Models of drug and stimulation impact on neural populations

Axel Hutt

Team MIMESIS

Outline

clinical cases

short-term projects

long-term projects

Outline

clinical cases

short-term projects

long-term projects

schizophrenia

symptoms

- appears in adolescence or early adulthood
- characterised by e.g. delusions and hallucinations
- affects 1% of population

treatment

medication and/or psychological counselling

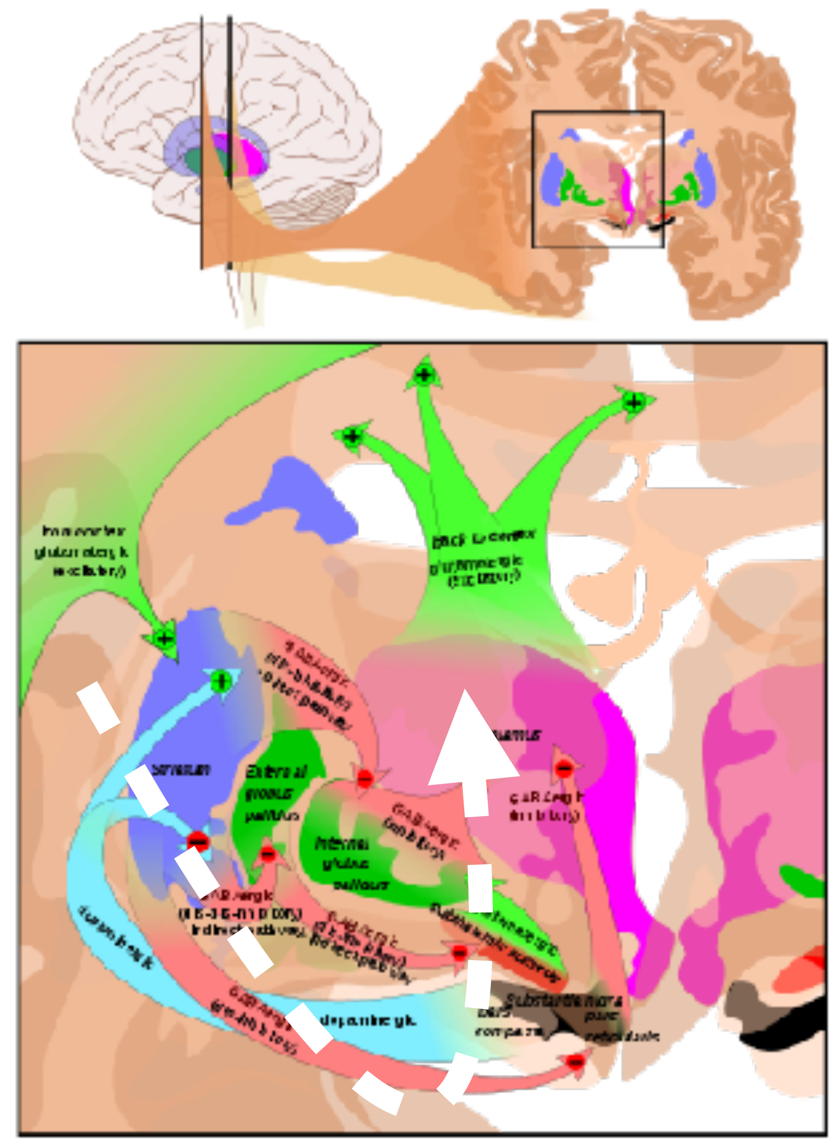
pharmacological medication limited in action

alternative modalities needed for non-pharmacological treatment

e.g. repetitive Transcranial Magnetic Stimulation (rTMS)

TMS in schizophrenia treatment

cortico-thalamic loop (CTL)



Cooperation partner:

Dr. Didier PINAULT,
(INSERM1114 Strasbourg)

Research aim:

- understanding **action of antipsychodic *clozapine*** on CTL
- understanding **action of rTMS** on CTL

Outline

clinical cases

short-term projects

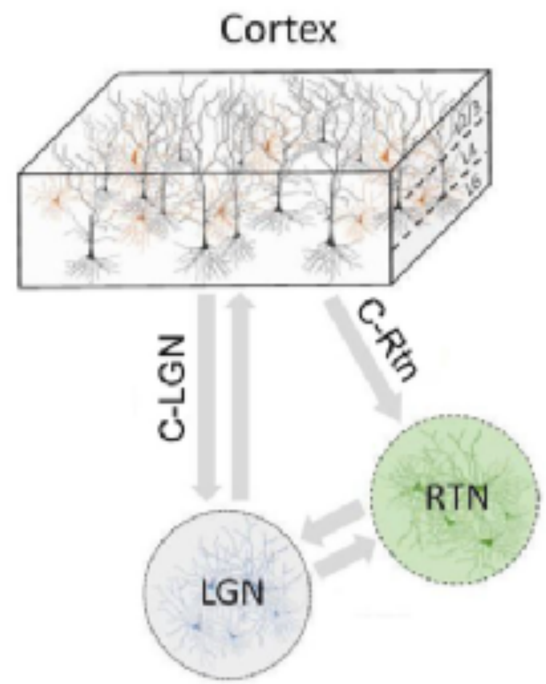
I: drugs **II: stimulation**

long-term projects

I) pharmacological effect of anti-psychotic drugs

a) dynamical model of action of *clozapine*

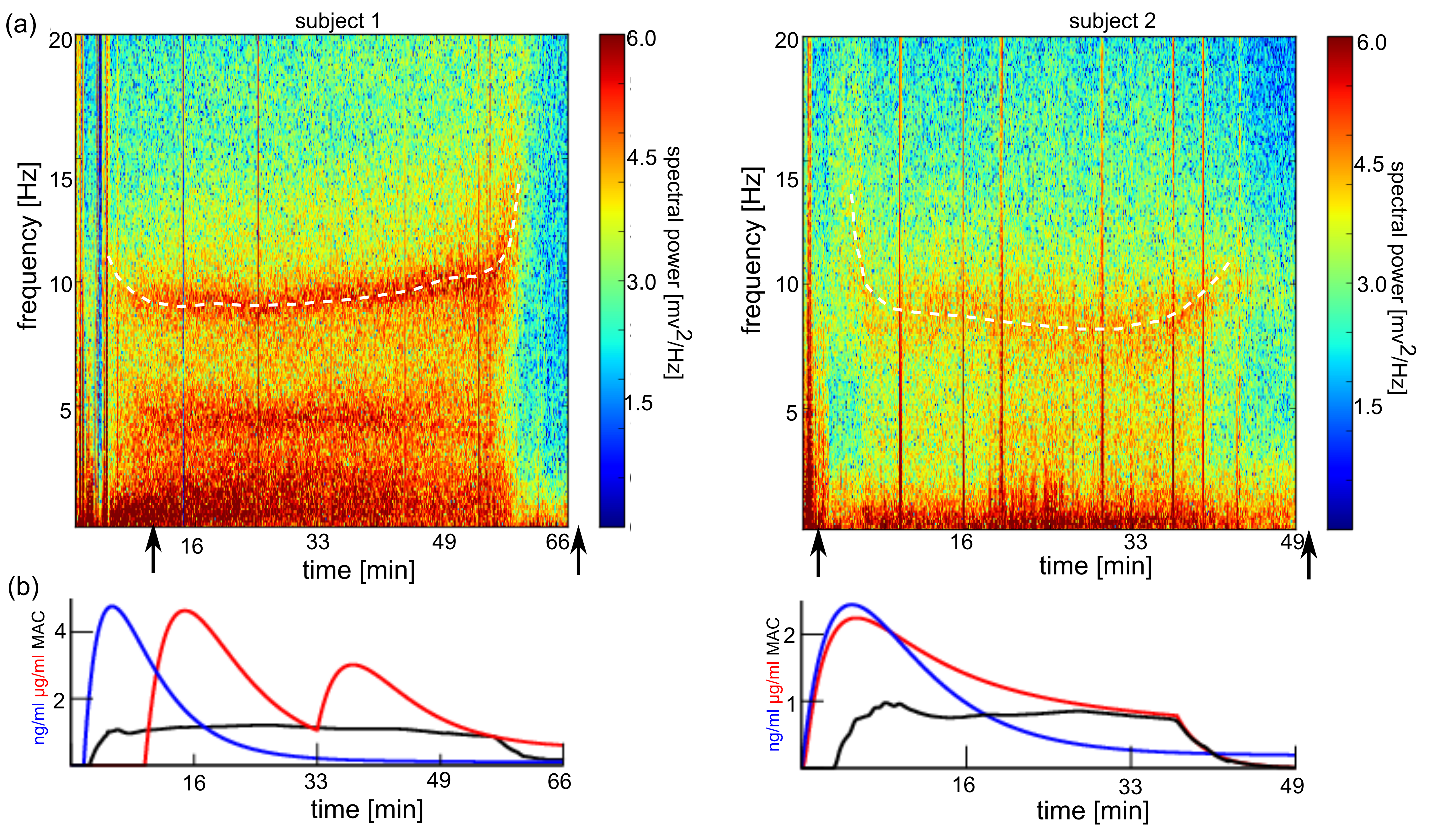
on cortico-thalamic loop



(NeuroImage 2018; eLife 2017; PLoSOne 2017; J. Neuroscience 2016)

