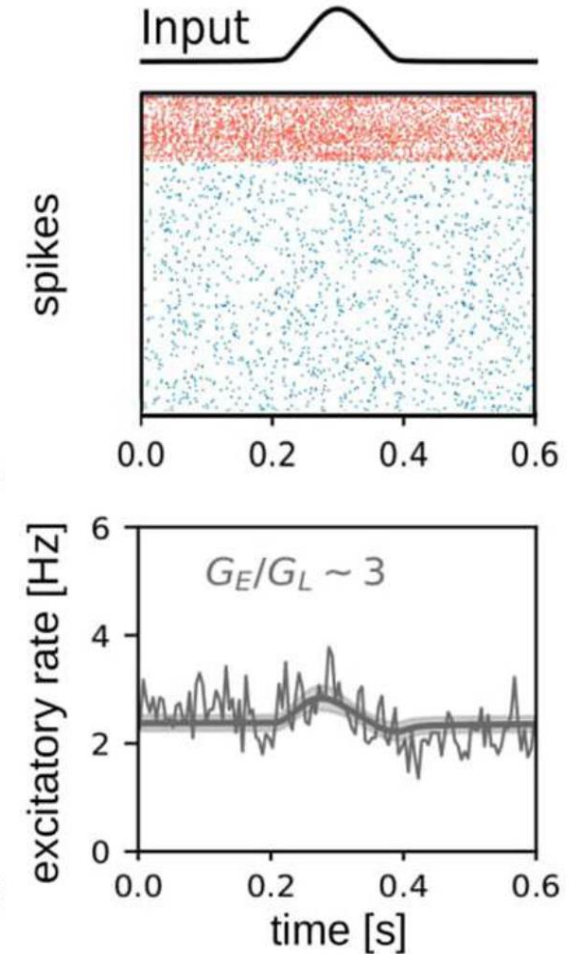
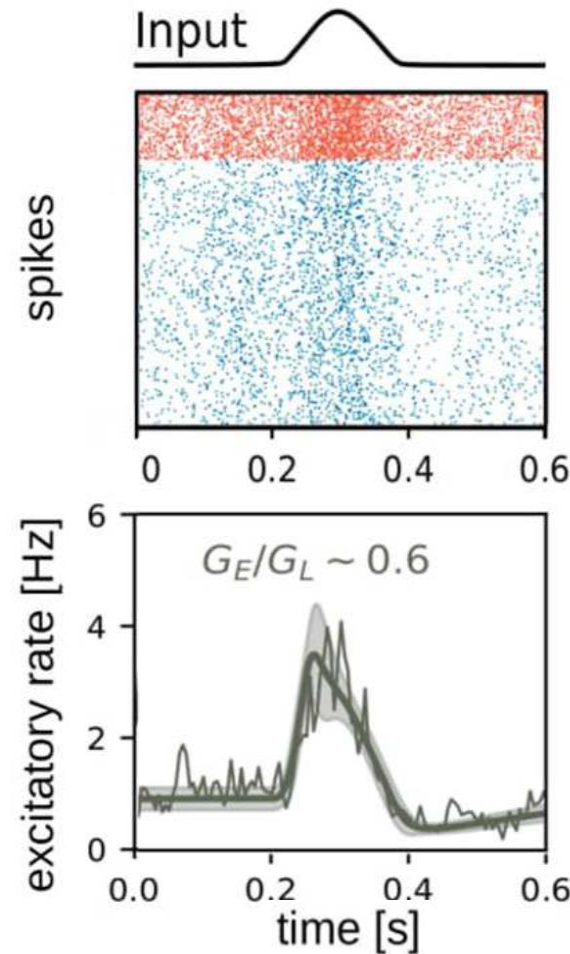


Mean-field model with adaptation

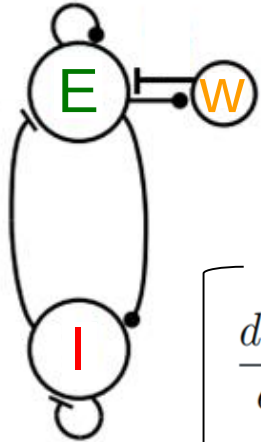


$$\begin{cases} \frac{d\nu_E}{dt} = \frac{\text{TF}_E(\nu_E, \nu_I, w) - \nu_E}{\tau_E} \\ \frac{d\nu_I}{dt} = \frac{\text{TF}_I(\nu_E, \nu_I) - \nu_I}{\tau_I} \\ \frac{dw}{dt} = \frac{-w + a(\langle V \rangle - E_l) + b\nu_E}{\tau_w} \end{cases}$$

- A system of 3 coupled equations can be written for Excitatory – Inhibitory populations + adaptation
- Reproduces **State dependent responses**

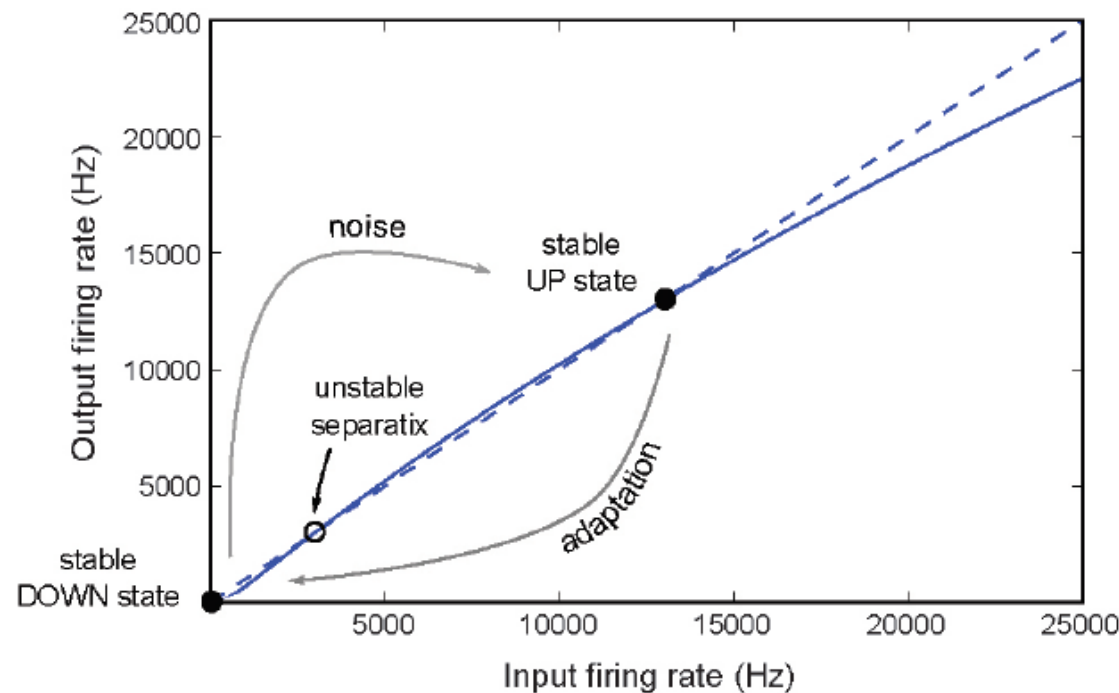


Mean-field model with adaptation

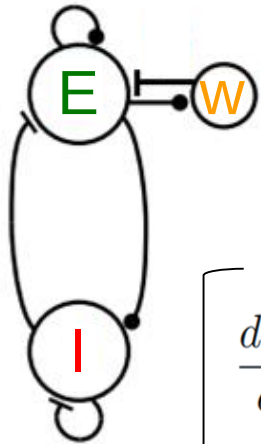


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- A system of 3 coupled equations can be written for Excitatory – Inhibitory populations + adaptation
- Reproduces **Up and Down states**

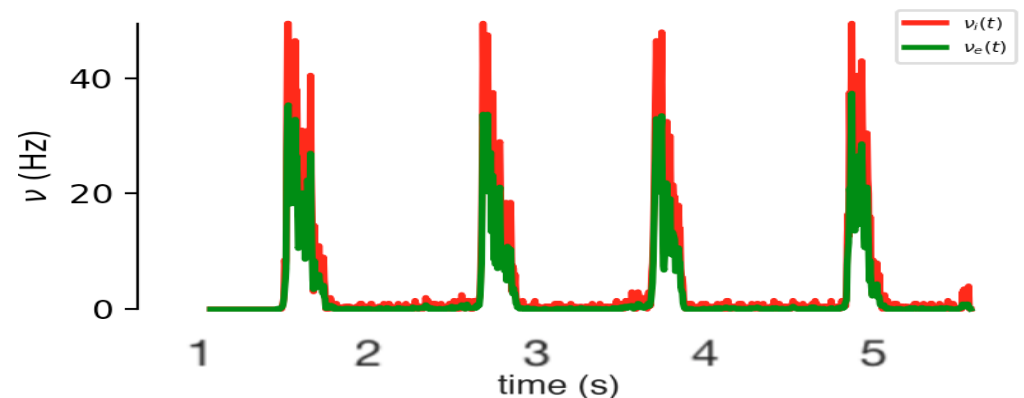
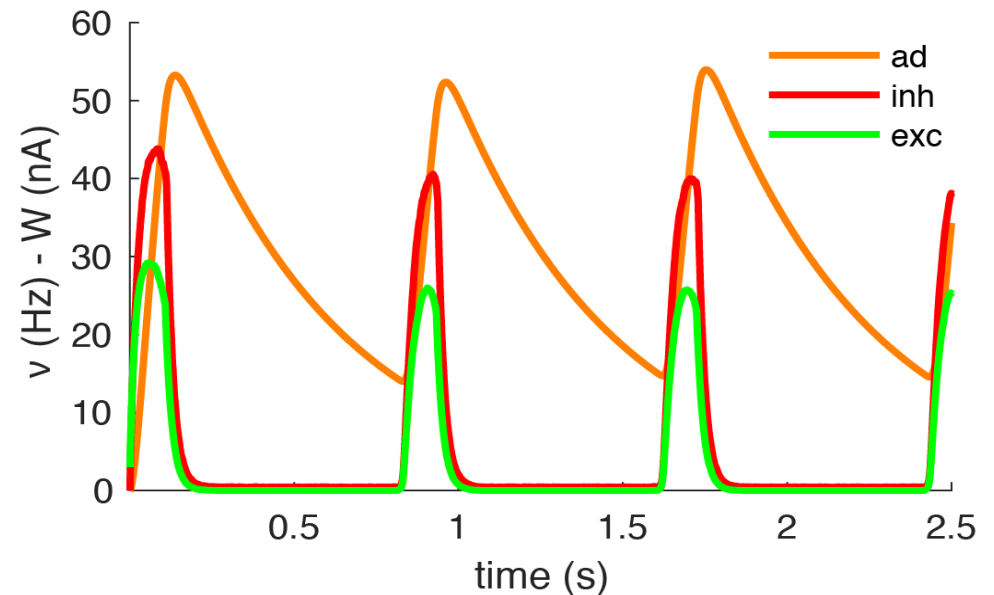


Mean-field model with adaptation



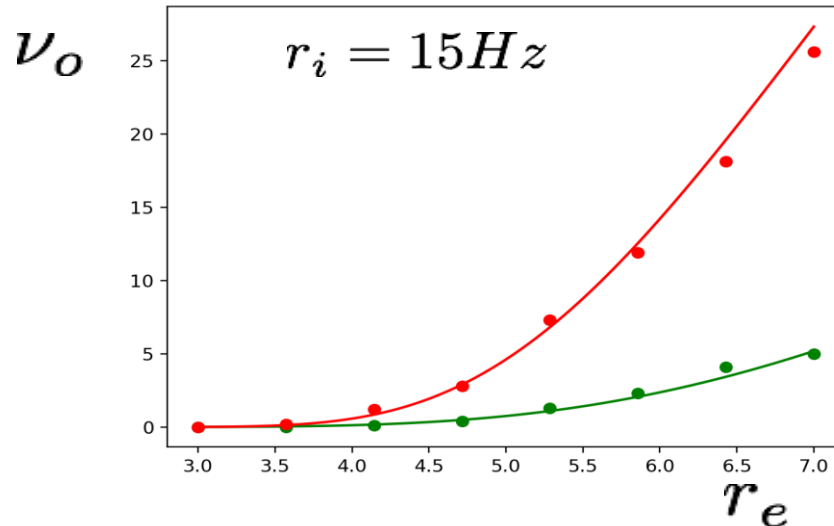
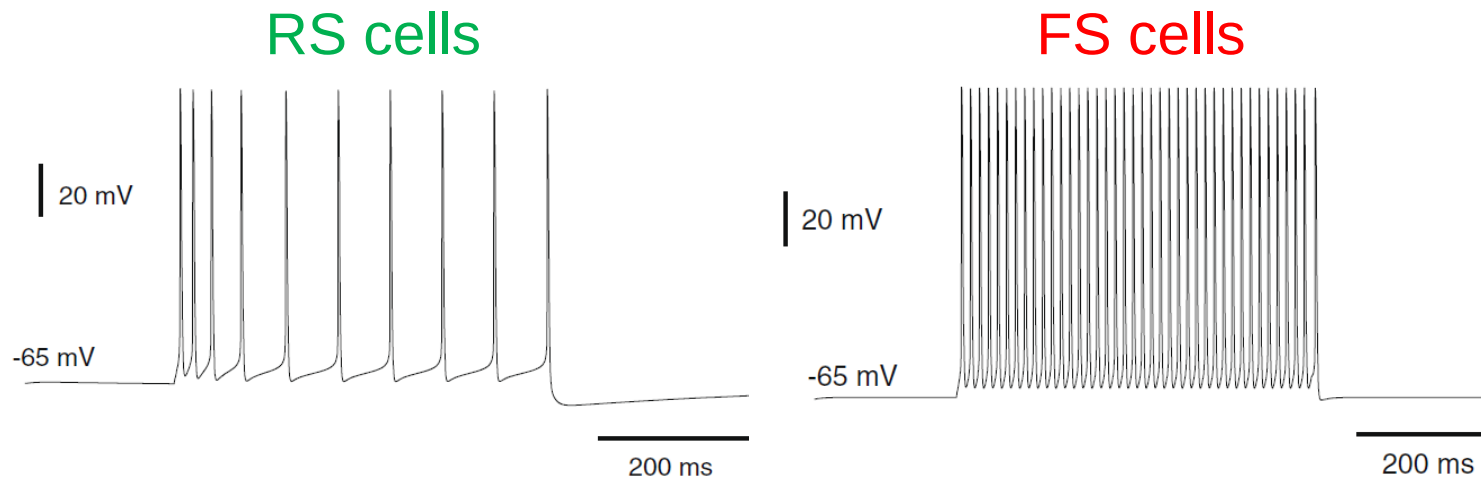
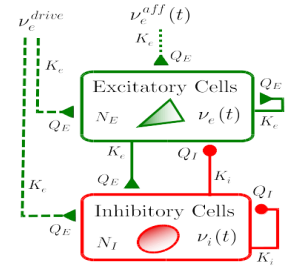
$$\left\{ \begin{aligned} \frac{d\nu_E}{dt} &= \frac{\text{TF}_E(\nu_E, \nu_I, w) - \nu_E}{\tau_E} \\ \frac{d\nu_I}{dt} &= \frac{\text{TF}_I(\nu_E, \nu_I) - \nu_I}{\tau_I} \\ \frac{dw}{dt} &= \frac{-w + a(\langle V \rangle - E_l) + b\nu_E}{\tau_w} \end{aligned} \right.$$

- A system of 3 coupled equations can be written for Excitatory – Inhibitory populations + adaptation
- Reproduces **Up and Down states**



Mean-field of HH model

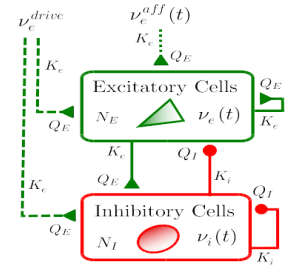
Calculation of the transfer functions



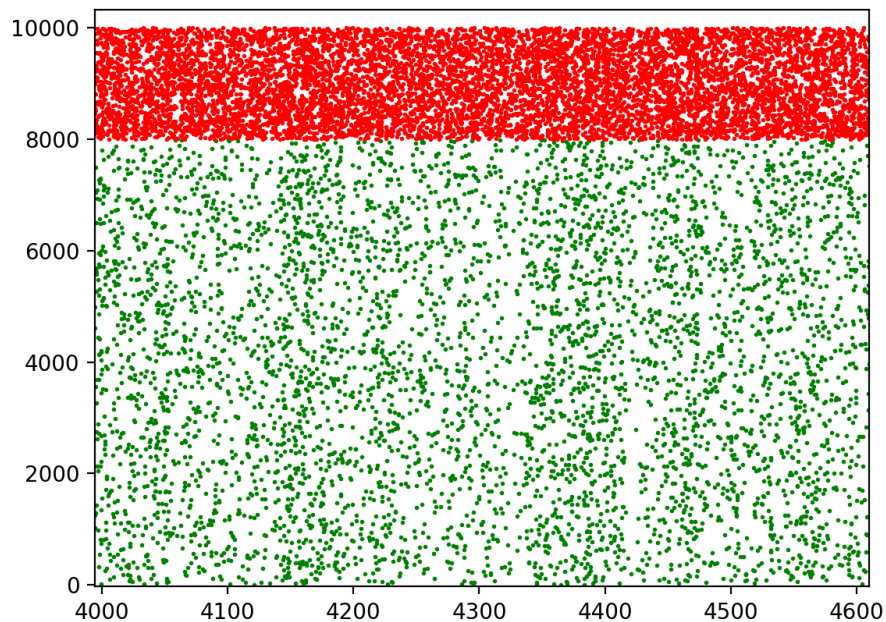
Carlu et al.,
J. Neurophysiol.
(2020)