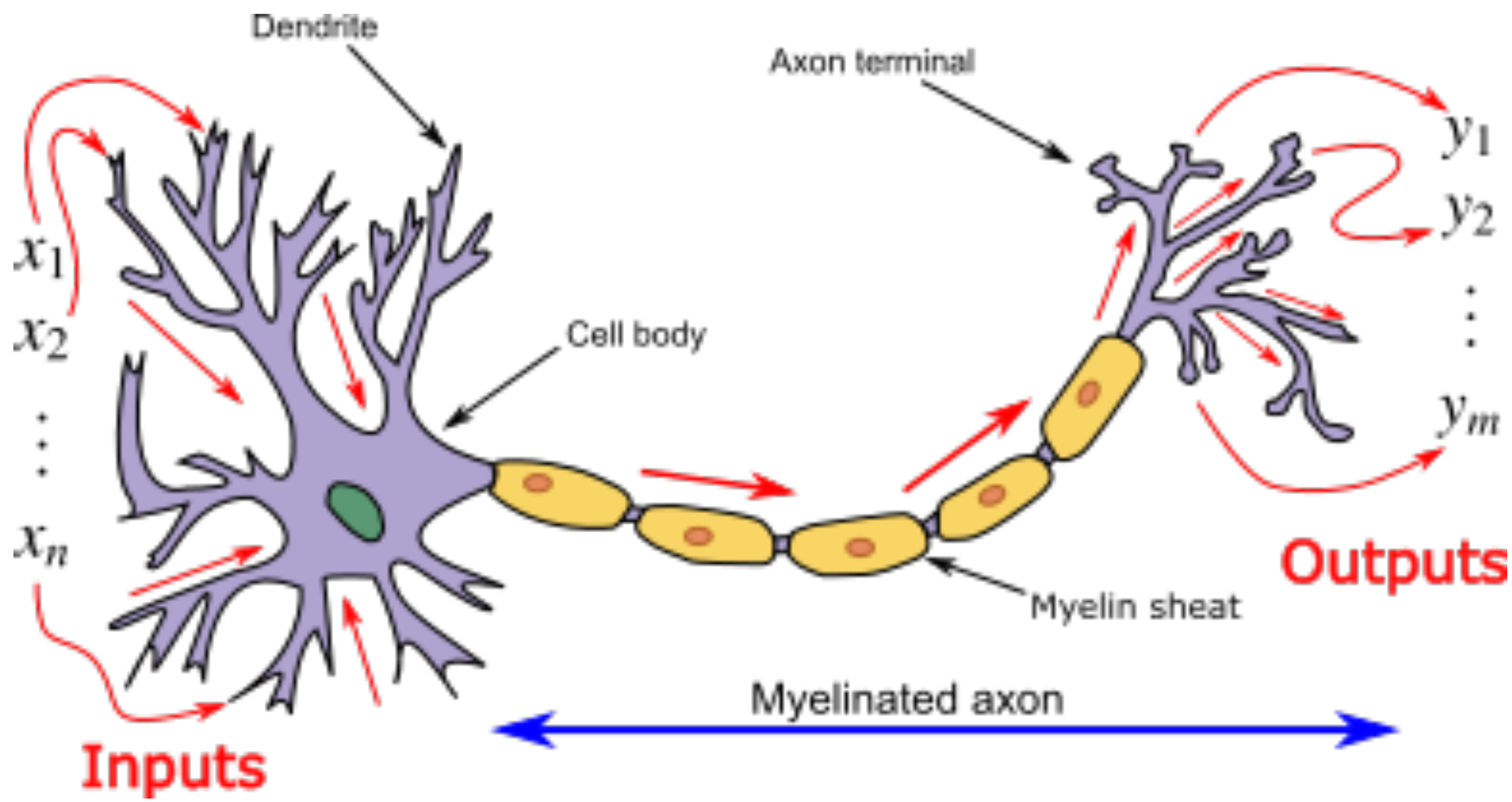
Some details on general anaesthesia

experimental data: frontal EEG in patients under surgery

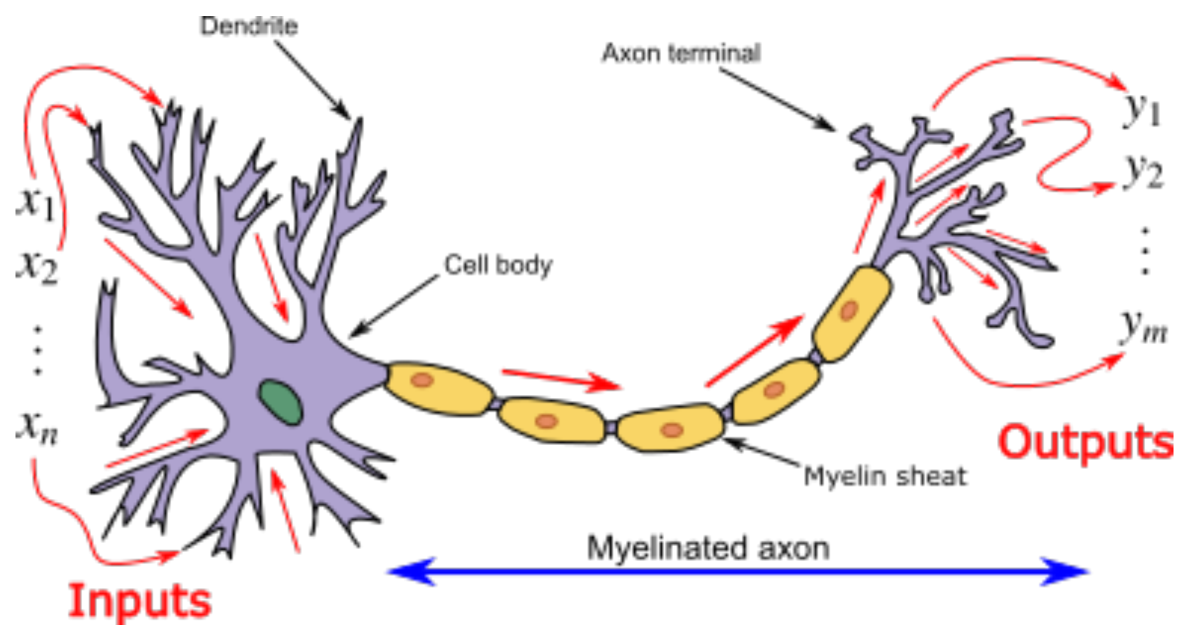


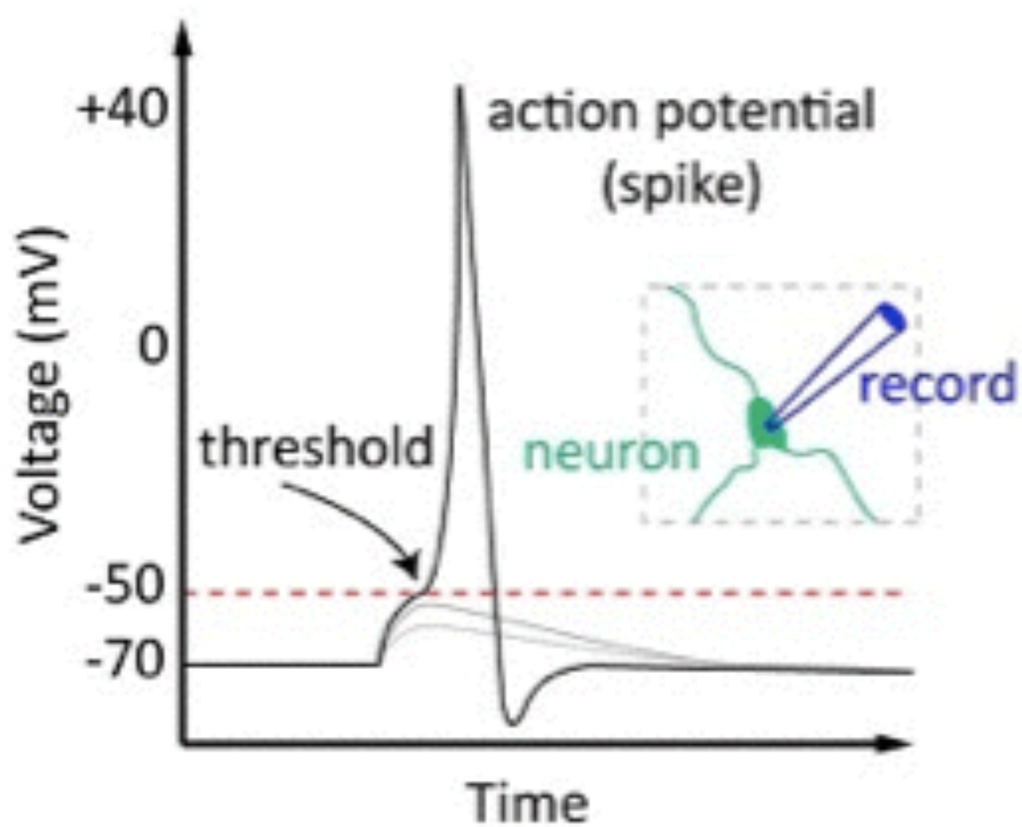
(Williams and Sleigh, Anaesth. Int. Care (1999))

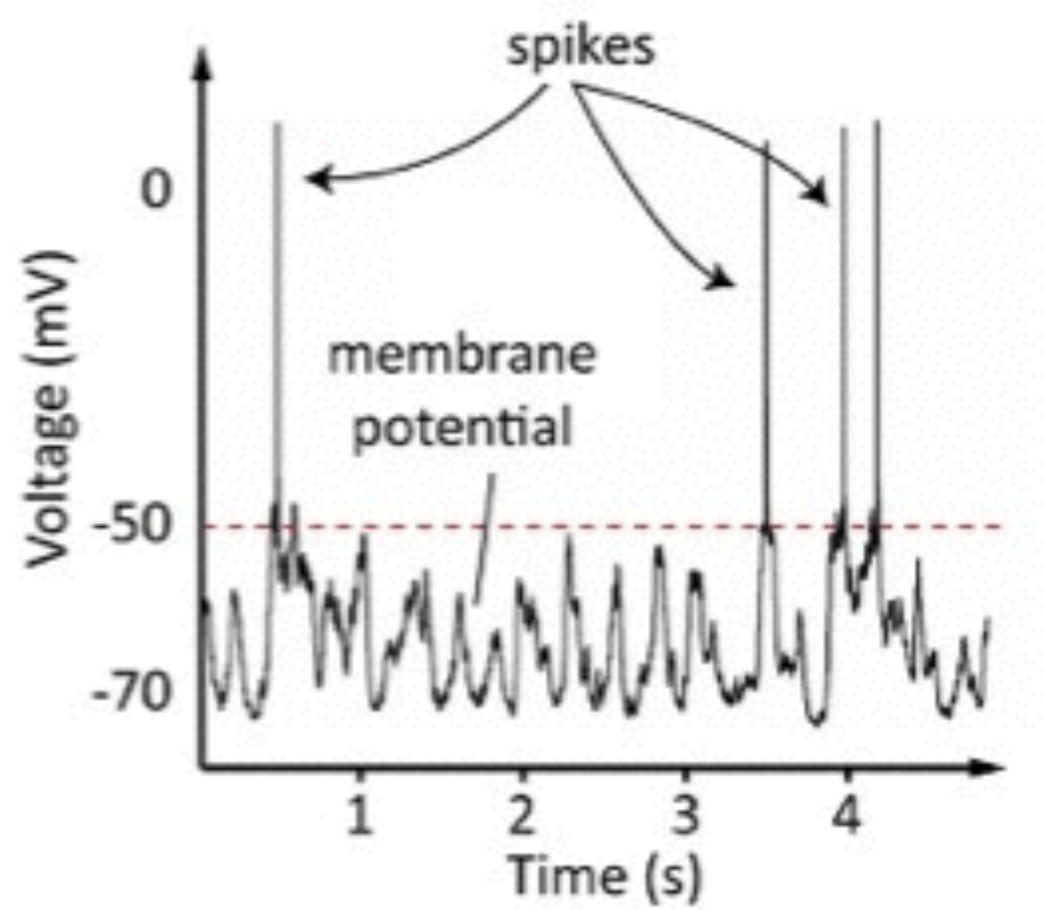
single neuron model:



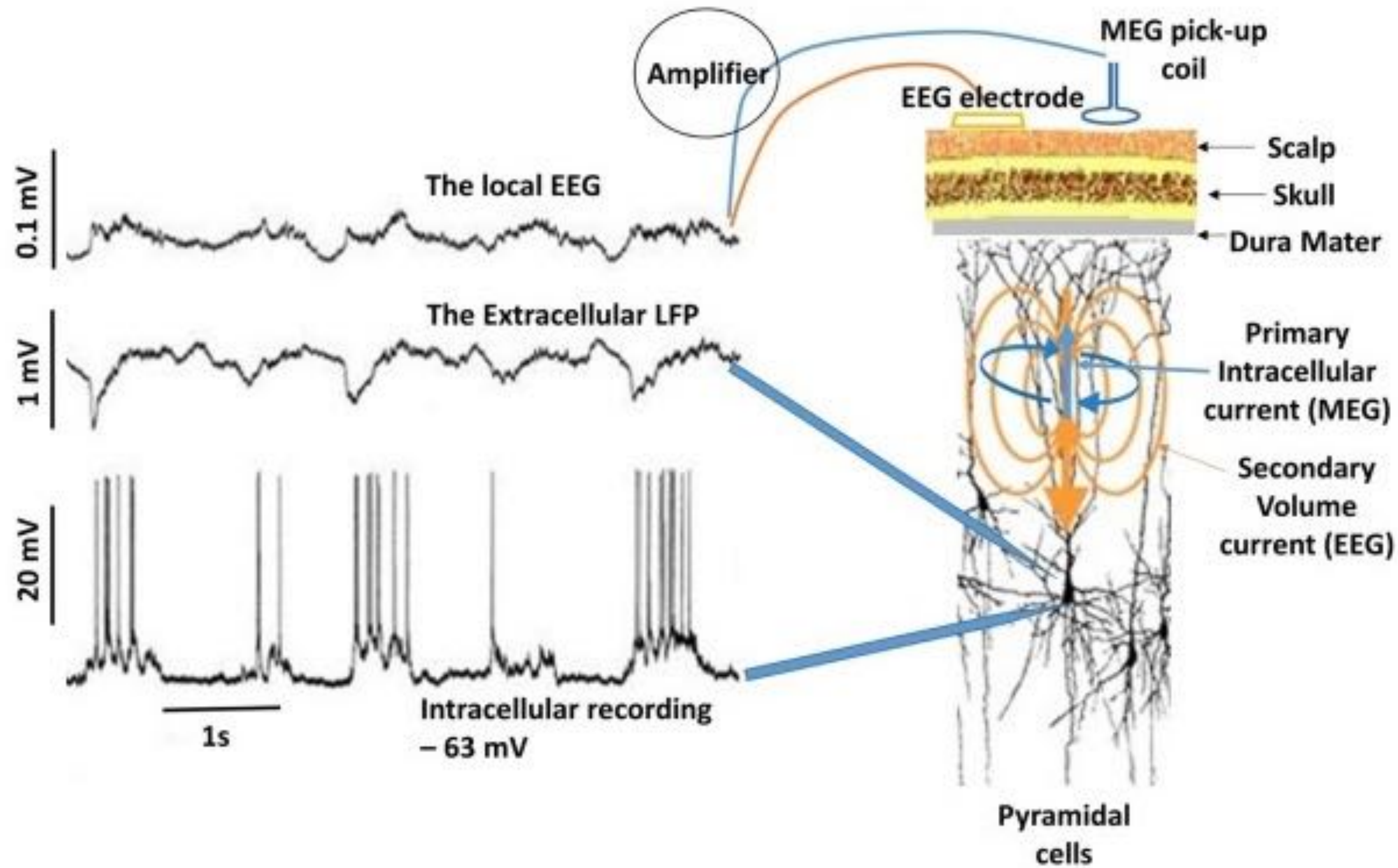
single neuron model:







single neuron + LFP + EEG model:



……some details on general anaesthesia

mathematical model:

extracellular potentials in areas:

$$\frac{1}{\alpha_e}\frac{du_e^n(t)}{dt} = -u_e^n(t) + bv_e^n(t) + S_{e\to e}^n(t) + S_{i\to e}^n(t) + S_{th\to i}(t-\tau_{th}) + I_e + A_e^n(t)$$

$$\frac{1}{\alpha_i}\frac{du_i^n(t)}{dt} = -u_i^n(t) + bv_i^n(t) + S_{e\to i}^n(t) + S_{i\to i}^n(t) + S_{th\to i}(t-\tau_{th}) + I_i + A_i^n(t)$$

$$\frac{1}{\alpha_{th}}\frac{du_{th}^n(t)}{dt} = -u_{th}^n(t) + bv_{th}^n(t) + S_{e\to th}^n(t-\tau_{th}) + S_{rtn\to th}^n(t-\tau_{rtn}) + I_{th} + A_{th}^n(t)$$

$$\frac{1}{\alpha_{rtn}}\frac{du_{rtn}^n(t)}{dt} = -u_{rtn}^n(t) + bv_{rtn}^n(t) + S_{e\to rtn}^n(t-\tau_{th}) + S_{th\to rtn}^n(t-\tau_{rtn}) + I_{rtn} + A_{rtn}^n(t)$$

adaption currents:

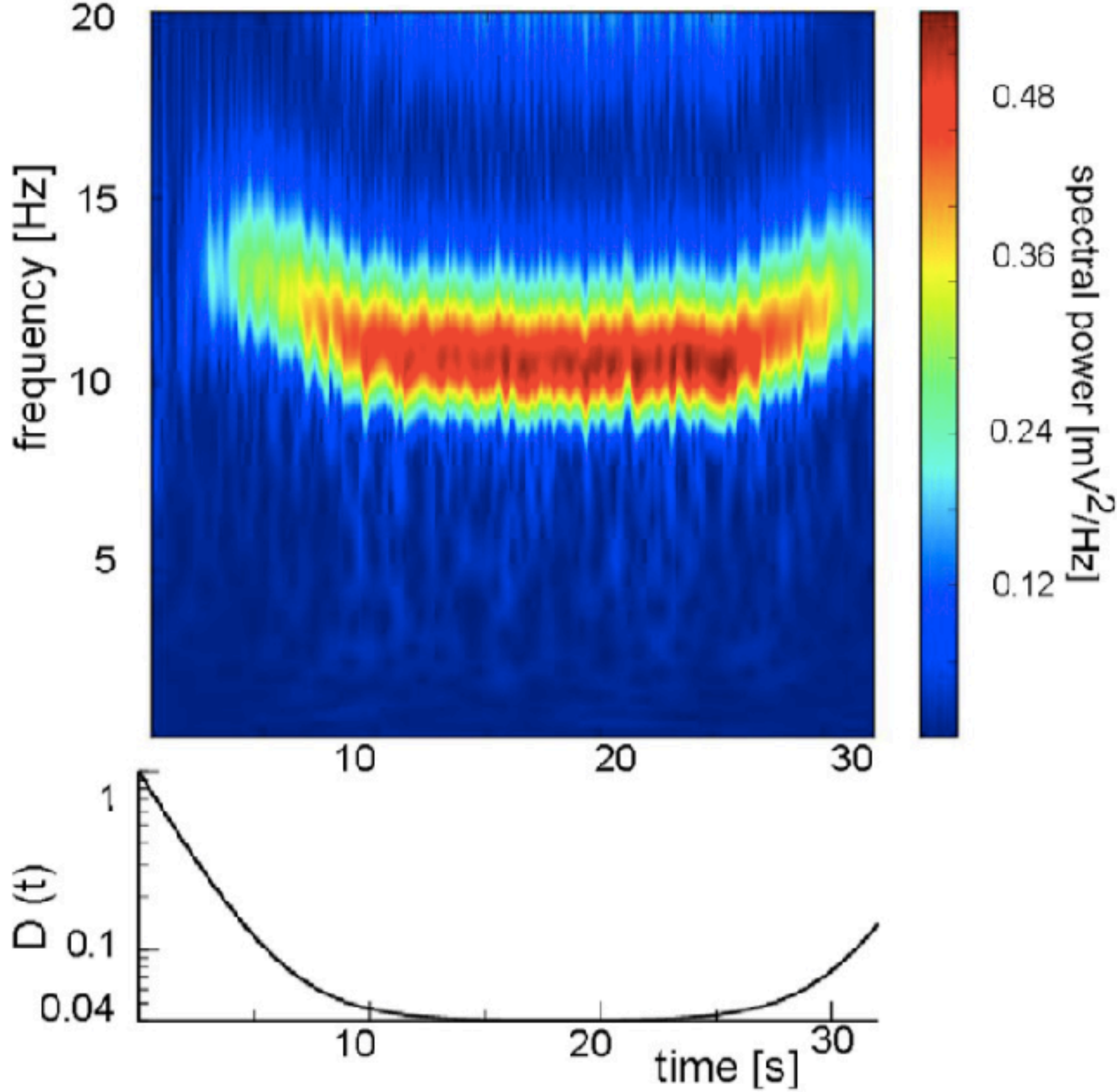
$$\frac{1}{a}\frac{dv_e^n(t)}{dt} = -v_e^n(t) + u_e^n(t) \ ; \ \frac{1}{a}\frac{dv_i^n(t)}{dt} = -v_i^n(t) + u_i^n(t)$$

$$\frac{1}{a}\frac{dv_{th}^n(t)}{dt} = -v_{th}^n(t) + u_{th}^n(t) \ ; \ \frac{1}{a}\frac{dv_{rtn}^n(t)}{dt} = -v_{rtn}^n(t) + u_{rtn}^n(t)$$