Mean-field of HH model

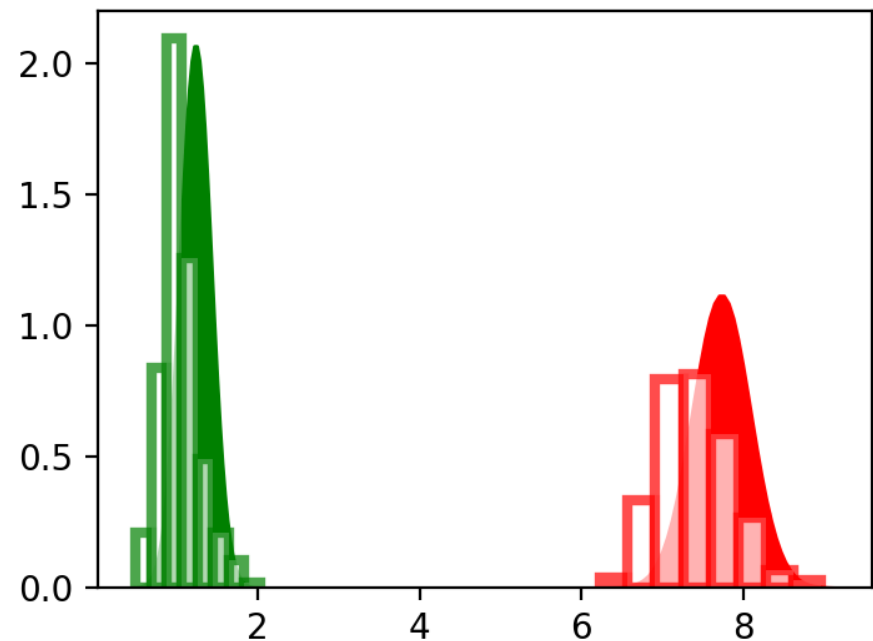
Prediction of spontaneous activity



AI state with HH models



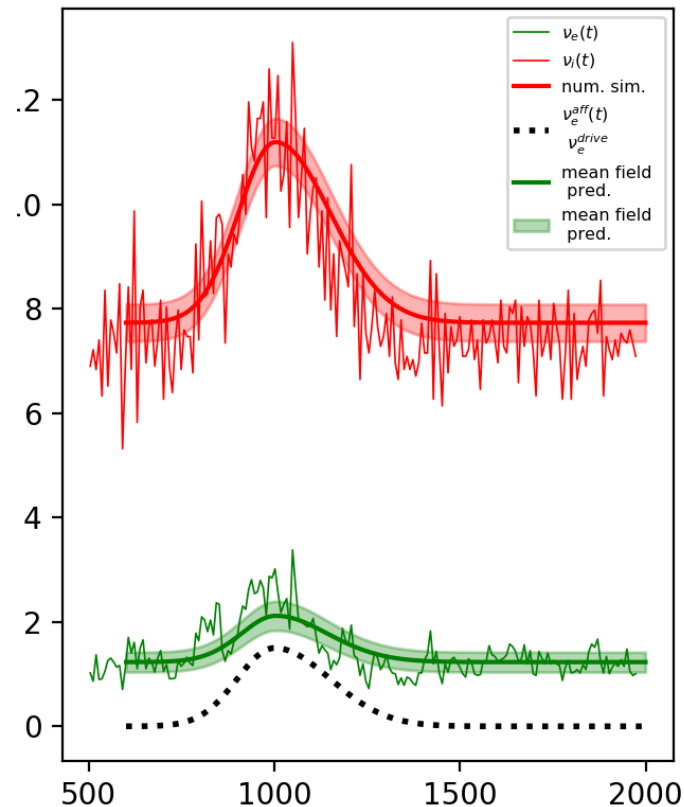
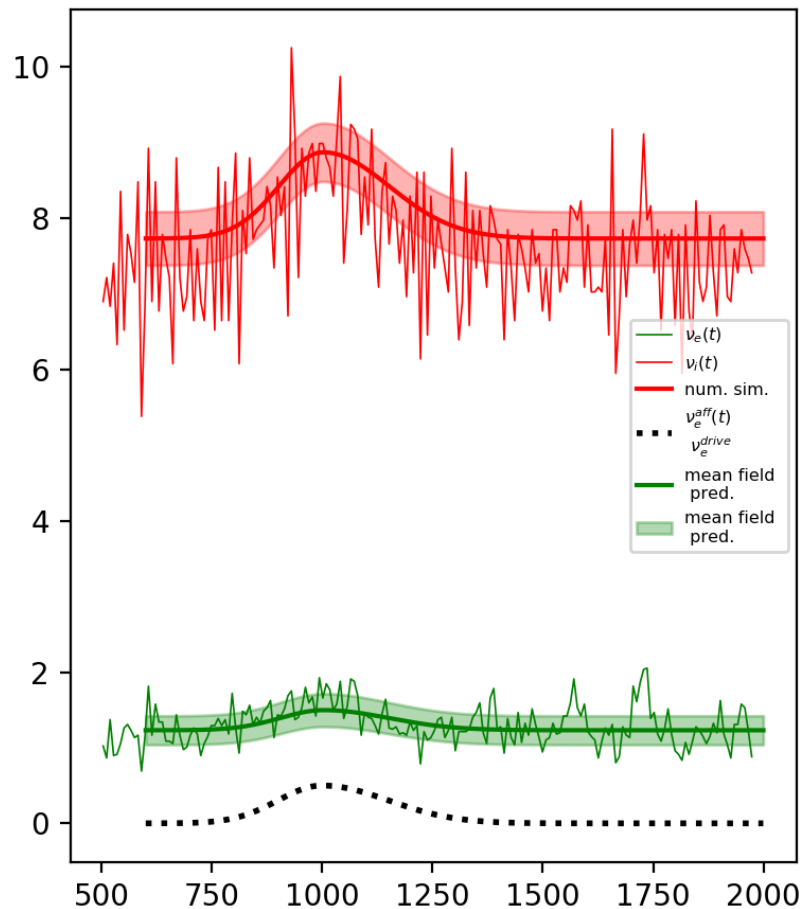
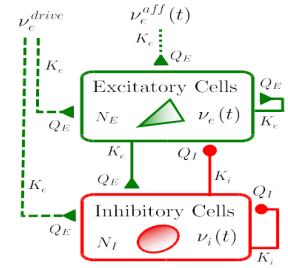
Mean-field prediction



Carlu et al.,
J. Neurophysiol.
(2020)

Mean-field of HH model

Prediction of the response of the HH network to two different stimuli

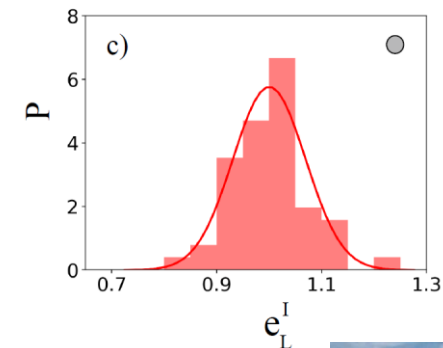
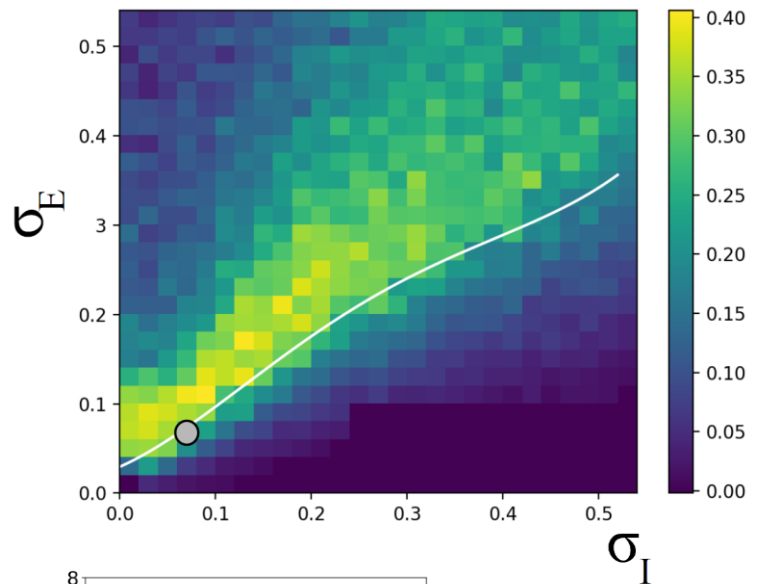
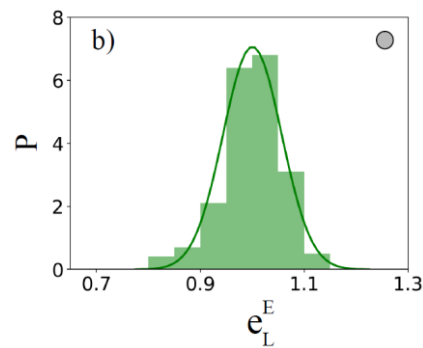
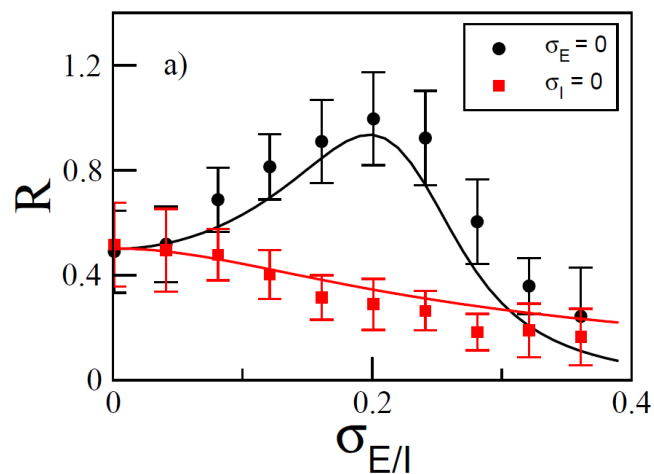


Carlu et al.,
J. Neurophysiol.
(2020)

Heterogeneous mean-field models

Extension of the mean-field model to heterogeneous networks
(work in progress)

$$\begin{aligned}\tau_m \dot{r}^E &= -r^E + \int dx P(x) F_x^E(r^E + \nu_{ext}, r^I, W) \\ \tau_m \dot{r}^I &= -r^I + \int dy P(y) F_y^I(r^E + \nu_{ext}, r^I) \\ \tau_w \dot{W} &= -W + br^E + a(V(r^E + \nu_{ext}, r^I, W) - E_L^E),\end{aligned}$$

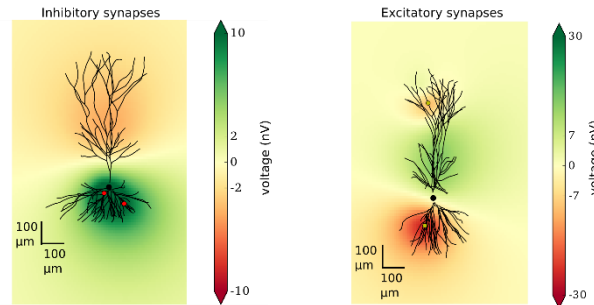


Di Volo & Destexhe,
Sci Reports 2021

Mean-field model of neurons with dendrites

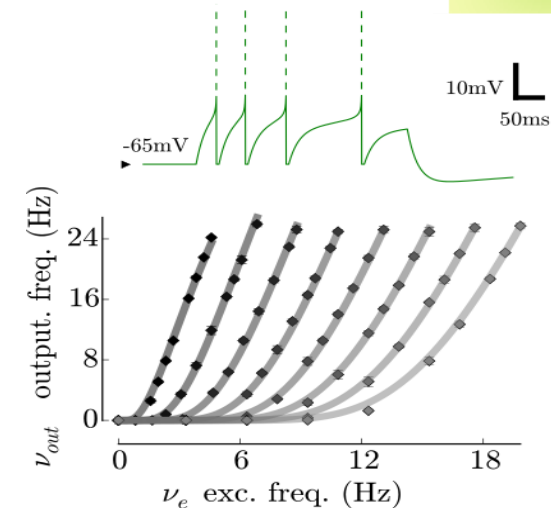
Extension of the mean-field model to neurons with dendrites
(work in progress)

1. Evaluate the transfer function

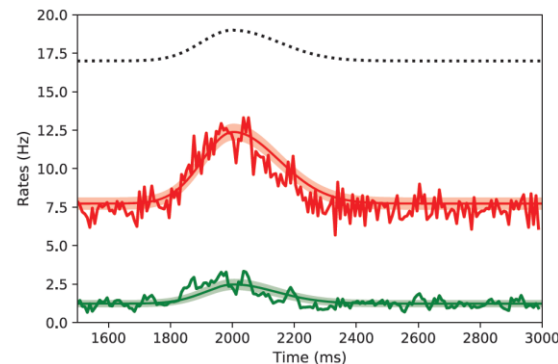


2. Integrate in mean-field models

$$\begin{cases} T \frac{\partial \nu_\mu}{\partial t} = (\mathcal{F}_\mu - \nu_\mu) + \frac{1}{2} c_{\lambda\eta} \frac{\partial^2 \mathcal{F}_\mu}{\partial \nu_\lambda \partial \nu_\eta} \\ T \frac{\partial c_{\lambda\eta}}{\partial t} = A_{\lambda\eta} + (\mathcal{F}_\lambda - \nu_\lambda) (\mathcal{F}_\eta - \nu_\eta) + \\ \quad c_{\lambda\mu} \frac{\partial \mathcal{F}_\mu}{\partial \nu_\lambda} + c_{\mu\eta} \frac{\partial \mathcal{F}_\mu}{\partial \nu_\eta} - 2c_{\lambda\eta} \end{cases}$$



3. Compare mean-field with numerical simulations

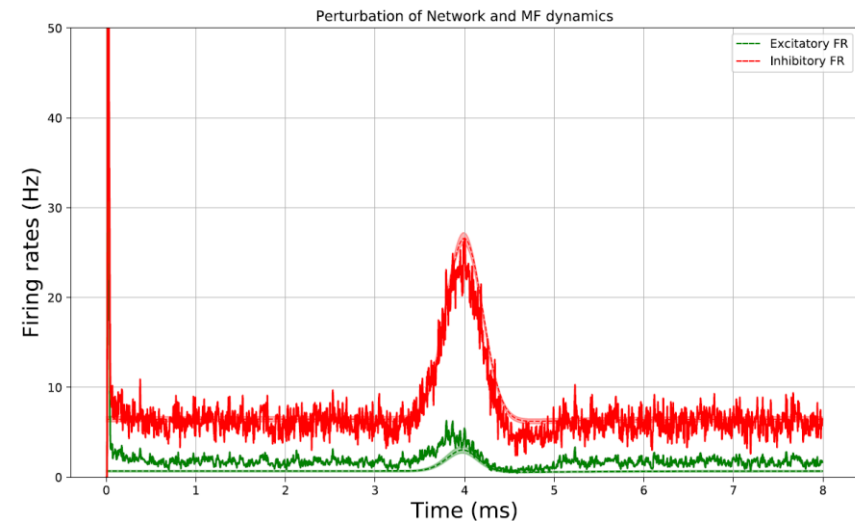
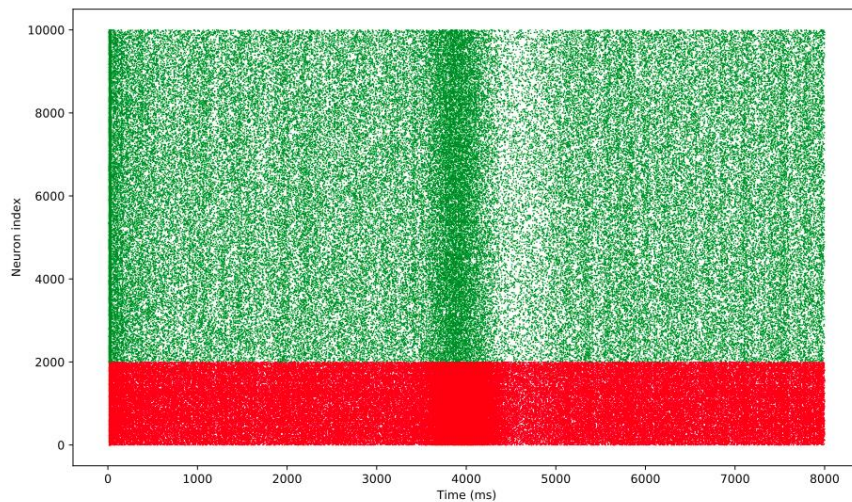


Mean-field model of neurons with dendrites

Extension of the mean-field model to neurons with dendrites
(work in progress)

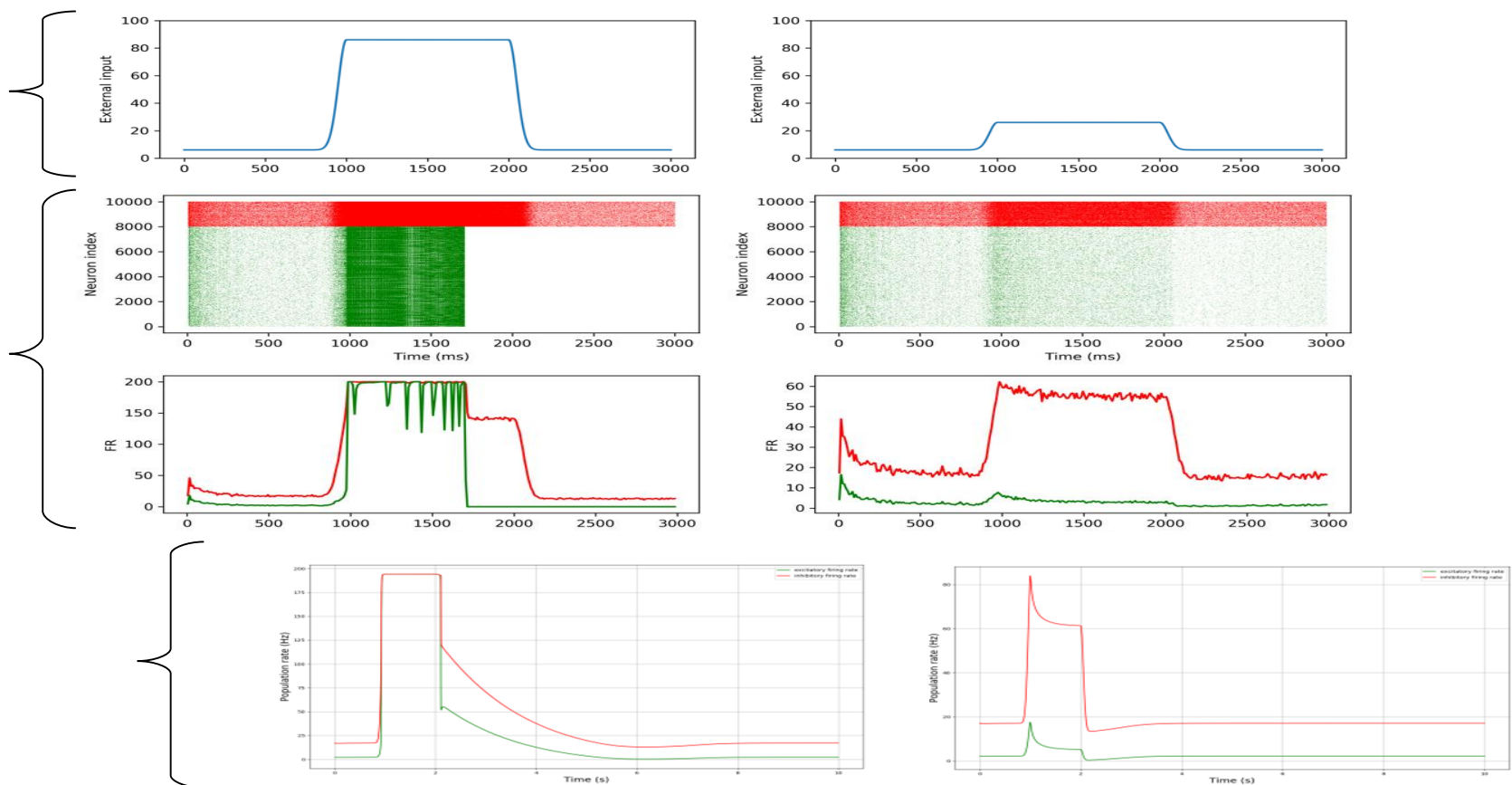
Preliminary results on networks of ball-and-stick neurons

Raster plot of the perturbed Network



Mean-field model of epileptic seizures

Extension of the mean-field model to epileptic seizures
(work in progress)

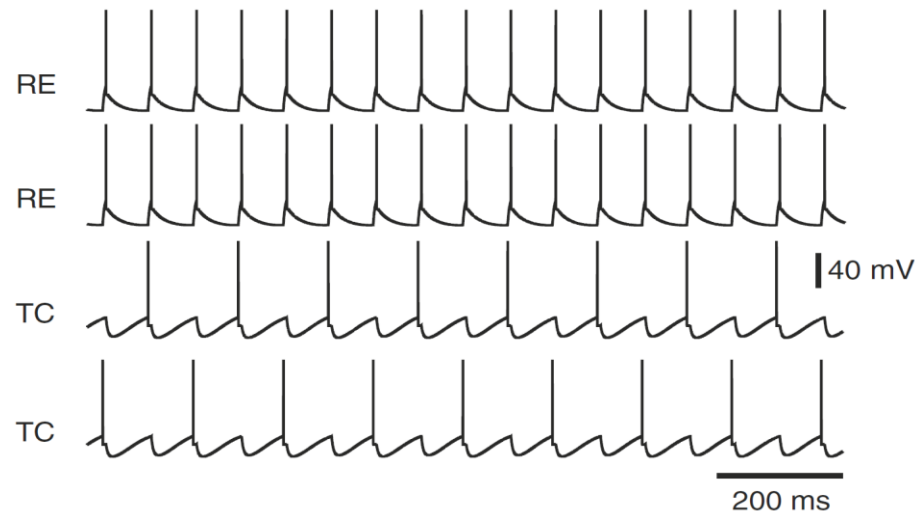
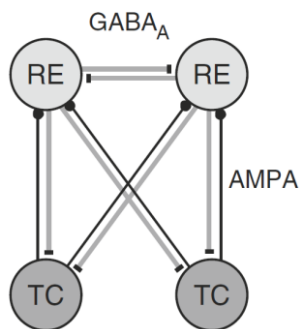
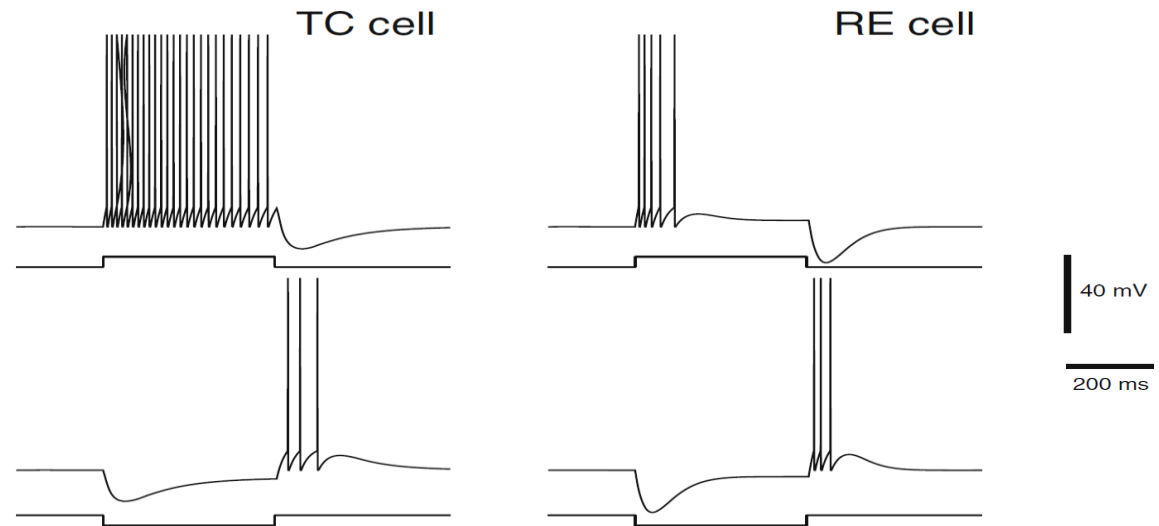


Depannemaecker et al., *in progress*

Mean-field model of thalamic networks

Mean-field model of thalamic circuits (work in progress)

Thalamic neurons
can be modeled
with the AdEx
model

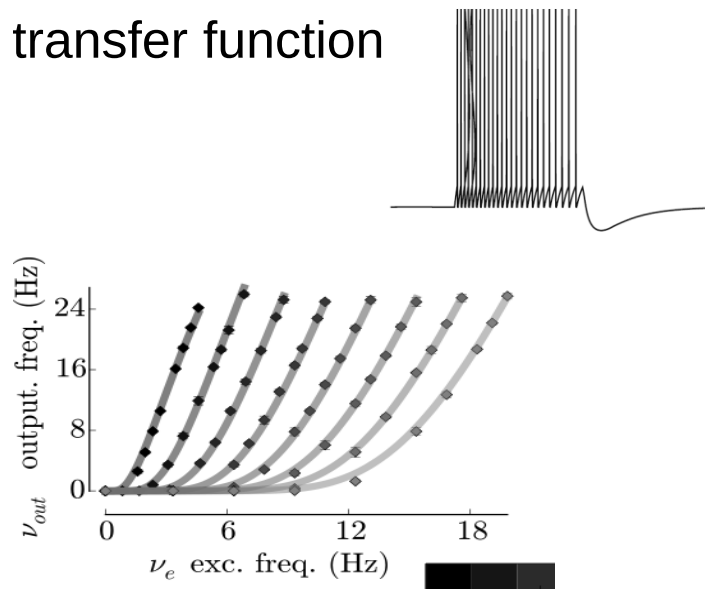


Guarino, Carlu et al.,
in progress

Mean-field model of thalamic networks

Mean-field model of thalamic circuits (work in progress)

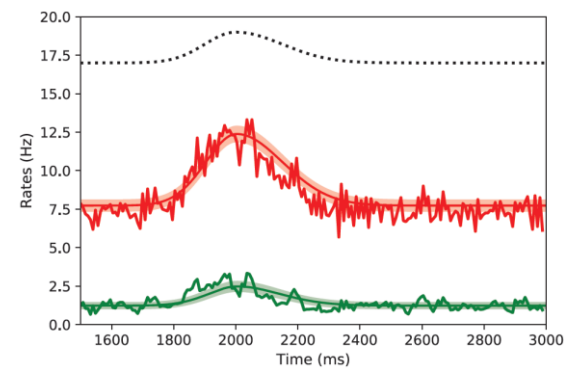
1. Evaluate the transfer function



2. Integrate in the AdEx mean-field model

$$\begin{cases} \frac{d\nu_E}{dt} = \frac{\text{TF}_E(\nu_E, \nu_I, w) - \nu_E}{\tau_E} \\ \frac{d\nu_I}{dt} = \frac{\text{TF}_I(\nu_E, \nu_I) - \nu_I}{\tau_I} \\ \frac{dw}{dt} = \frac{-w + a(\langle V \rangle - E_l) + b\nu_E}{\tau_w} \end{cases}$$

3. Compare mean-field with numerical simulations

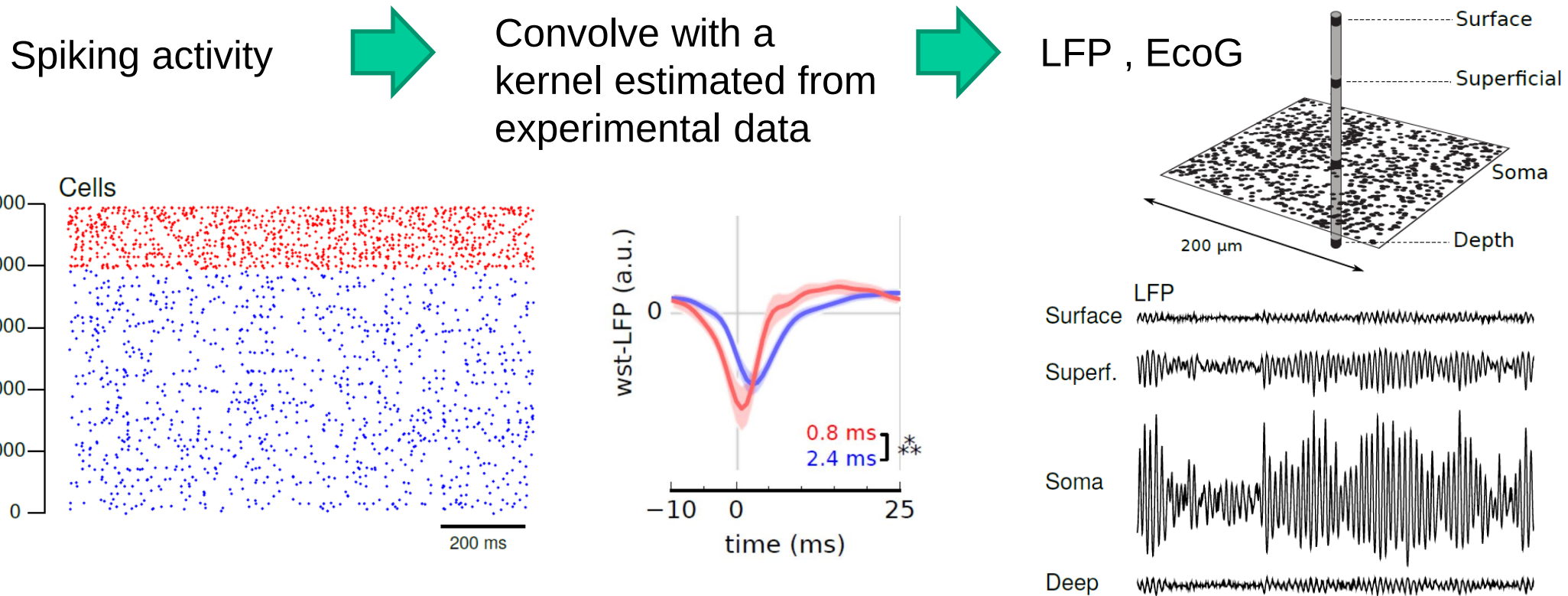


Guarino, Carlu et al.,
in progress

Linking mean-field models to brain signals

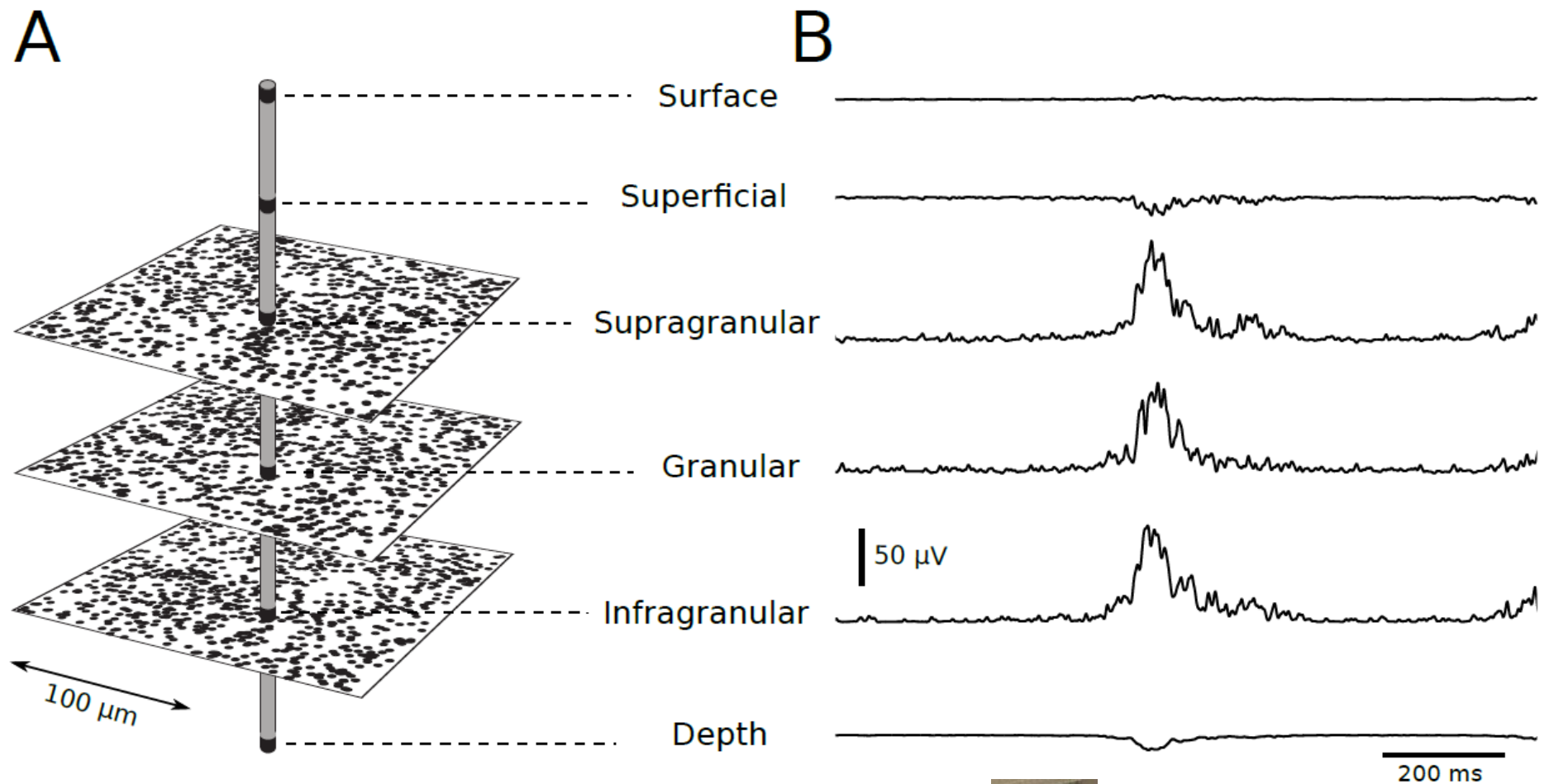
Linking mean-field models to brain signals