......some details on general anaesthesia

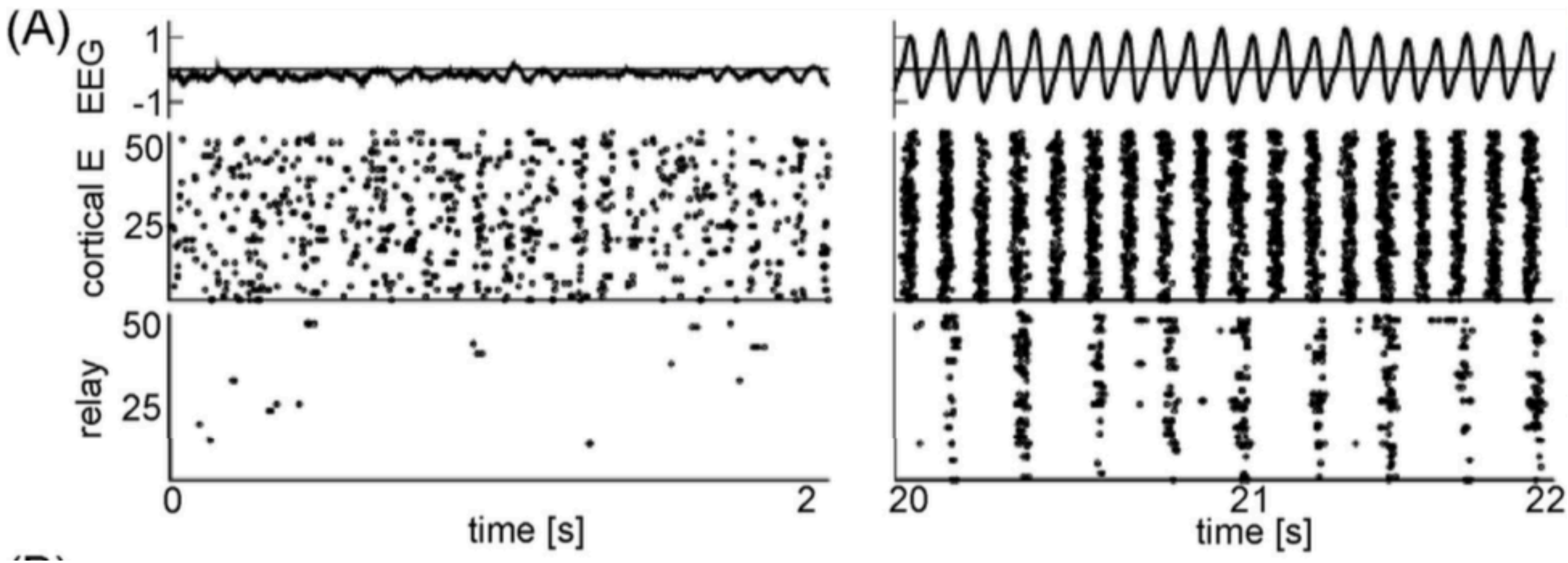
simulated
EEG spectrum

noise



……some details on general anaesthesia

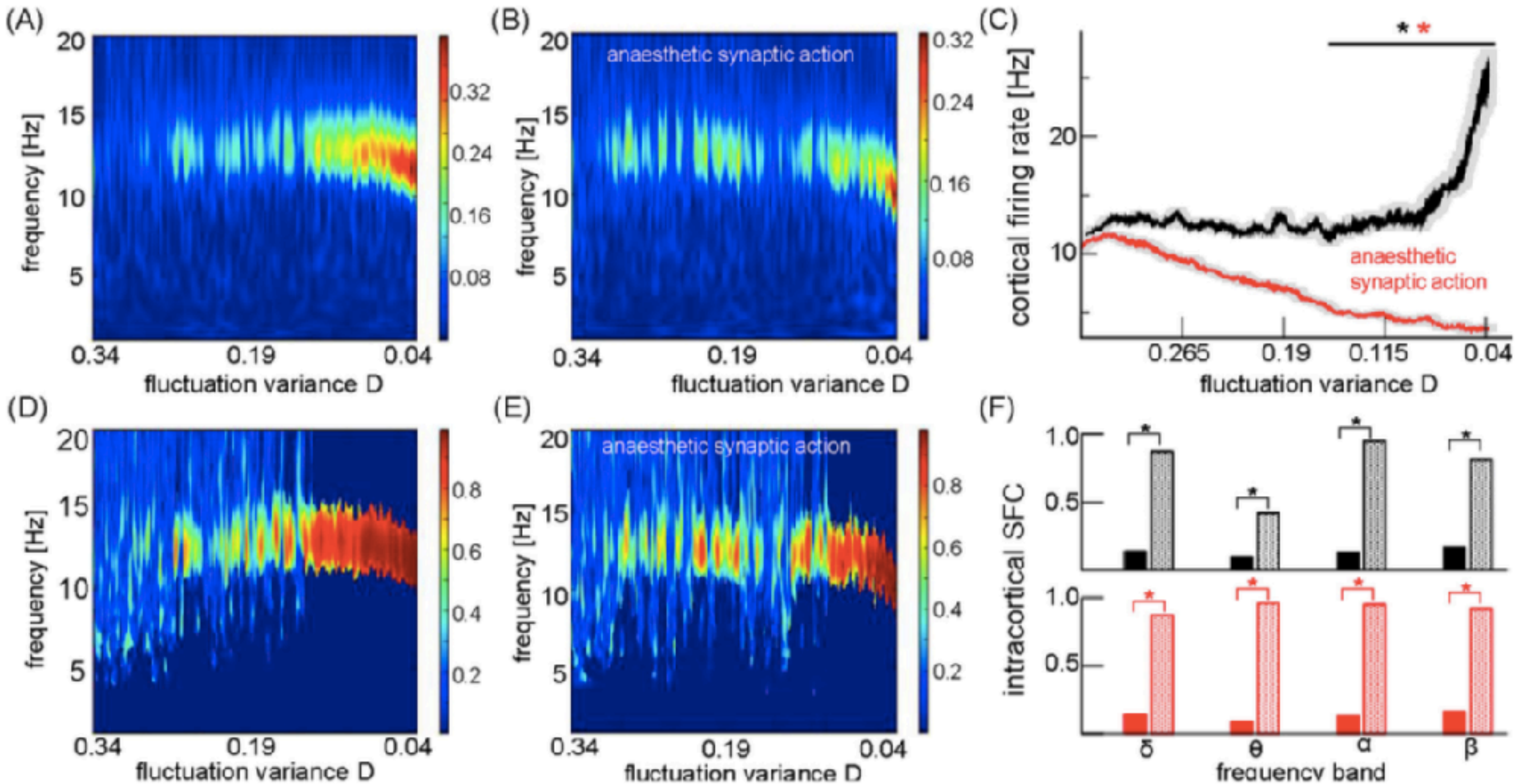
spiking activity in different areas



spike synchronisation by denoising

……some details on general anaesthesia

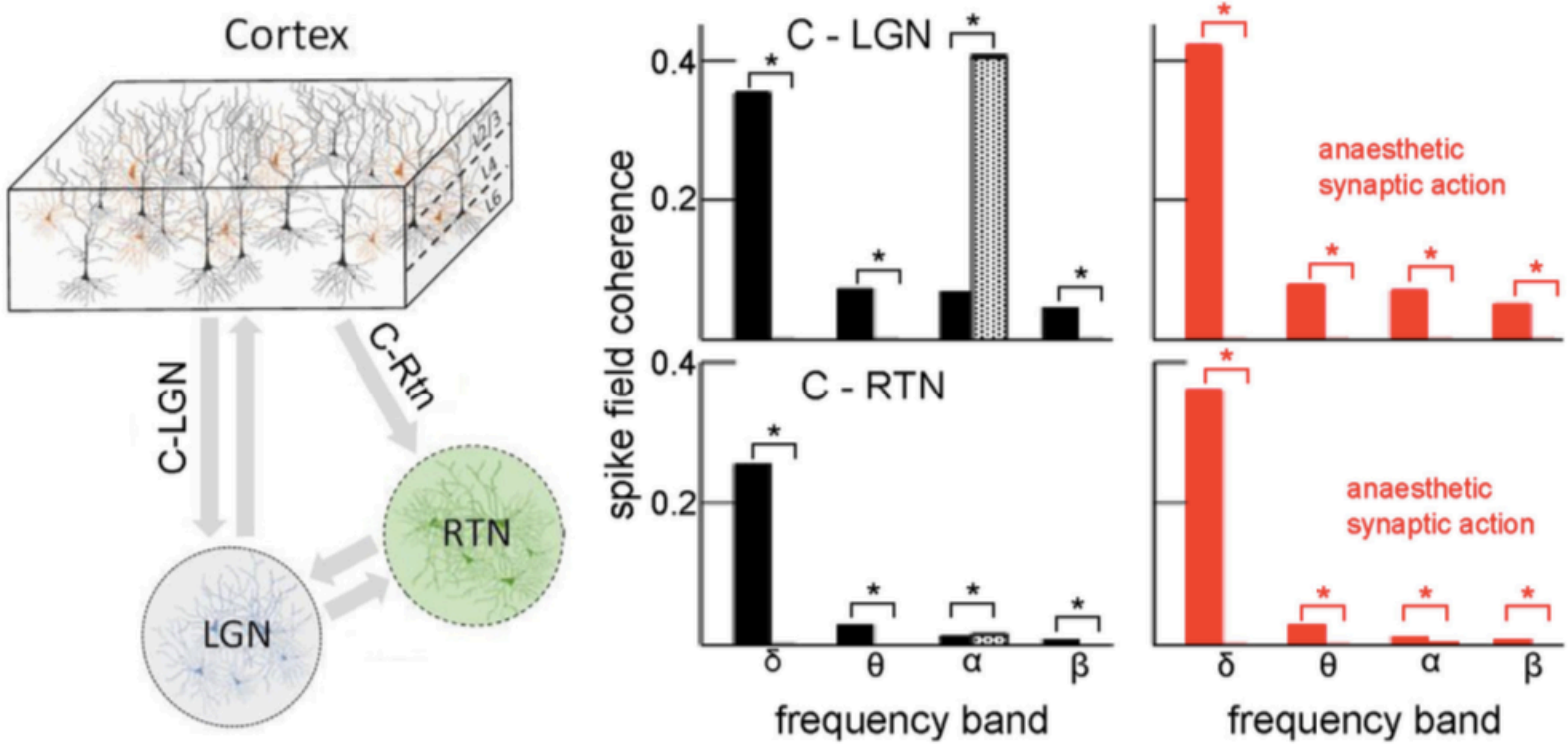
synchronisation in cortical population



awake EEG is asynchronous,
sedative EEG is synchronous

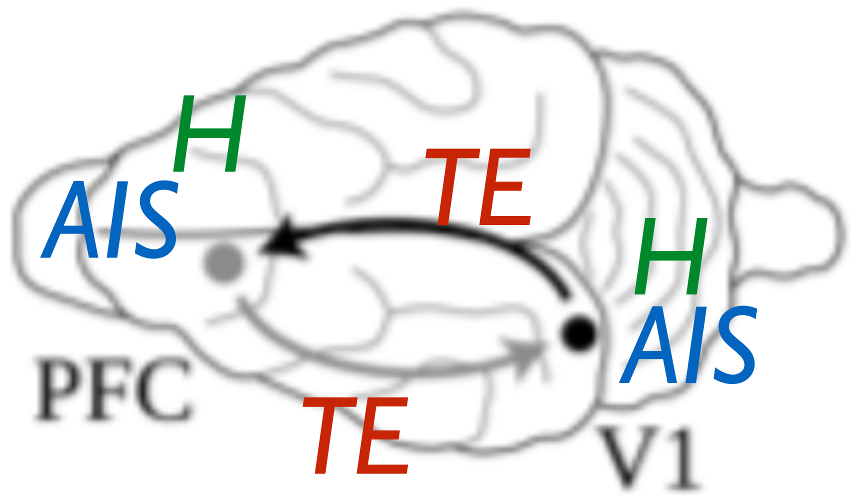
……some details on general anaesthesia

functional connectivity



found in experiment ?

information theoretic measures:



transfer entropy (TE):
how much information is transferred ?