LFP/EcoG/EEG: the kernel method



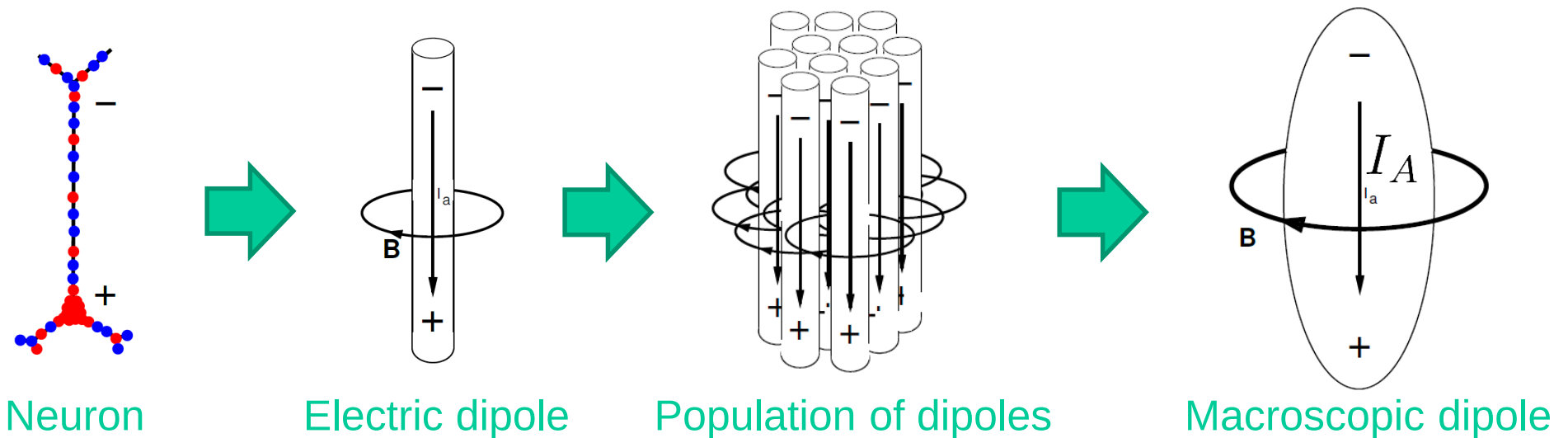
Linking mean-field models to brain signals

LFP/EcoG/EEG: the kernel method



Linking mean-field models to brain signals

Genesis of MEG signals from mean-field models



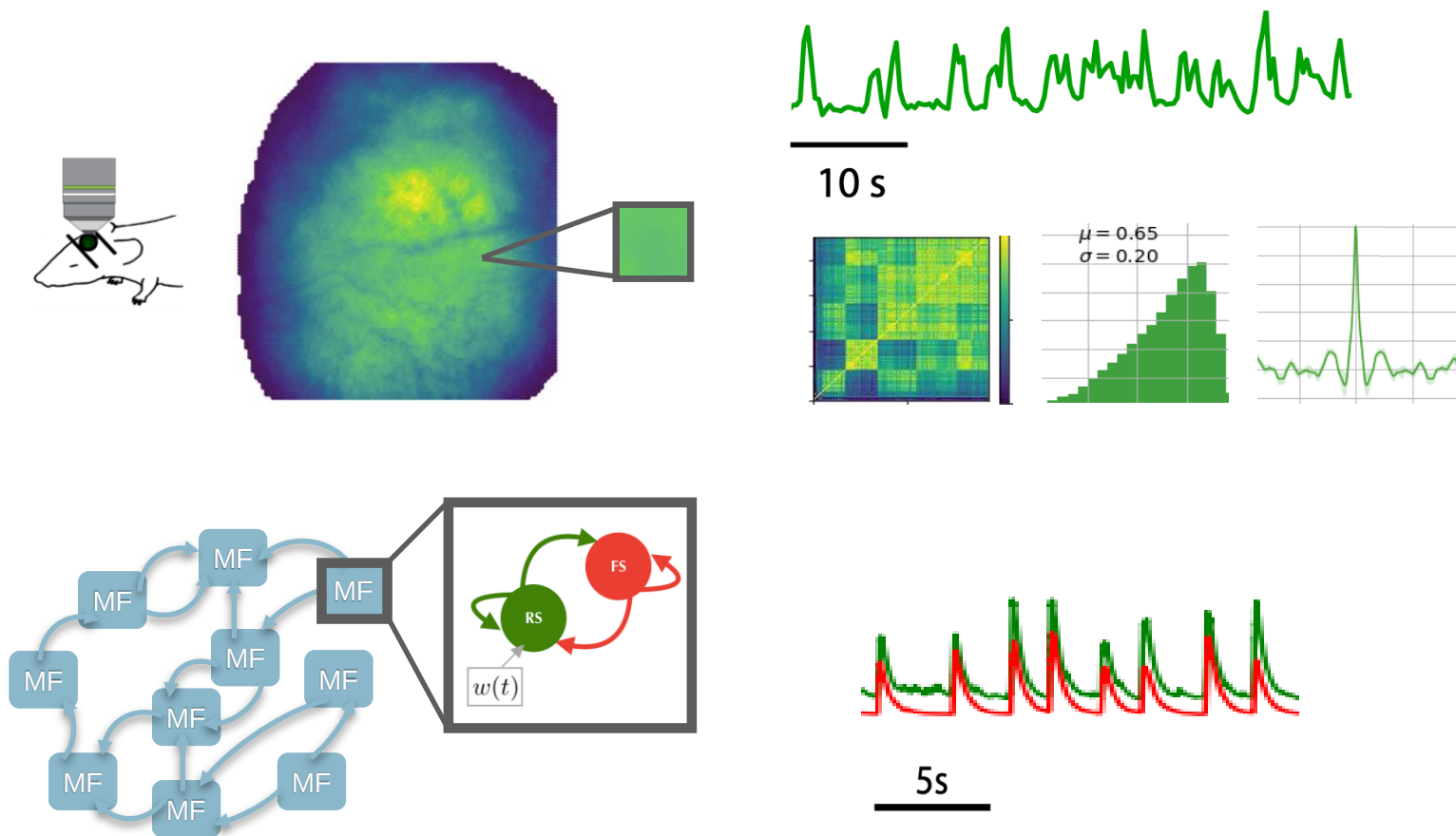
$$\vec{B}(\vec{p}) = \frac{\mu_0}{4\pi} \int_C \frac{I_A(m_e, m_i) d\vec{l} \times \vec{d}_i}{|\vec{d}|^3}$$

$I_A(m_e, m_i)$ = macroscopic axial current, can be estimated from the population activities of the mean-field model m_e, m_i



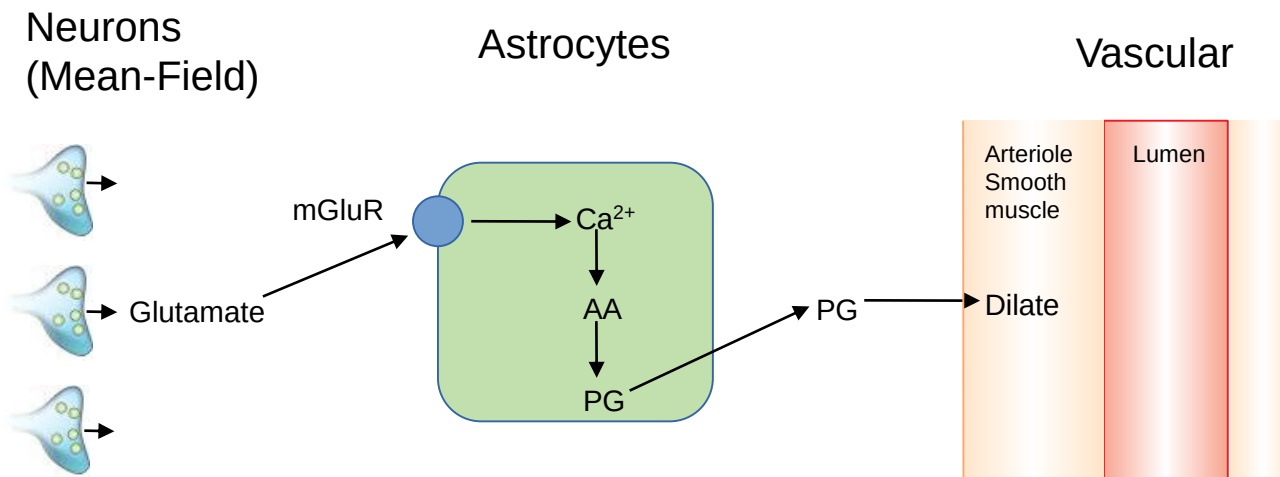
Linking mean-field models to brain signals

Calcium imaging signals from mean-field models

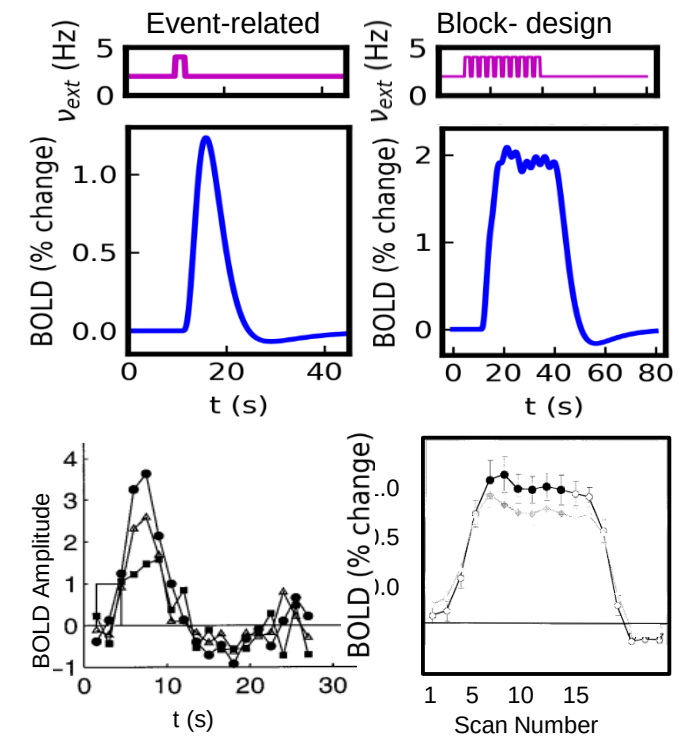


Linking mean-field models to brain signals

Genesis of the BOLD signal from mean-field models

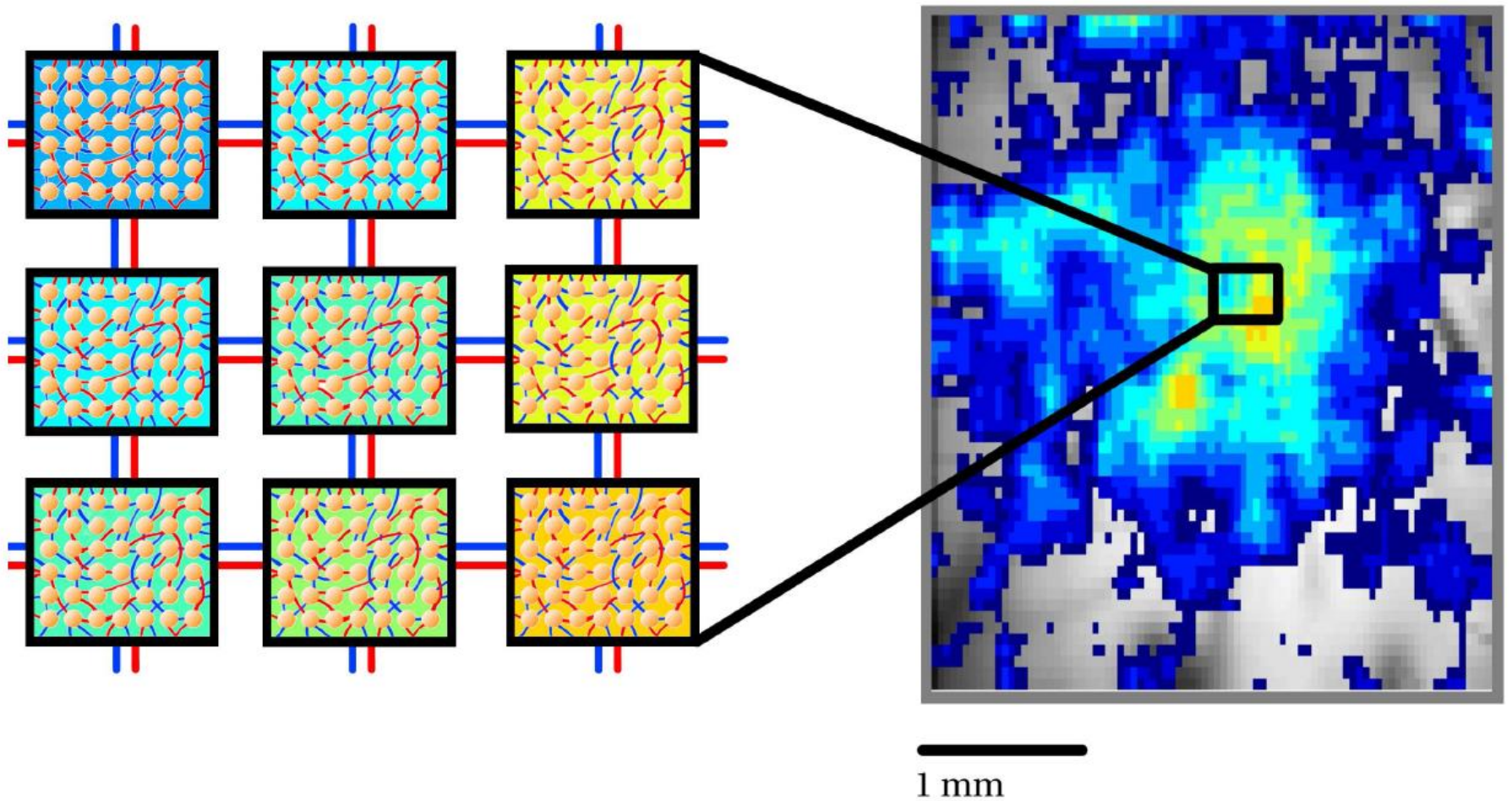


Experimental protocols

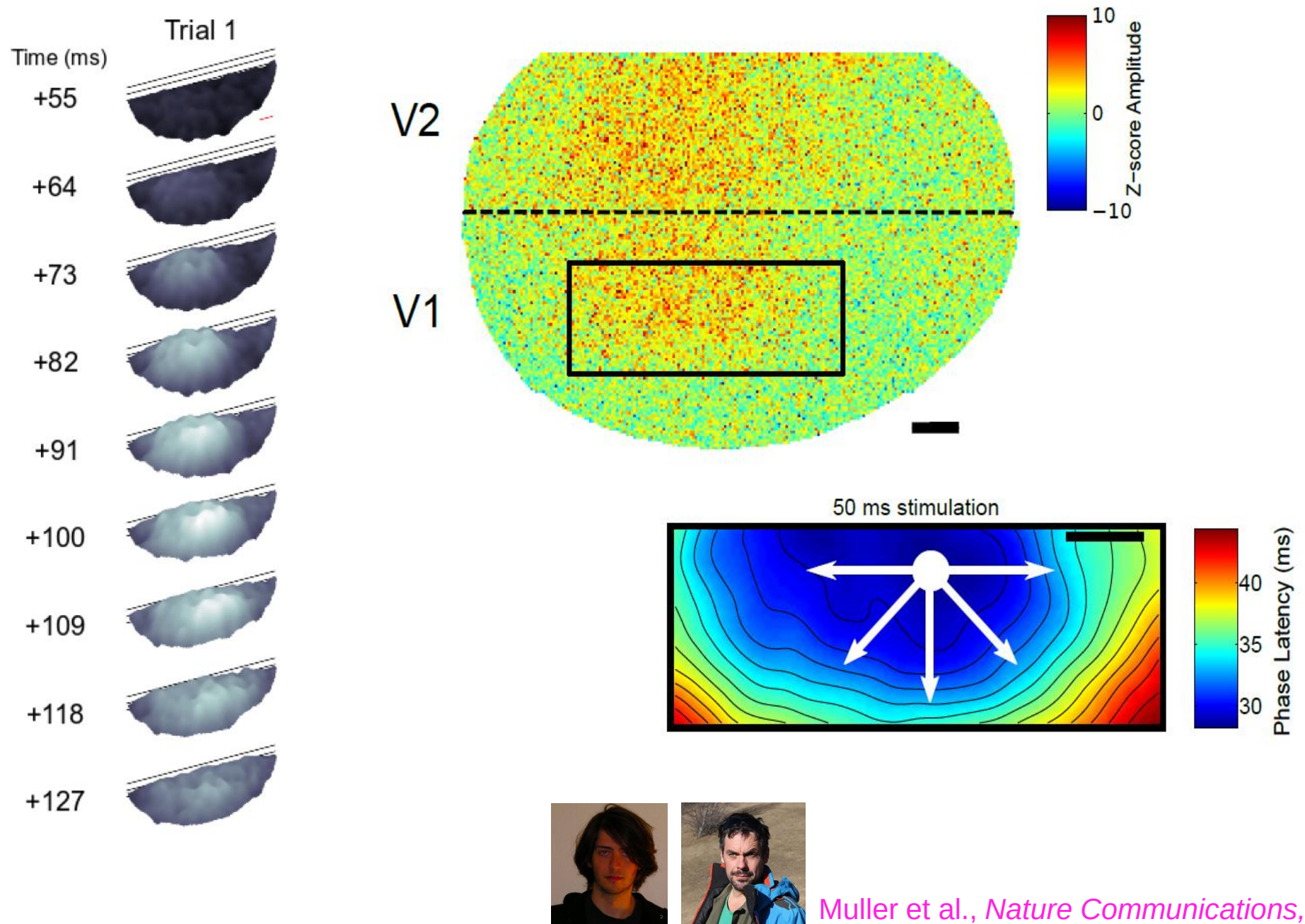


Modeling the mesoscopic scale

Networks of mean-field units



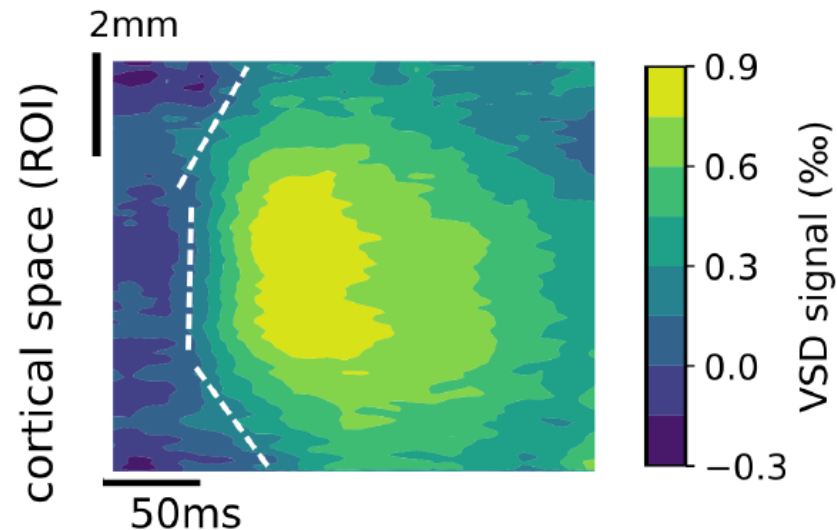
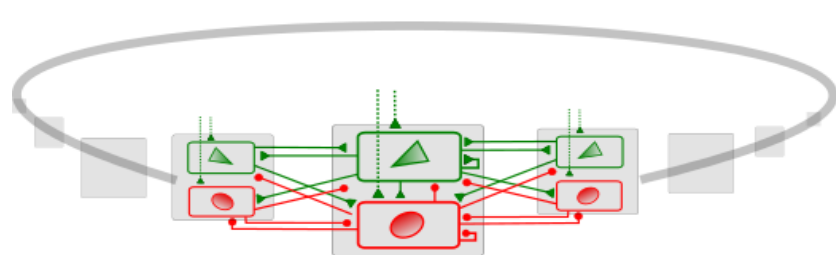
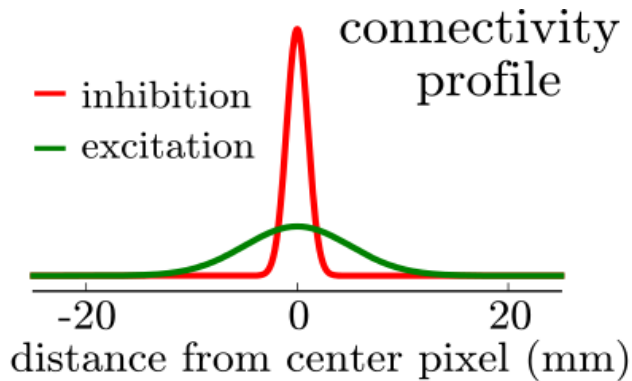
Propagating waves in monkey V1



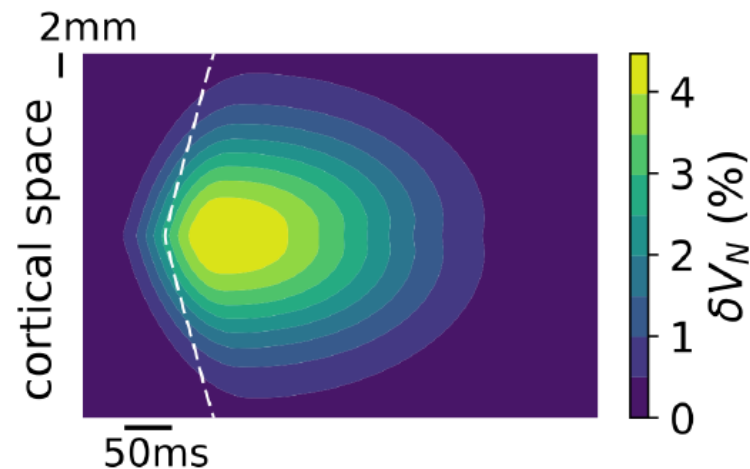
Model of cortical propagating waves

Calibration of the mean-field model to mesoscopic phenomena:
propagating waves in V1

Network of mean-field units



Experiments

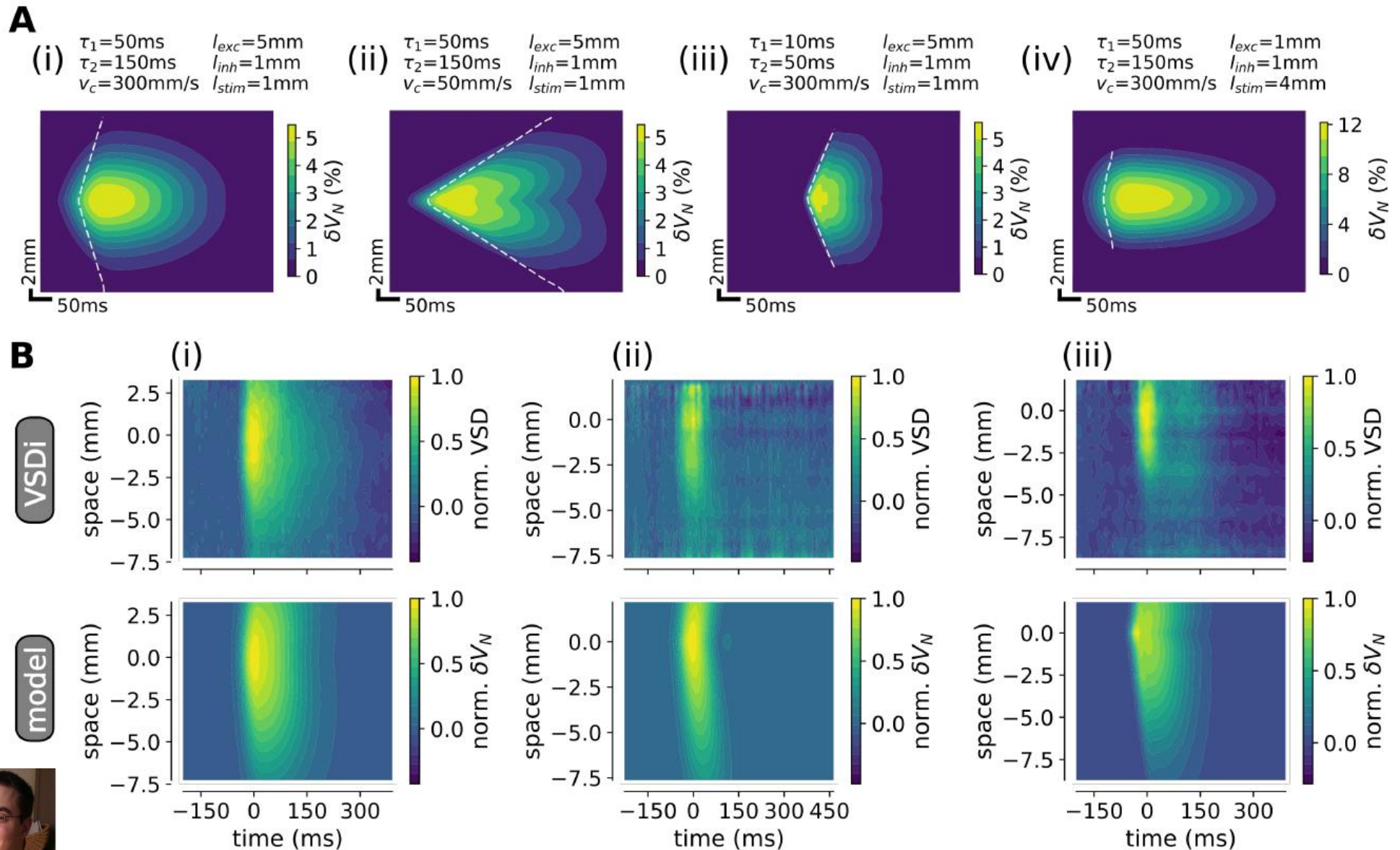


Mean-field model



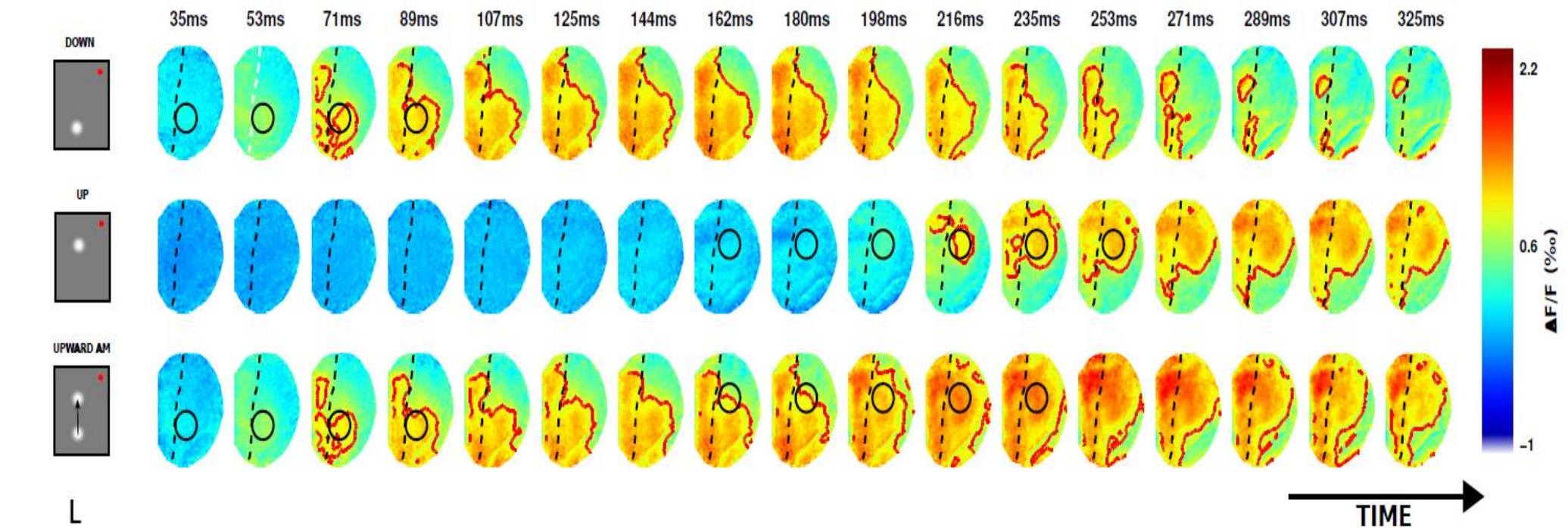
Model of cortical propagating waves

Calibration of the mean-field model to experimental recordings

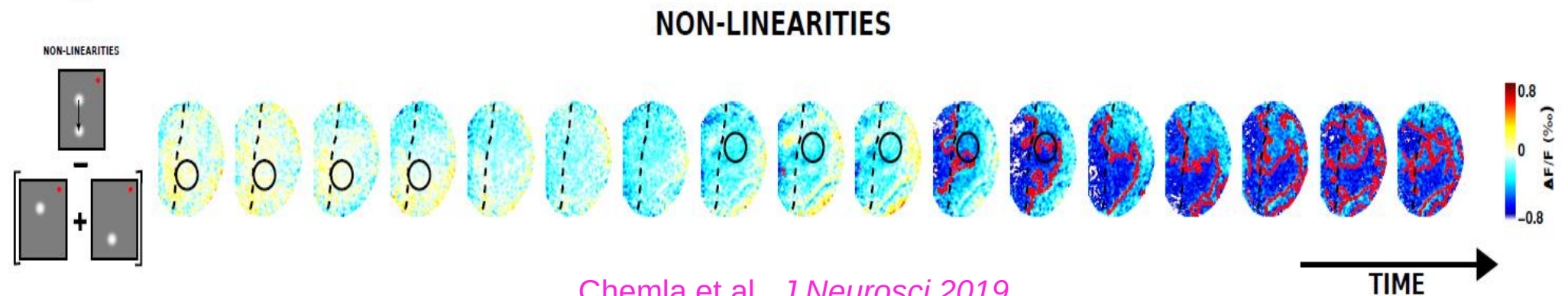


Model of cortical propagating waves

“Collision experiment” between two propagating waves



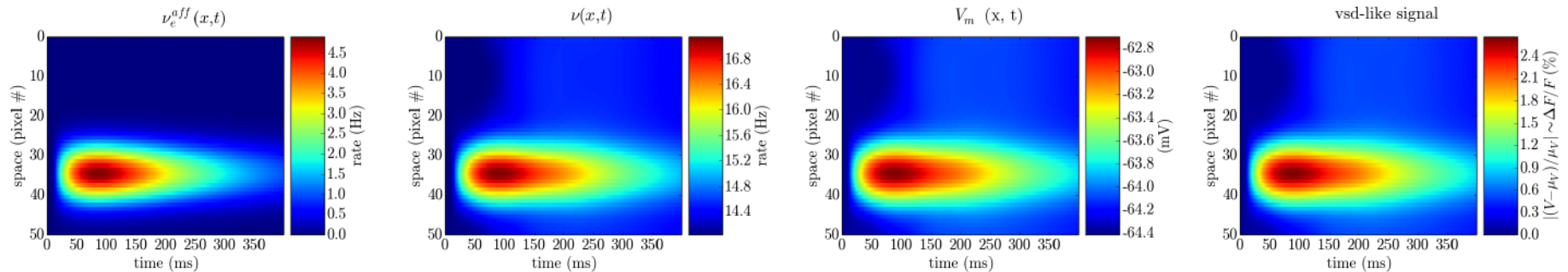
The cortical representation of IrAM at the surface of V1 in two behaving macaque monkeys involved in a fixation task, shows a **spread of activity**: a cortical correlate of the illusory motion (*Jancke et al., 2004*).