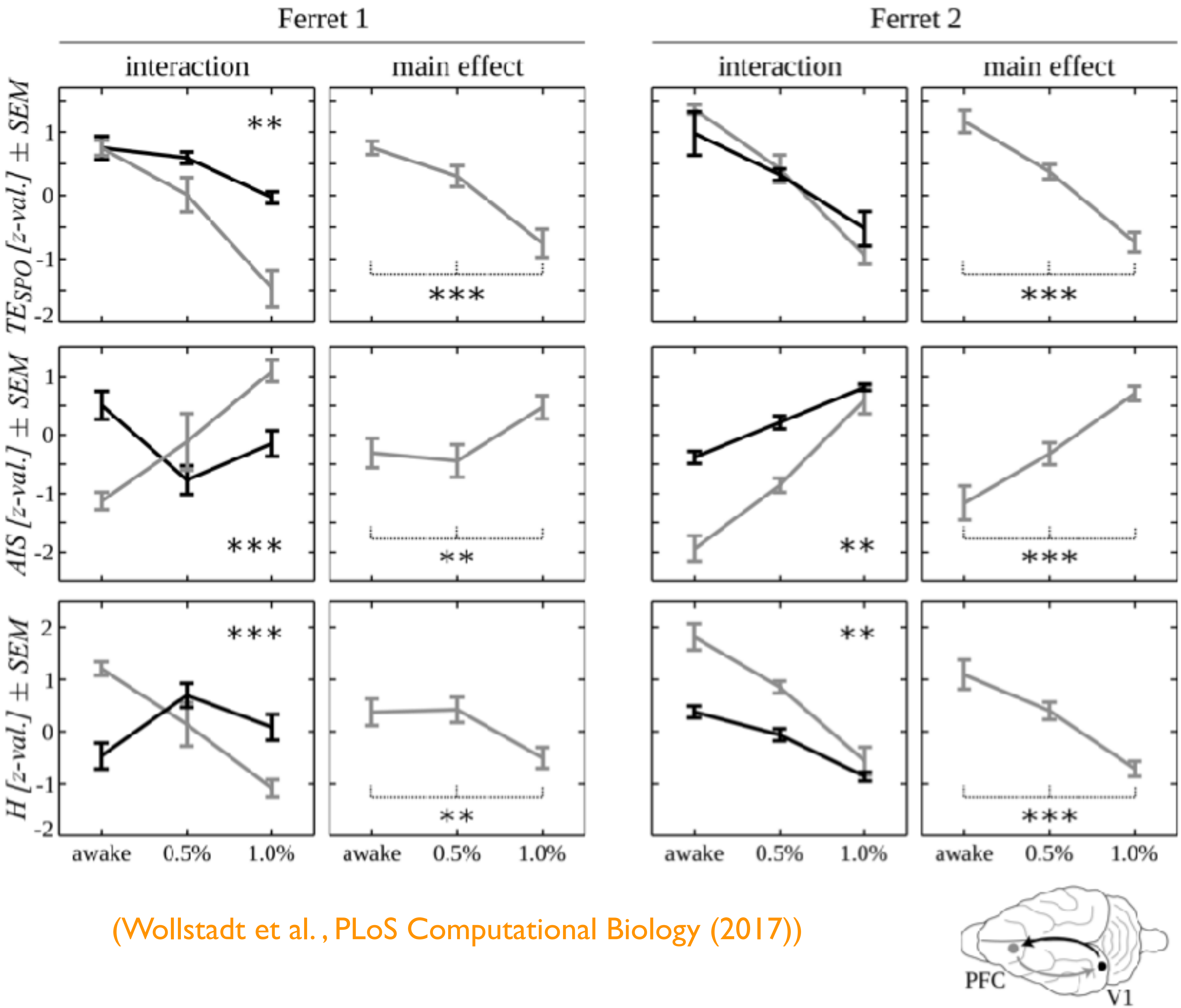
$TE \leq H$

active information storage (AIS):
how much information is stored ?

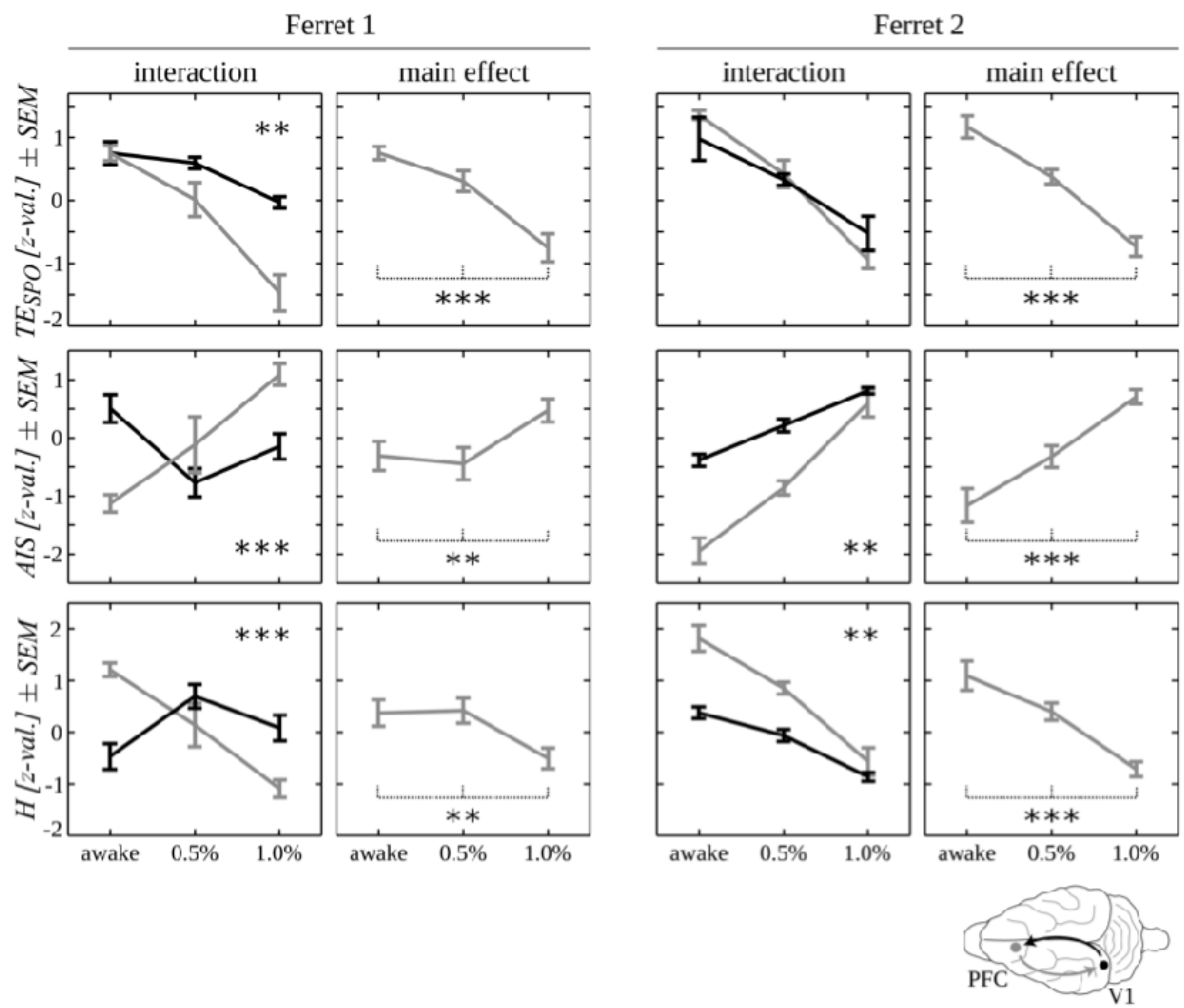
$AIS \leq H$

differential entropy (H):
how much information is available ?

information transfer during ferret resting state under anesthesia



(Wollstadt et al. , PLoS Computational Biology (2017))



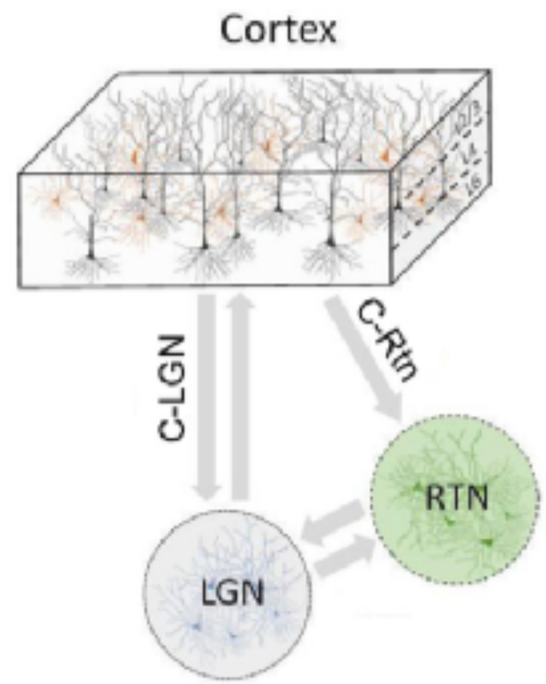
- reduction of information transfer V1 ▻ PFC
- enlargement of stored information in V1
- reduction of available information in V1

(Wollstadt et al. , PLoS Computational Biology (2017))

I) pharmacological effect of anti-psychotic drugs

a) dynamical model of action of *clozapine*

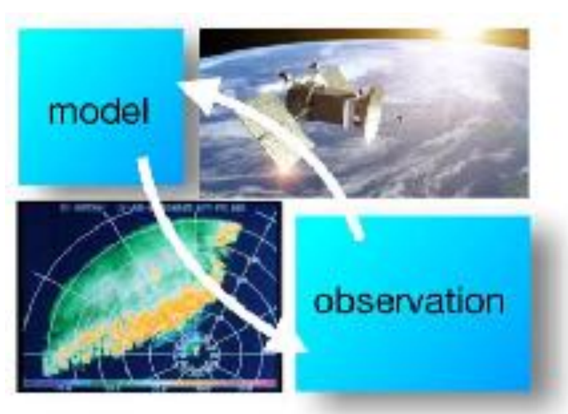
on cortico-thalamic loop



(NeuroImage 2018; eLife 2017; PLoSOne 2017; J. Neuroscience 2016)

b) comparison to observations (D. PINAULT) and

model adaption (e.g. Kalman filter) —> thesis of Joséphine RIEDINGER



Frontiers Research Topic on *Data Assimilation in Life Sciences* (2018); Frontiers Re
Topic on *Data Assimilation of Nonlocal Observations* (2019),
Frontiers in Applied Mathematics and Statistics

Front. Appl. Math. Stat. 2018; Meteor. Zeit. 2018; Neuroinformatics 2018;
J. Math. Neurosci. 2018