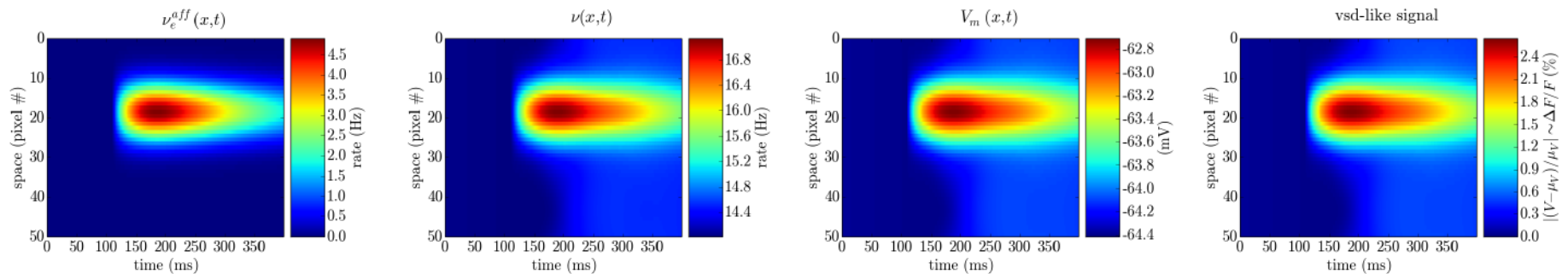
Model of cortical propagating waves

Model of the “Collision experiment” between two propagating waves

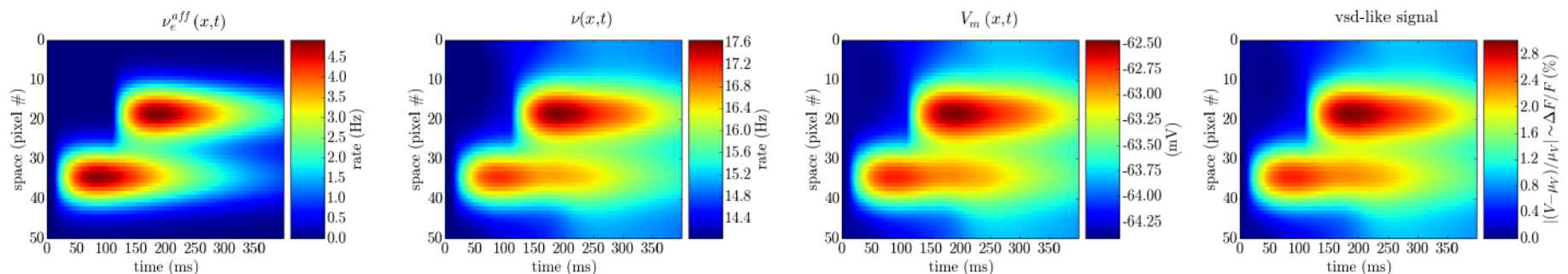
A



B

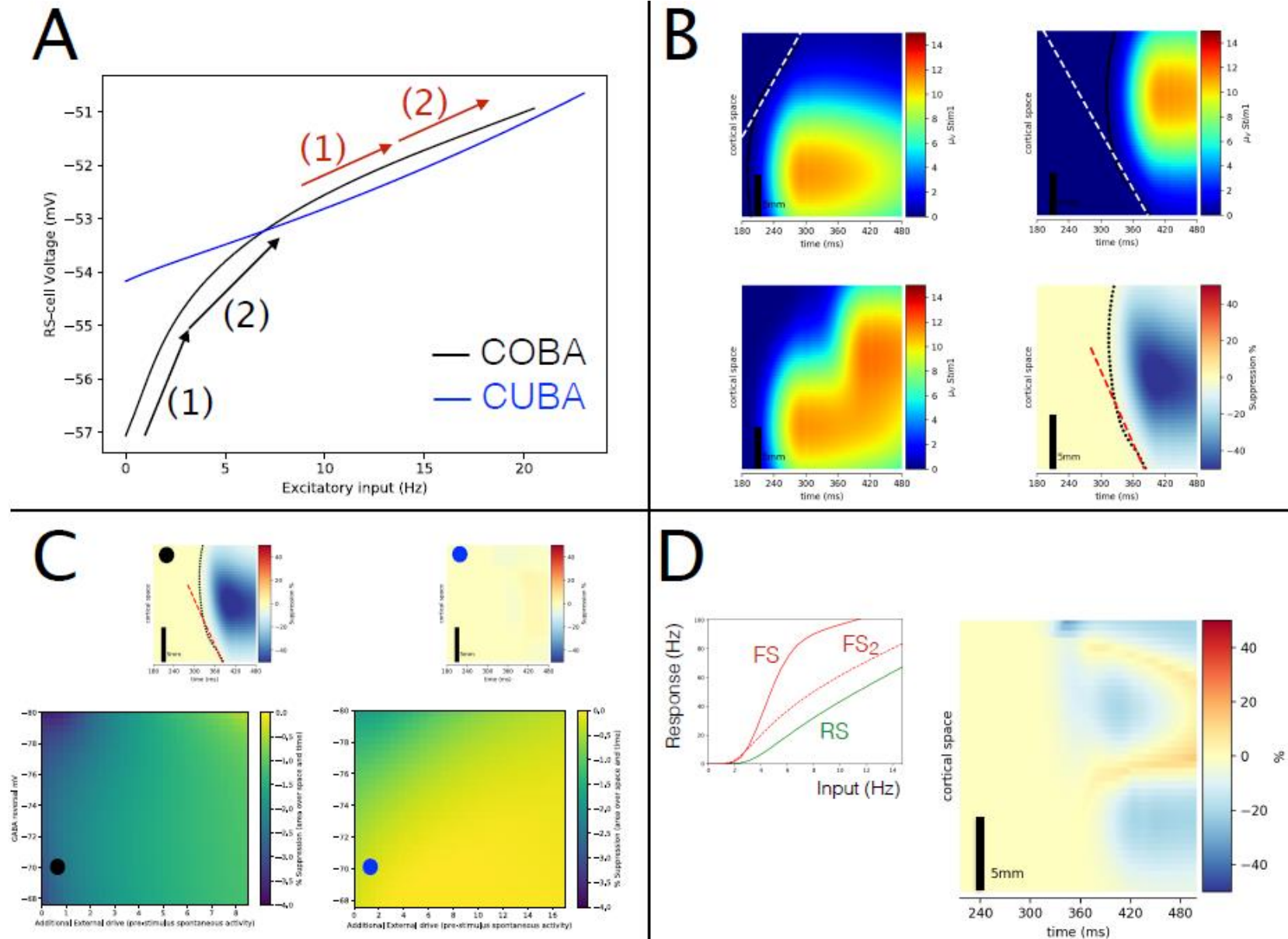


C



Model of cortical propagating waves

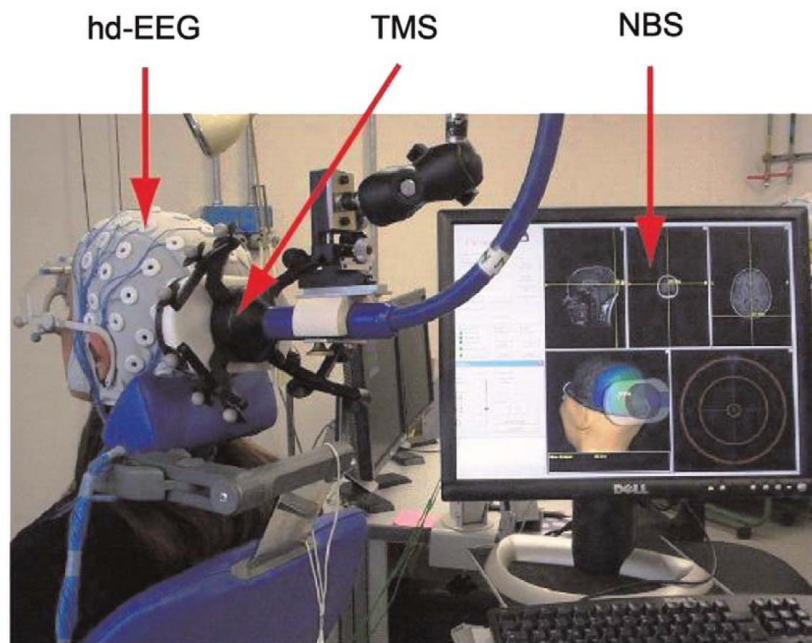
Model of the “Collision experiment” between two propagating waves



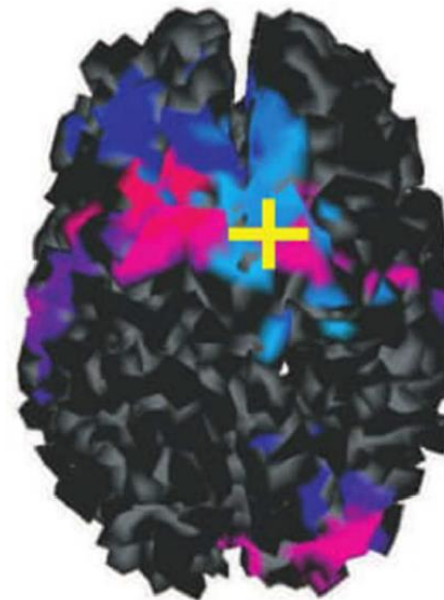
Modeling the macroscopic scale

Motivation: state-dependent responsiveness

Brain responses to TMS stimuli depend on brain state



Wake



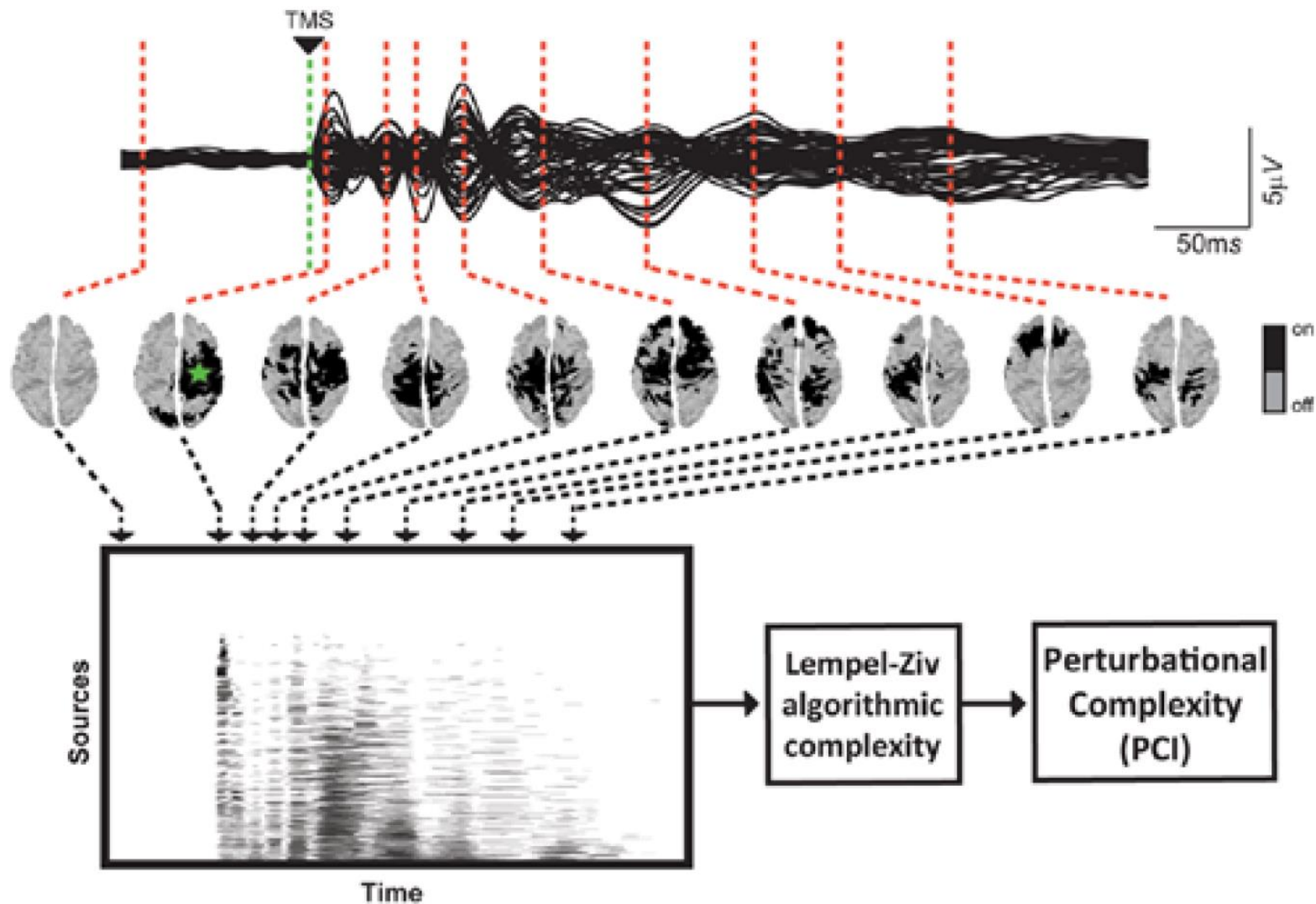
Slow-wave sleep



Massimini et al., *Science* 2005

Motivation: state-dependent responsiveness

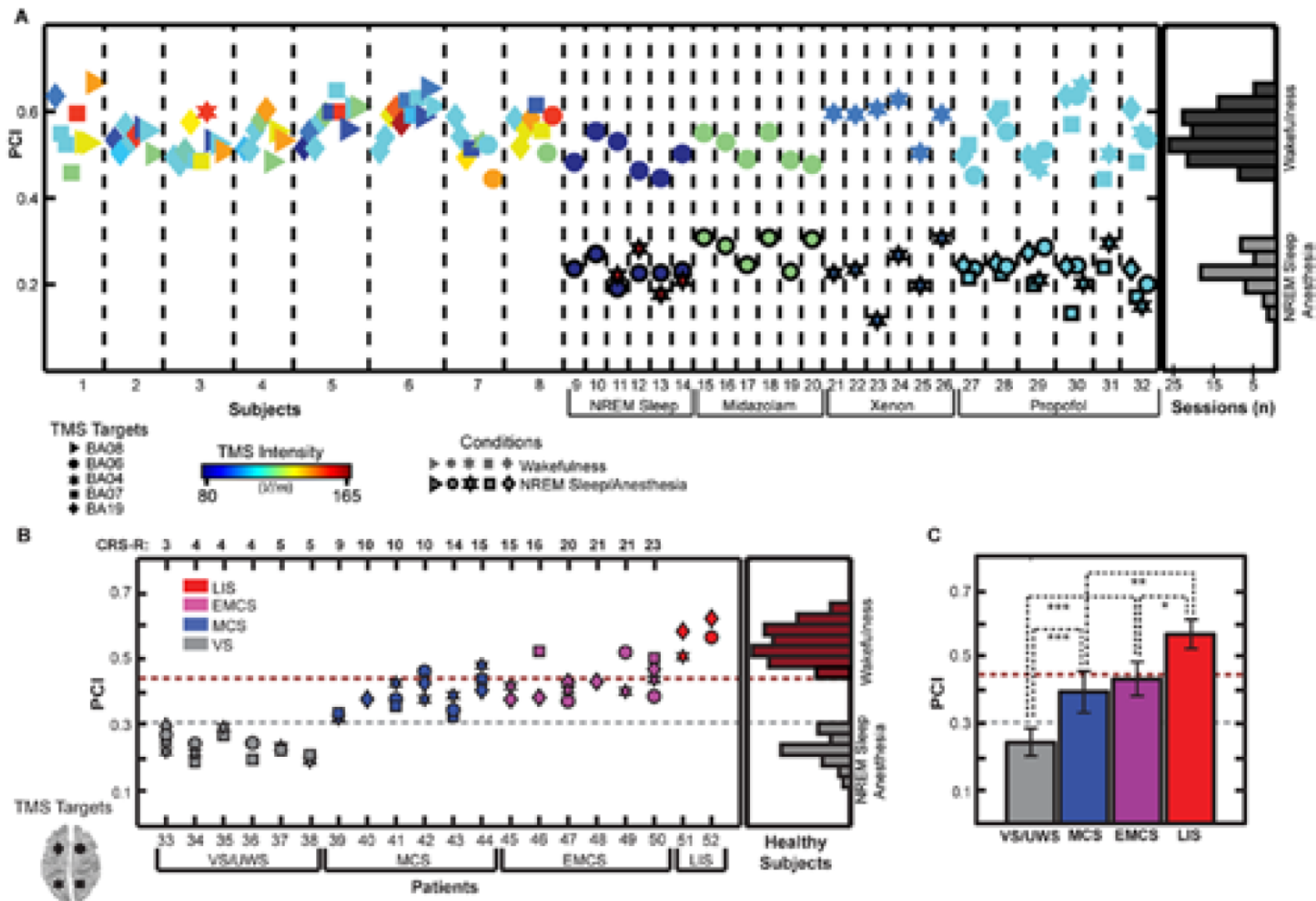
Measuring the complexity of brain responses:
The Perturbational Complexity Index (PCI)



Motivation: state-dependent responsiveness

Measuring the complexity of brain responses:

The Perturbational Complexity Index (PCI)