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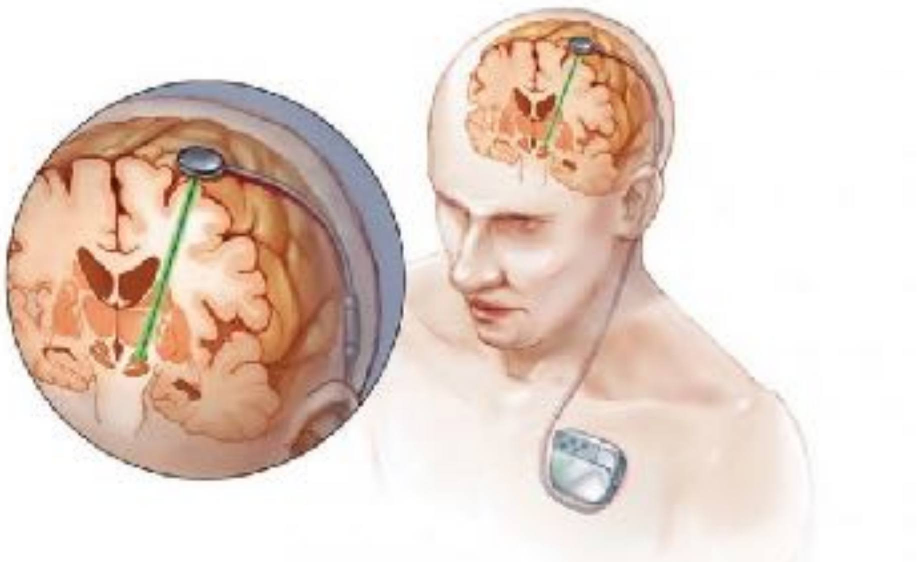
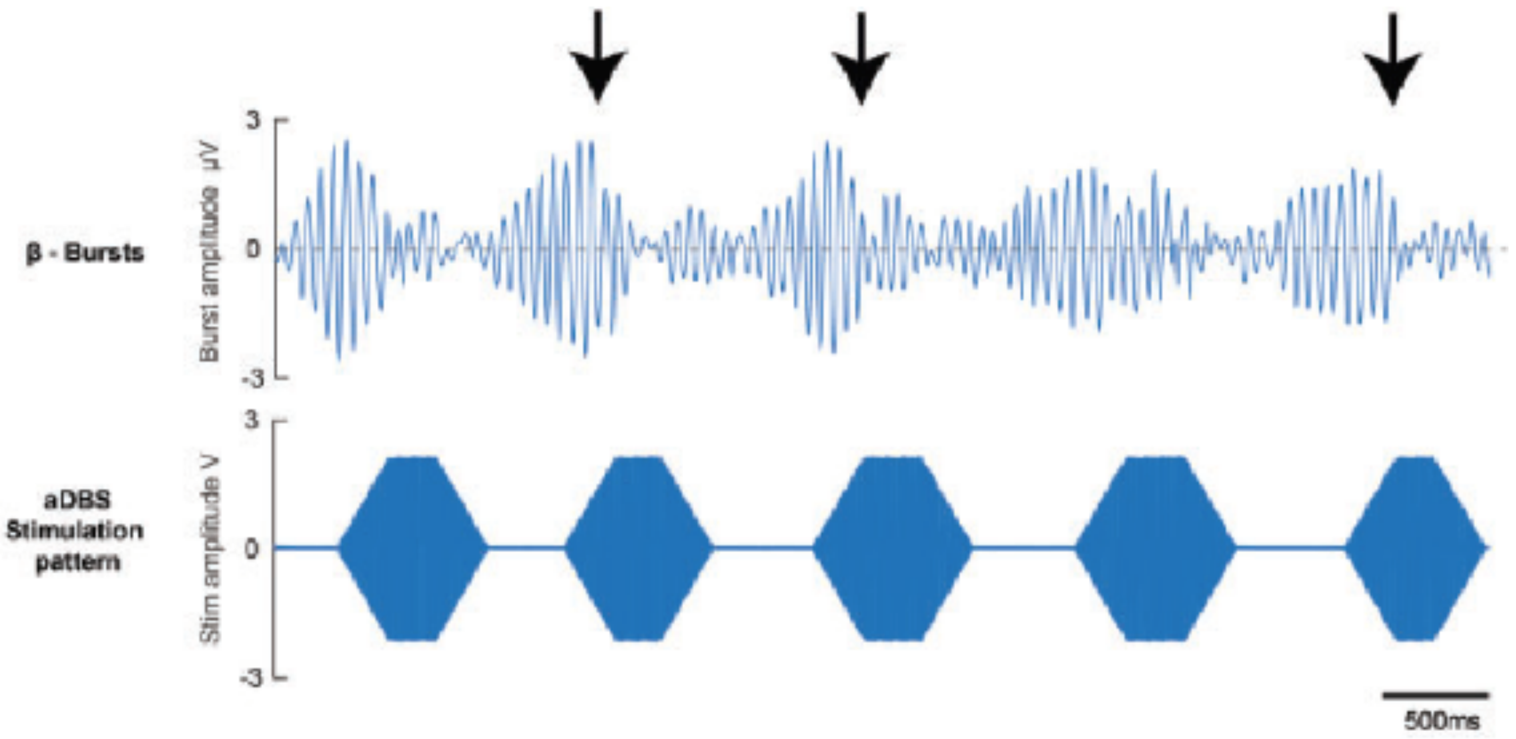
I: drugs II: stimulation

long-term projects

Motivation

Deep Brain Stimulation (DBS)

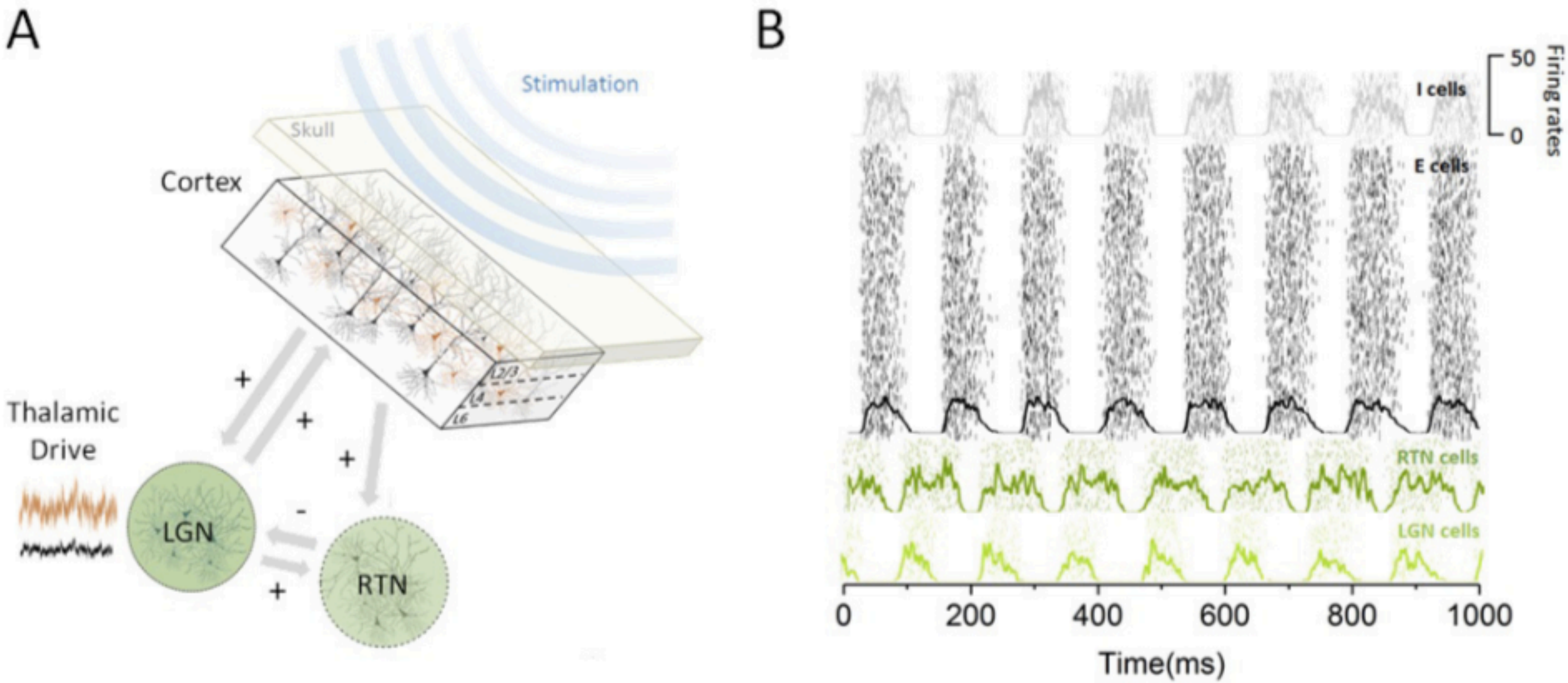




monopolar stimulation with 130 Hz

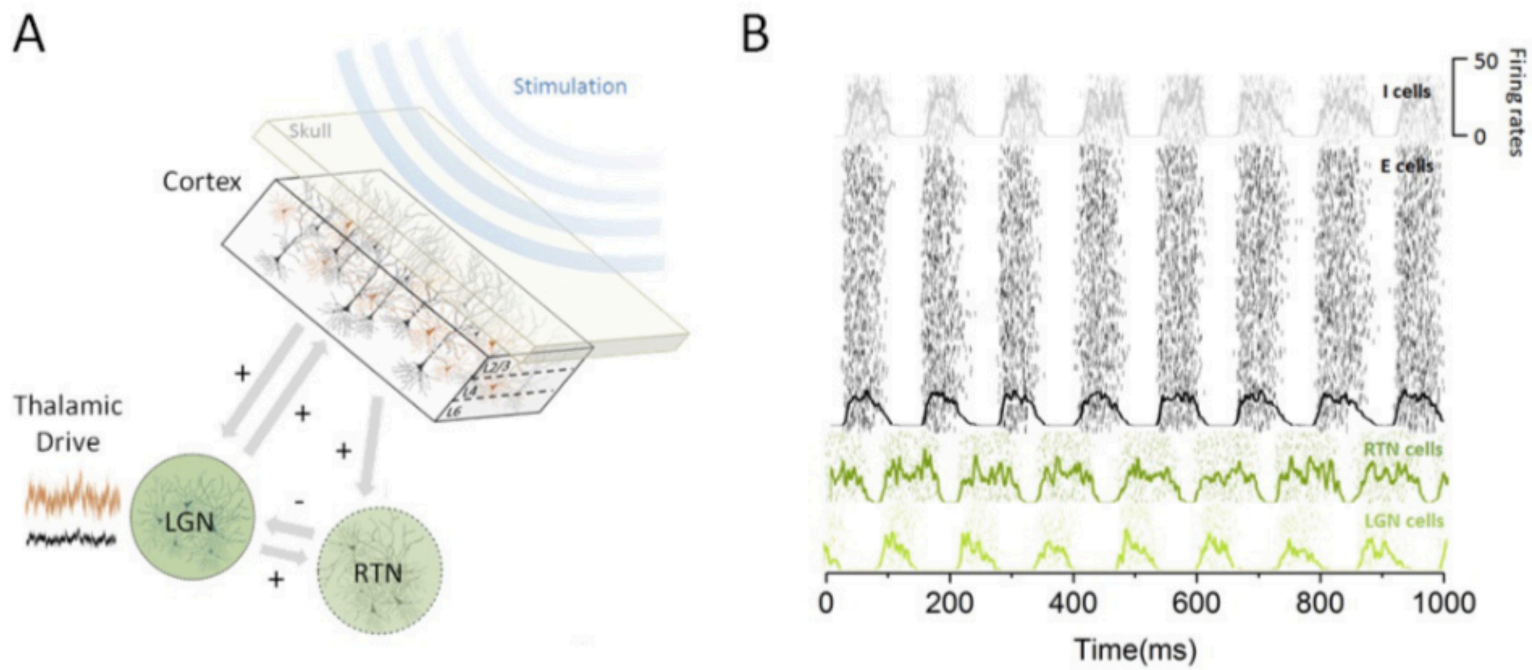
(Tinkhauser et al. (2017), Brain 140: 1053–1067)

Cortical stimulation under task and rest condition



(Lefebvre et al., eLife (2017); doi: https://doi.org/10.7554/eLife.32054)

Cortical stimulation under task and rest condition



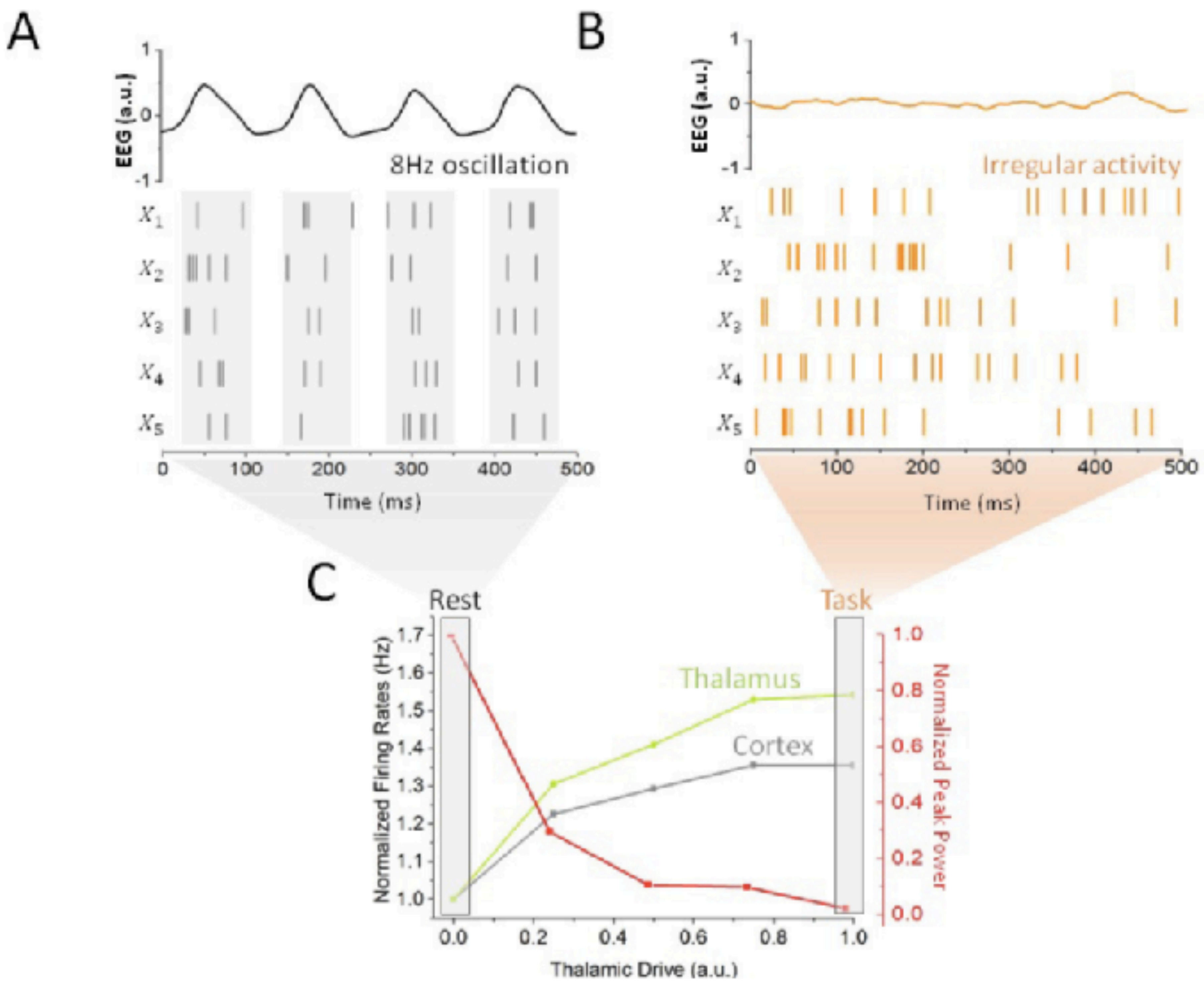
evolution equations of each area:

$$\alpha_n^{-1}\frac{du_n^j(t)}{dt} = -u_n^j(t) + b\, v_n^j(t) + \sum_m S_{nm}(t) + I_n + \sqrt{2D_n}\,\xi_n^j(t) + S_{e,i}(t)$$

$$a_n^{-1}\frac{dv_n^j(t)}{dt} = -v_n^j(t) + u_n^j(t)$$

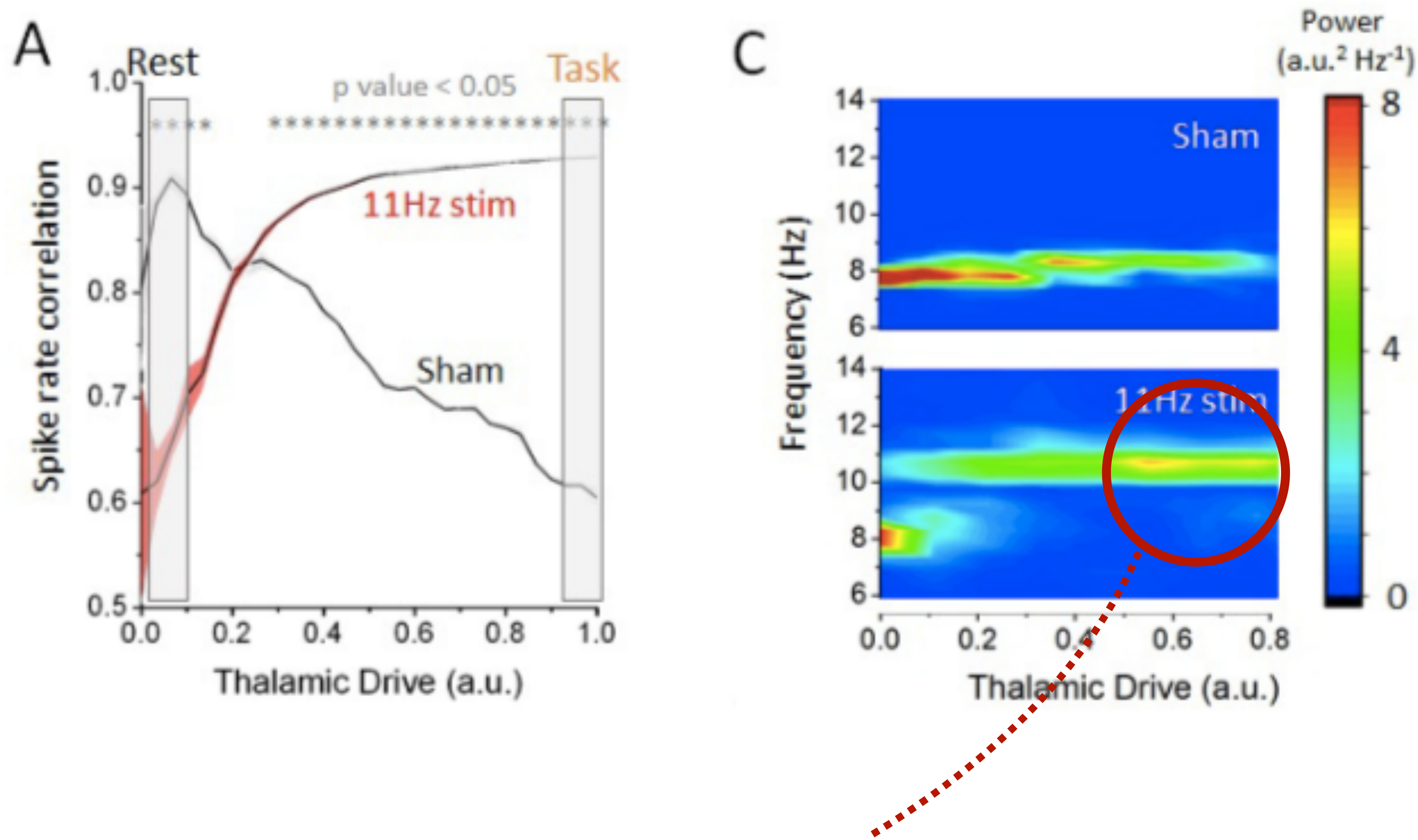
(Lefebvre et al., eLife (2017); doi: https://doi.org/10.7554/eLife.32054)

no cortical stimulation



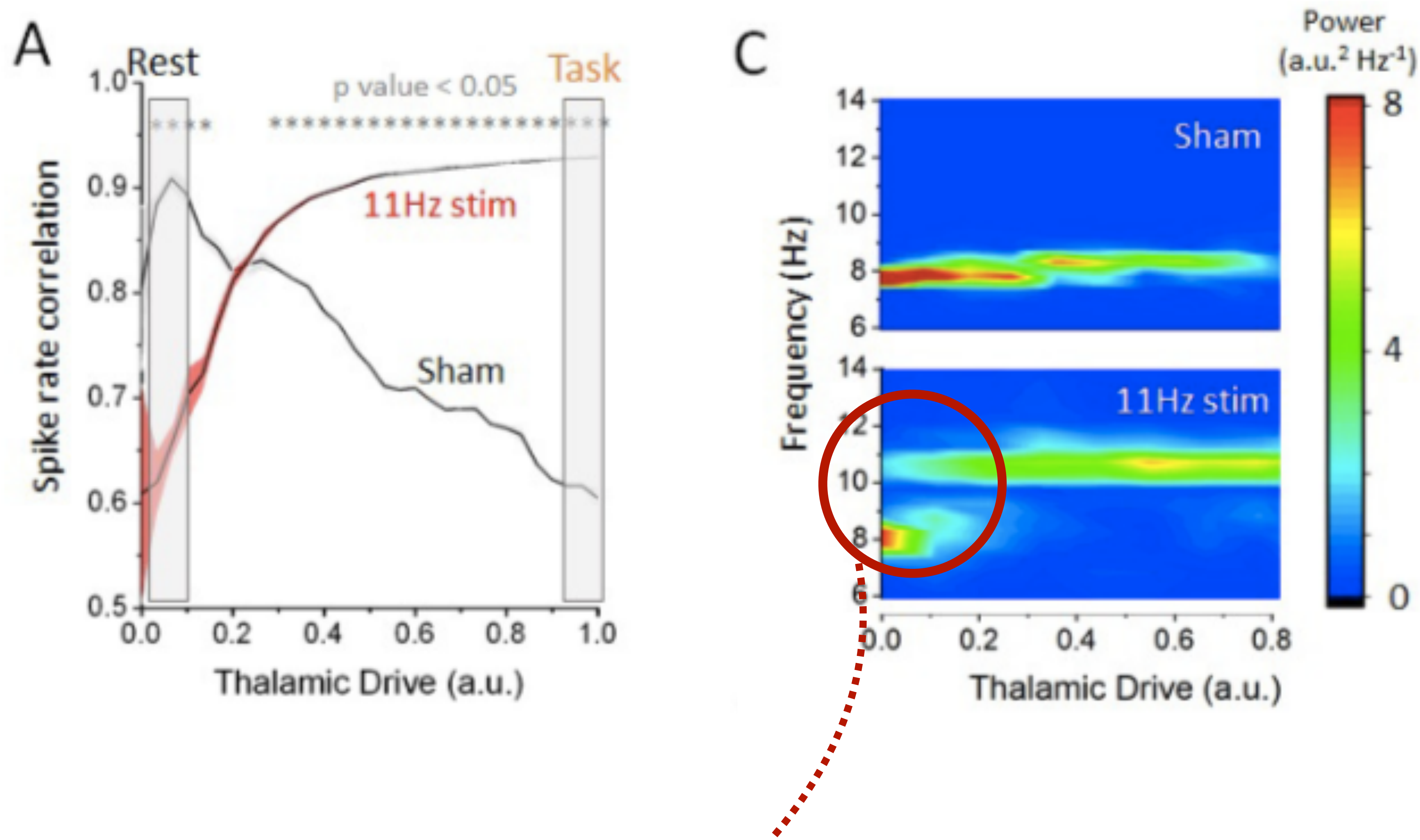
thalamic noise stimulation desynchronizes EEG