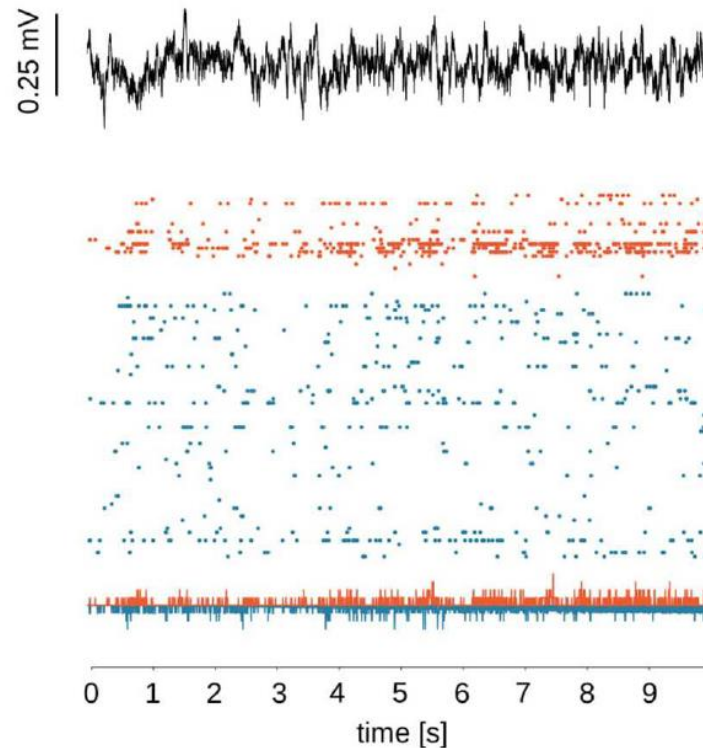
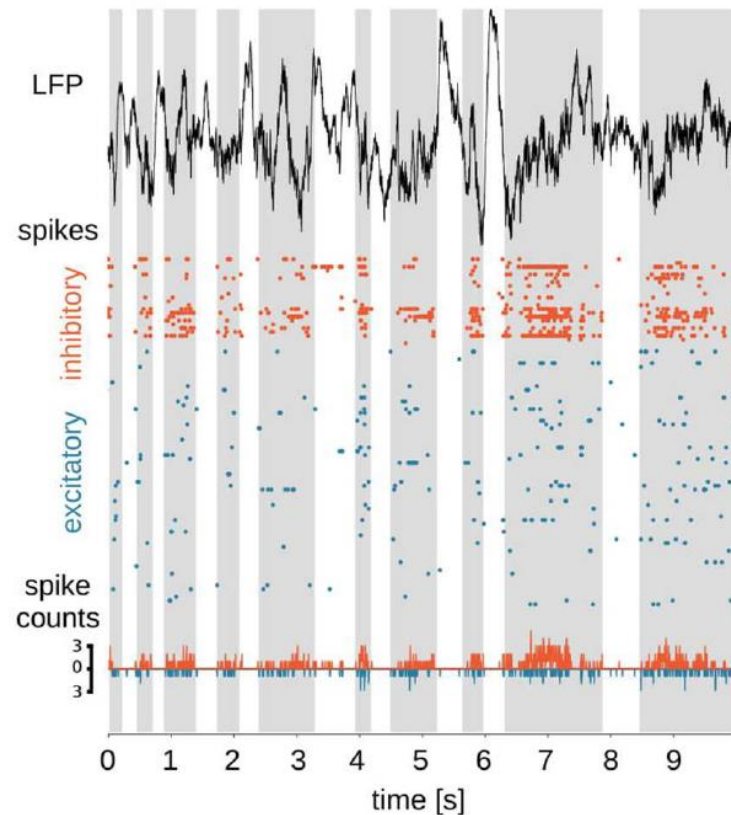


Building a whole-brain model

First step: start from the spiking neuron level

Human slow-wave sleep

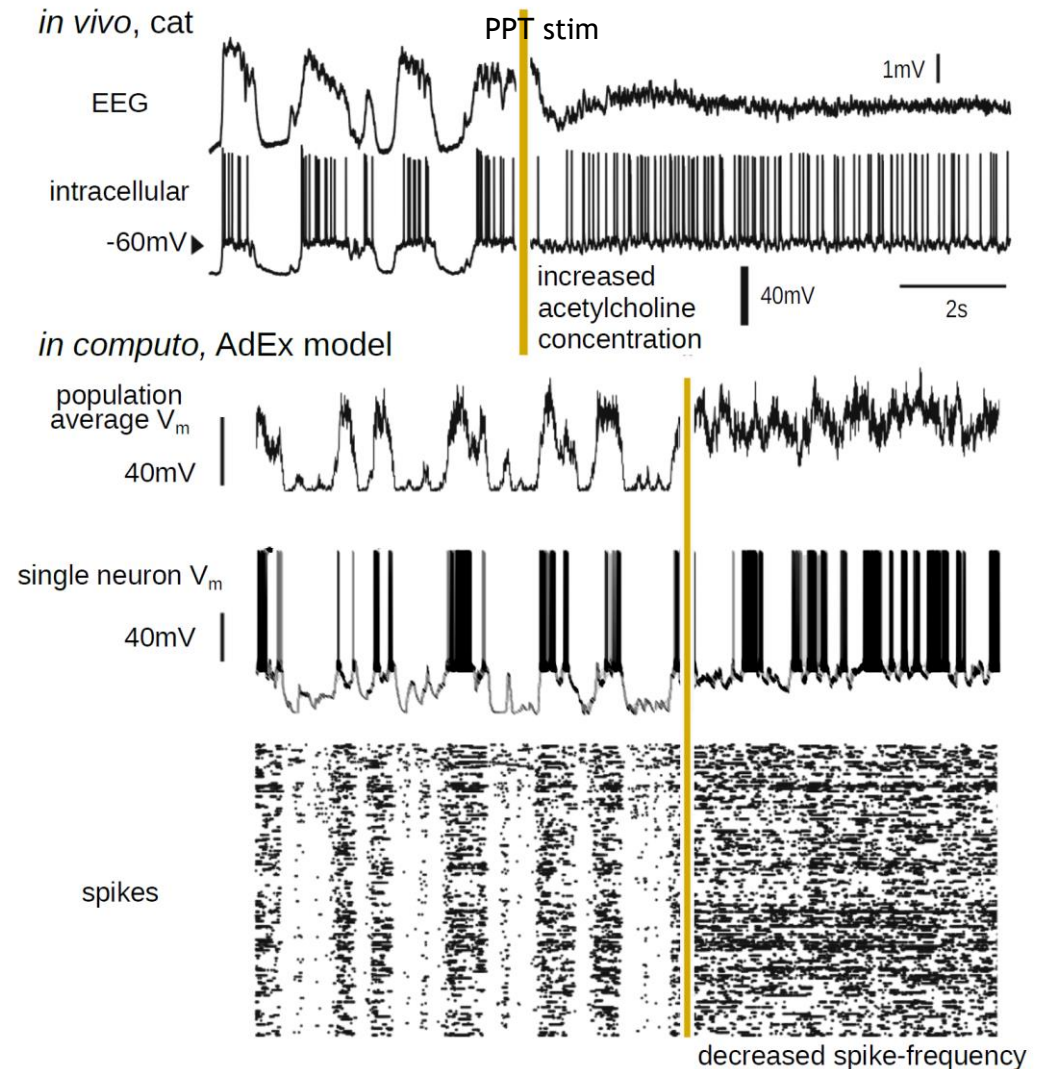
Wakefulness



Building a whole-brain model

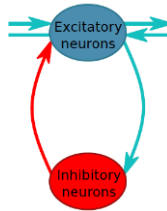
First step: start from the spiking neuron level

Basis of the model:
spiking (AdEx) network
model of the transition
between Up/Down
states and
asynchronous states.
(induced by ACh)



Building a whole-brain model

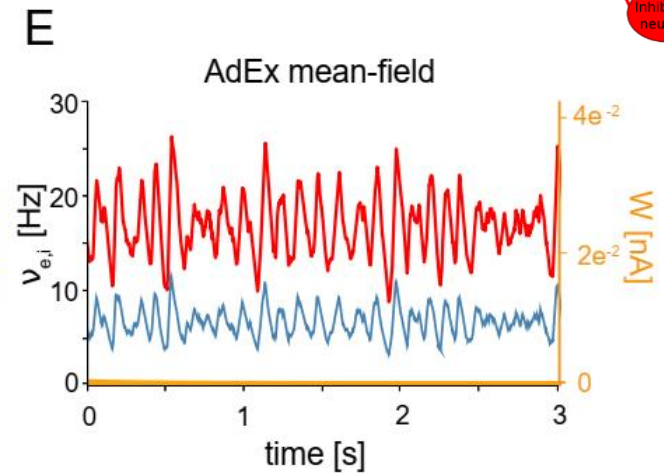
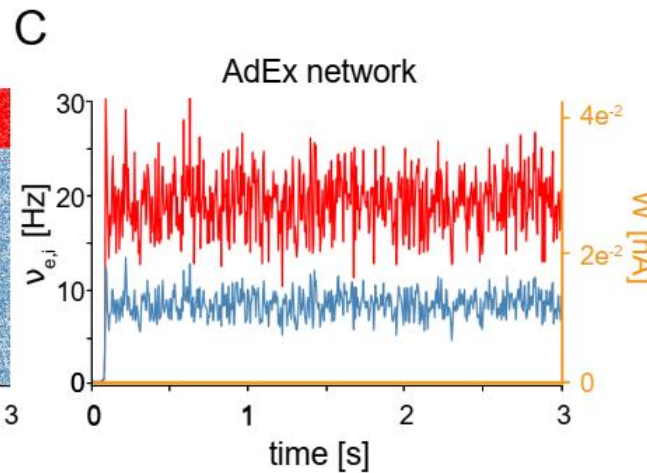
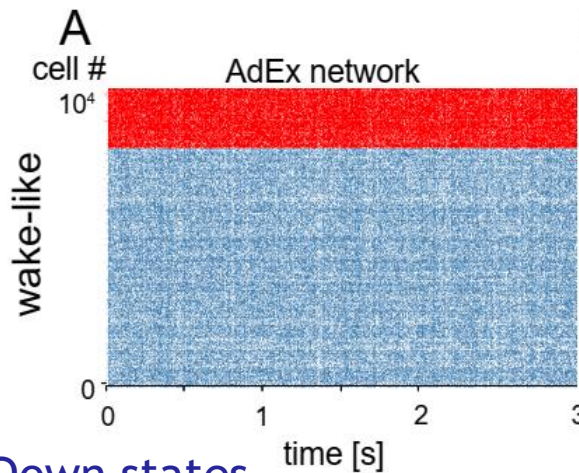
Second step: build mean-field model of neuronal populations



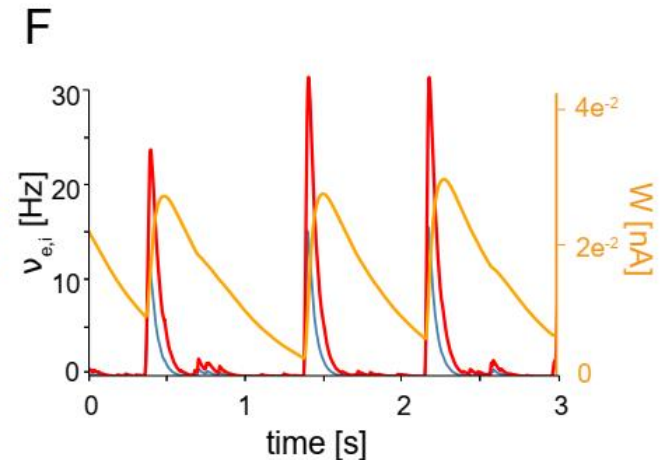
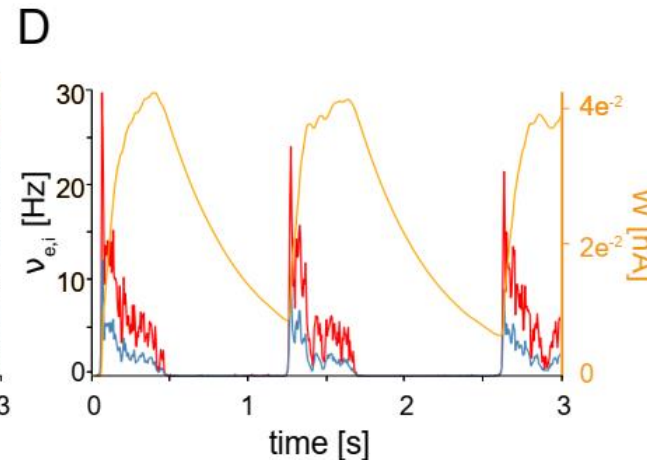
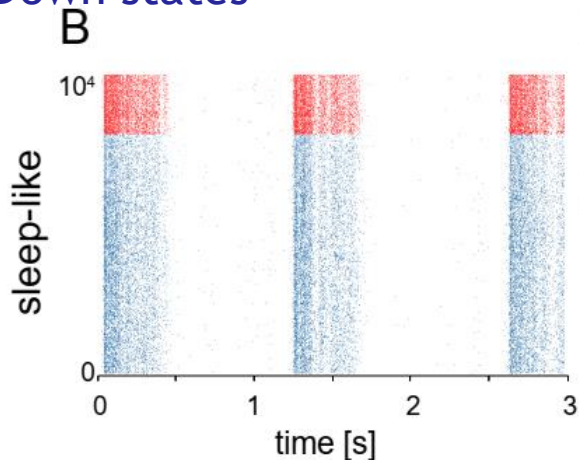
AdEx network

Mean-field model

Asynchronous

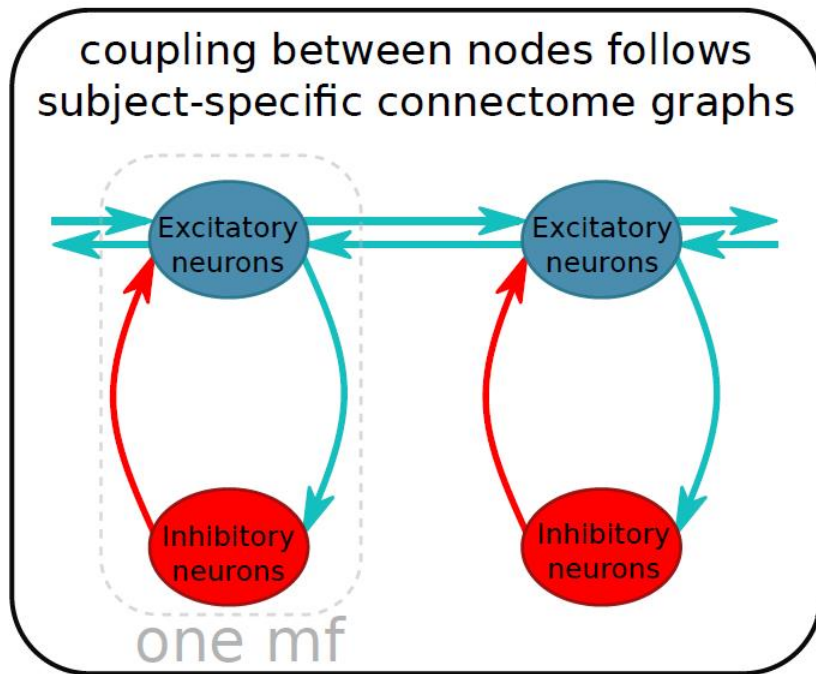


Up/Down states

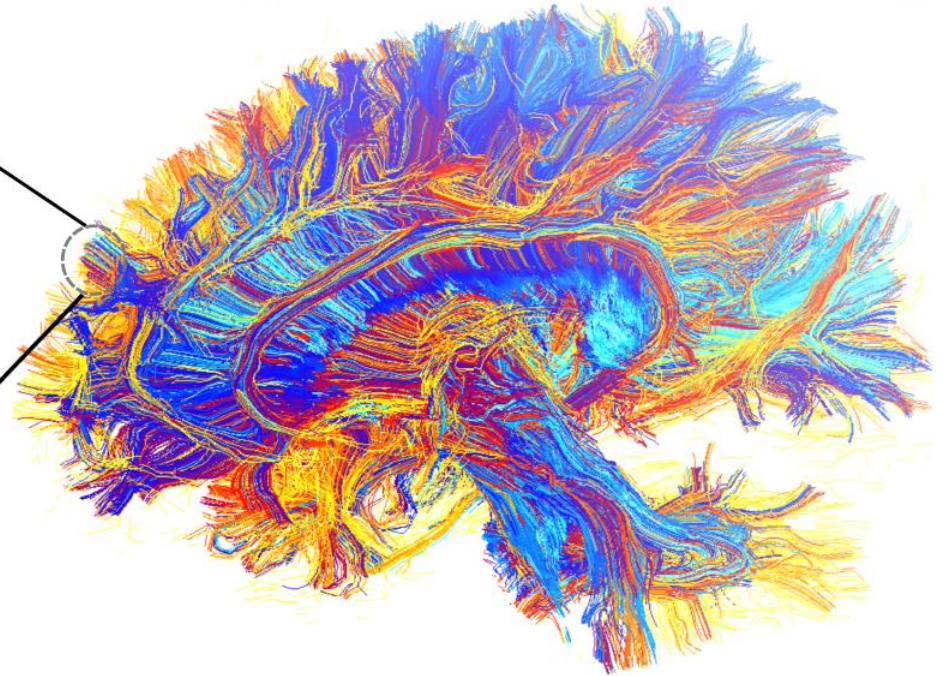


Building a whole-brain model

Third step: integration of mean-field models at the whole-brain level:
The Virtual Brain simulator



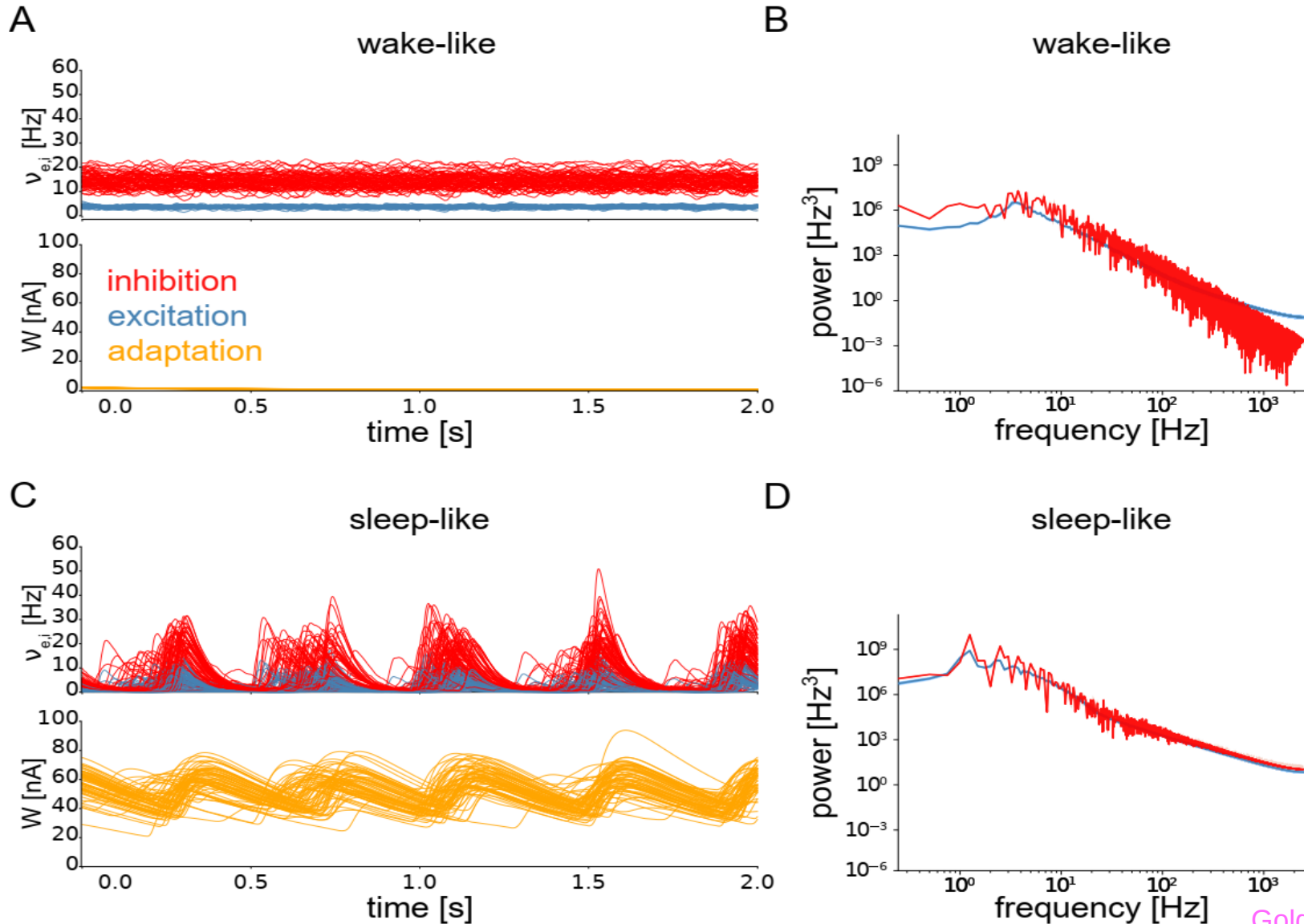
Diffusion magnetic resonance imaging



Goldman et al., *bioRxiv*, 2020;
Frontiers Comp Neuro, 2023

Building a whole-brain model

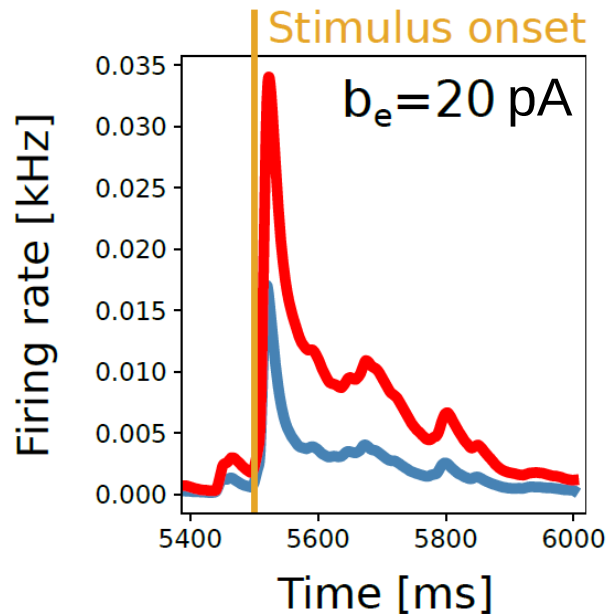
Fourth step, simulate the whole-brain model: spontaneous activity



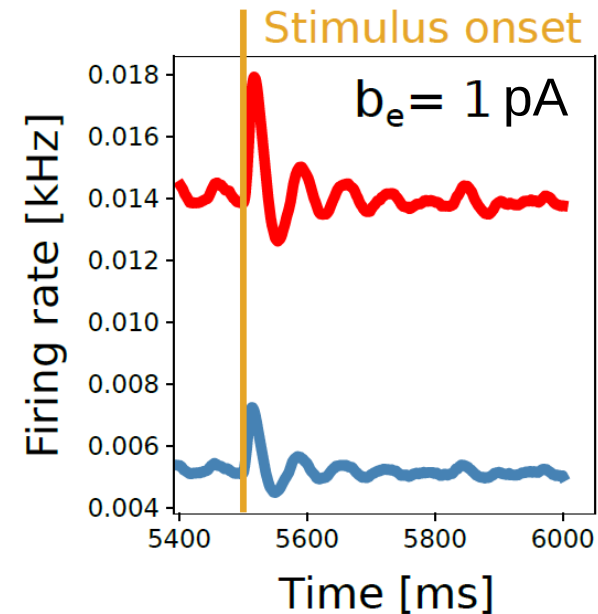
Modeling responsiveness in different brain states

Fourth step: simulate the whole-brain model: evoked responses

Up/Down states

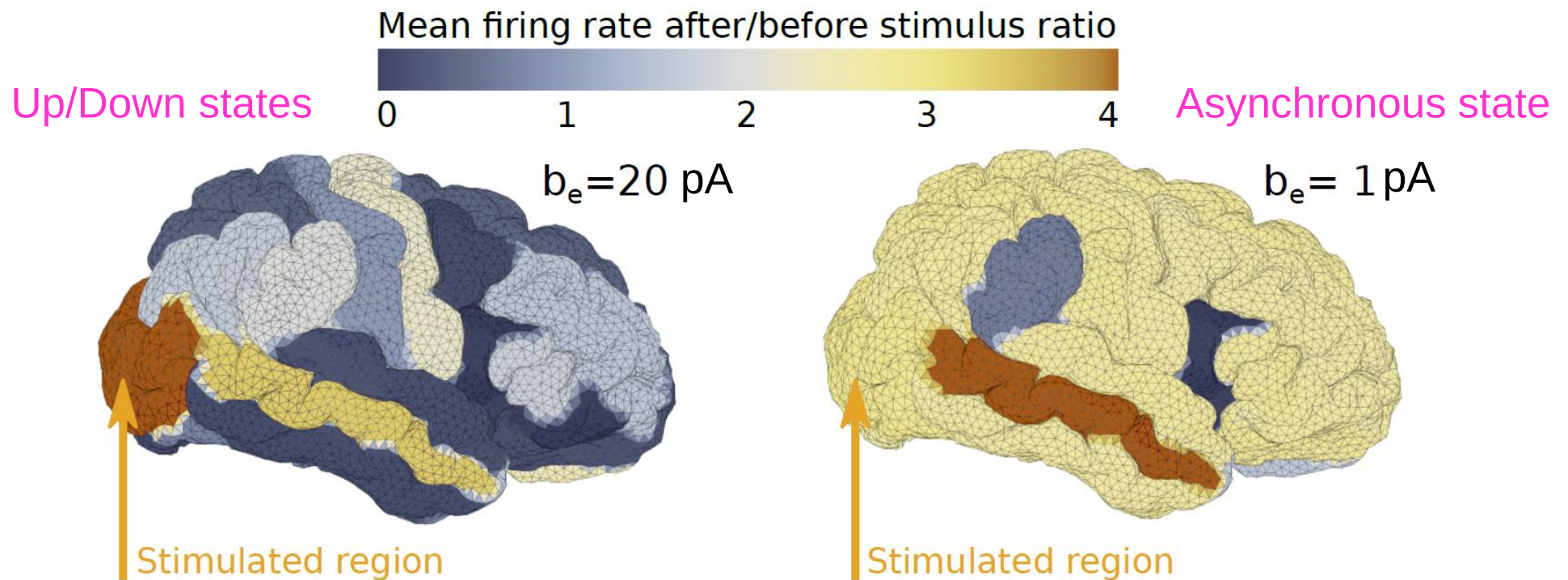


Asynchronous state



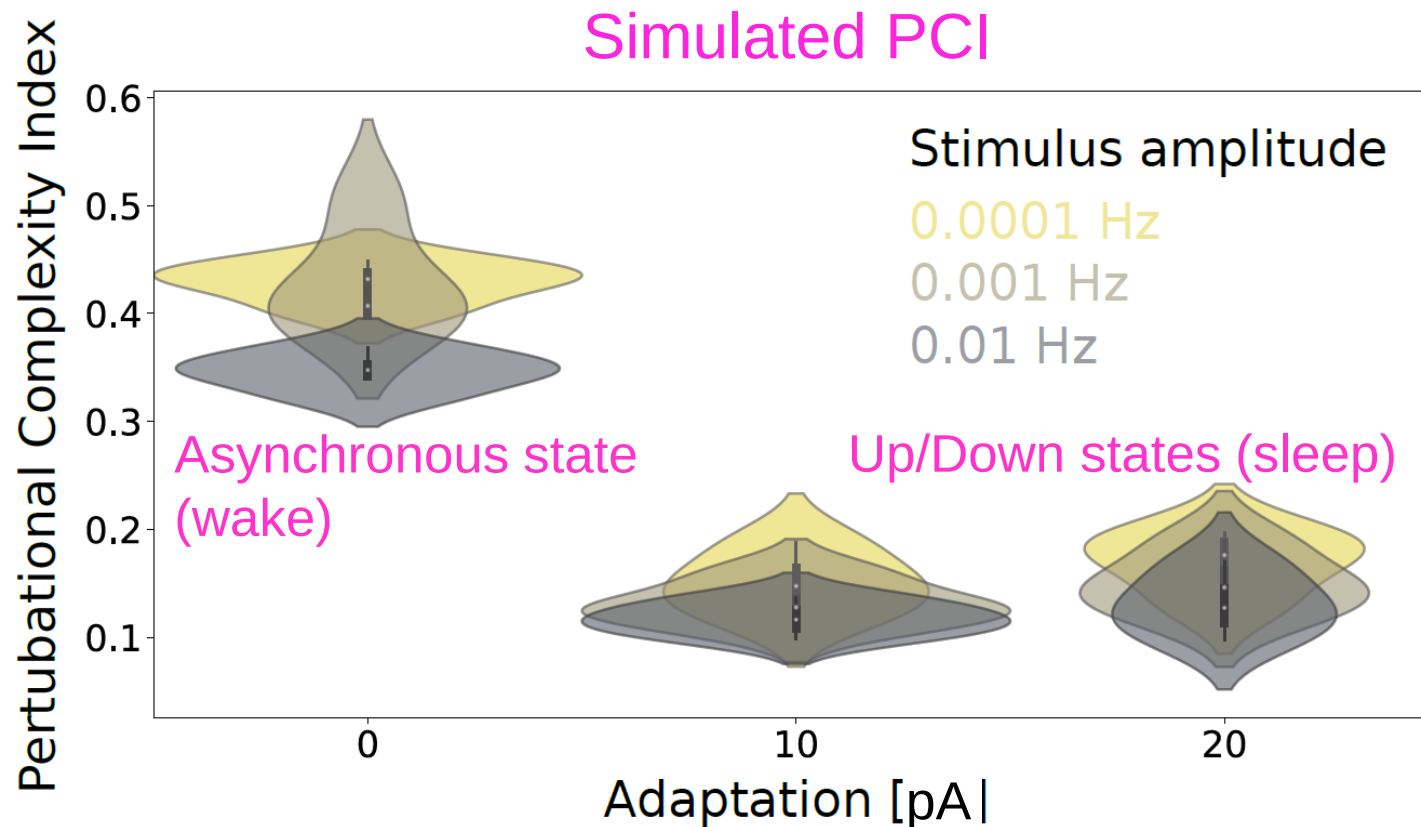
Modeling responsiveness in different brain states

Fourth step: simulate the whole-brain model: evoked responses



Perturbational complexity index (PCI)

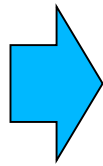
Fourth step: simulate the whole-brain model: evoked responses



Conclusions: multiple scales of brain activity

Mean-field models are key to relate neural activity at different scales

Neuroscience data:
Multi-electrode
2-photon,
VSD imaging,
fMRI, etc...



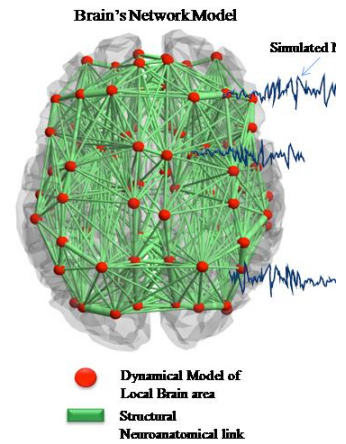
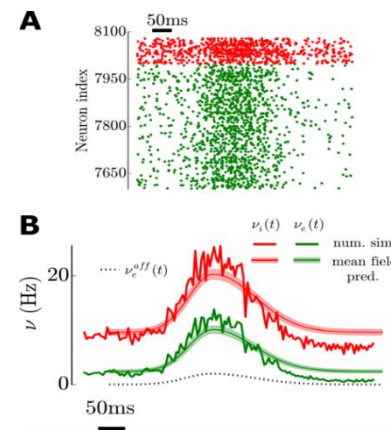
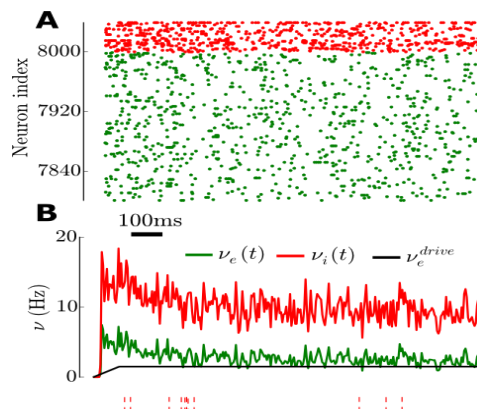
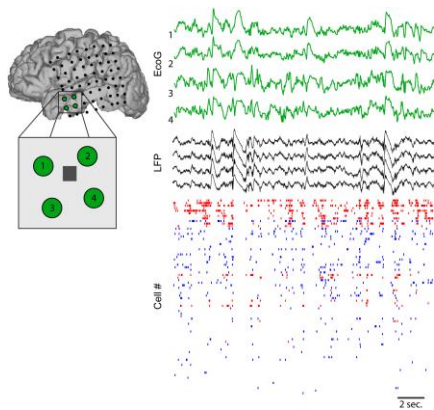
Network models:
Spiking
networks
based on
exp. data



Mean-field models:
Mean-field
models of
spiking
networks



Large-scale:
Integration of
mean-field
in Whole-
Brain models
(TVB)



Conclusions

- Semi-analytic mean-field framework can model a wide range of systems (IF networks, AdEx, Hodgkin-Huxley, Morris-Lecar, models with dendrites, heterogeneous networks...)
- Can be used to simulate different brain states: desynchronized (AI) or synchronized (Up/Down states), or hypersynchronized (seizures)
- Can be related to various brain signals, LFP, EcoG, EEG, VSD, MEG, Ca²⁺ imaging, BOLD...
- Integration in TVB allows one to simulate the whole brain
- The model can reproduce the response to stimulation in humans (HBP work, still in progress)