cortical stimulation with 11Hz



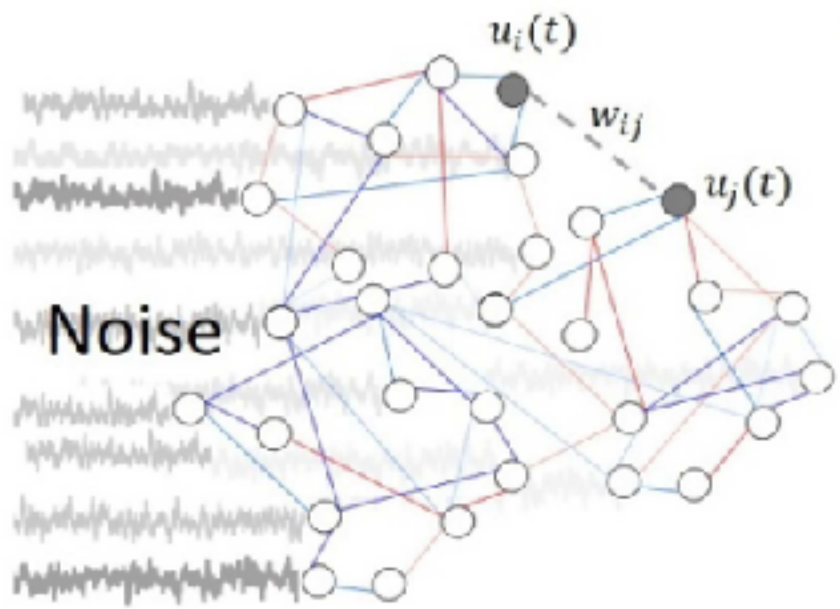
thalamic noise stimulation enhances EEG at stimulation frequency

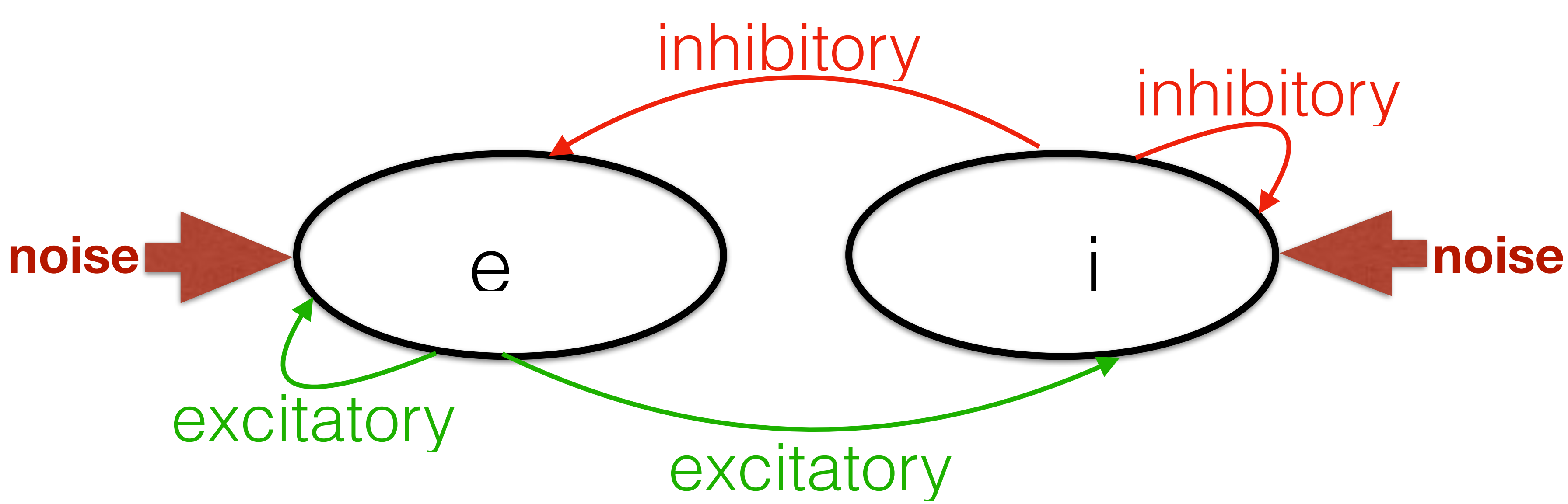
cortical stimulation with 11Hz



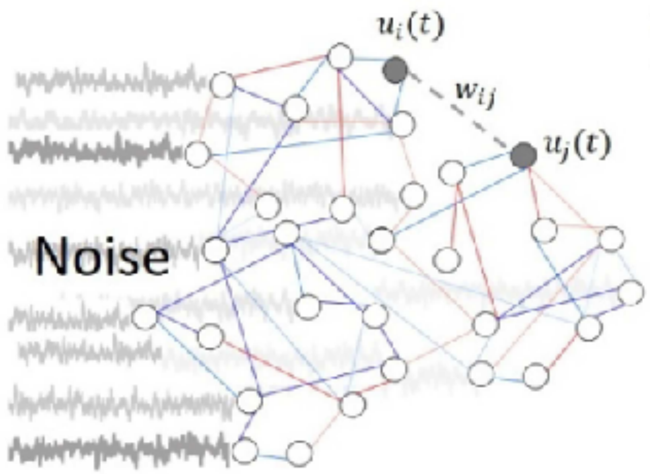
clinical finding: no stimulus response observed in certain patients

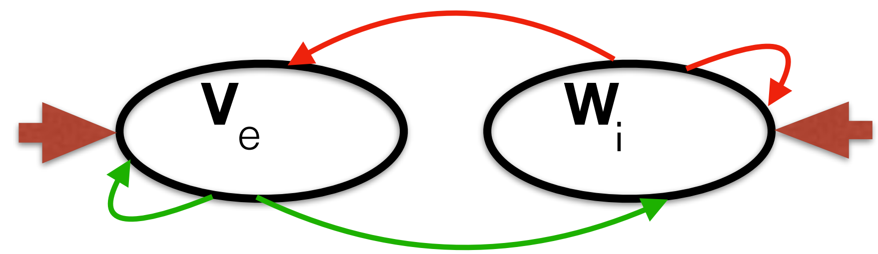
Analytical description of stochastic stimulation





(A. Hutt, J. Lefebvre, D. Hight and H. Kaiser,, [Frontiers in Applied Mathematics and Statistics 5:69 (2020)]())





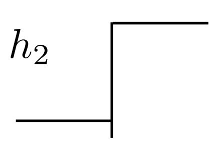
model:

$$\hat{L}V_n = \sum_{m=1}^{N} F_{nm} h_1[V_m] - \sum_{m=1}^{N} M_{nm} h_2[W_m] + I_0^{(1)} + \xi_n{}^{(1)}(t)$$

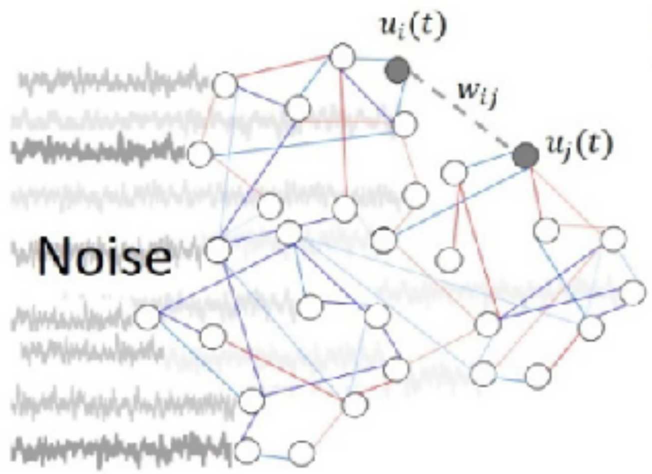
$$\hat{L}W_n = -\sum_{m=1}^{N} F_{nm} h_2[W_m] + \sum_{m=1}^{N} M_{nm} h_1[V_m] \ + I_0^{(2)} + \xi_n{}^{(2)}(t)$$

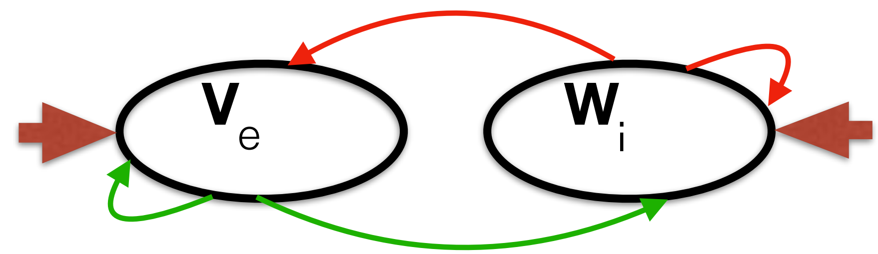
$$\hat{L} = \frac{d}{dt} + 1$$

h_1, h_2



(A. Hutt, J. Lefebvre, D. Hight and H. Kaiser,, Frontiers in Applied Mathematics and Statistics 5:69 (2020))





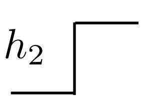
model:

$$\hat{L}V_n = \sum_{m=1}^{N} F_{nm} h_1[V_m] - \sum_{m=1}^{N} M_{nm} h_2[W_m] + I_0^{(1)} + \xi_n{}^{(1)}(t)$$

uncorrelated noise

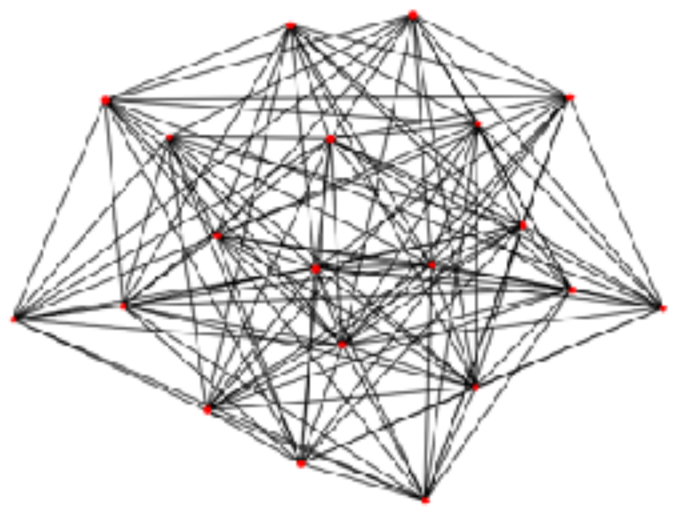
$$\hat{L}W_n = -\sum_{m=1}^{N} F_{nm} h_2[W_m] + \sum_{m=1}^{N} M_{nm} h_1[V_m] + I_0^{(2)} + \xi_n{}^{(2)}(t)$$

$$\hat{L} = \frac{d}{dt} + 1 \qquad h_1, h_2$$

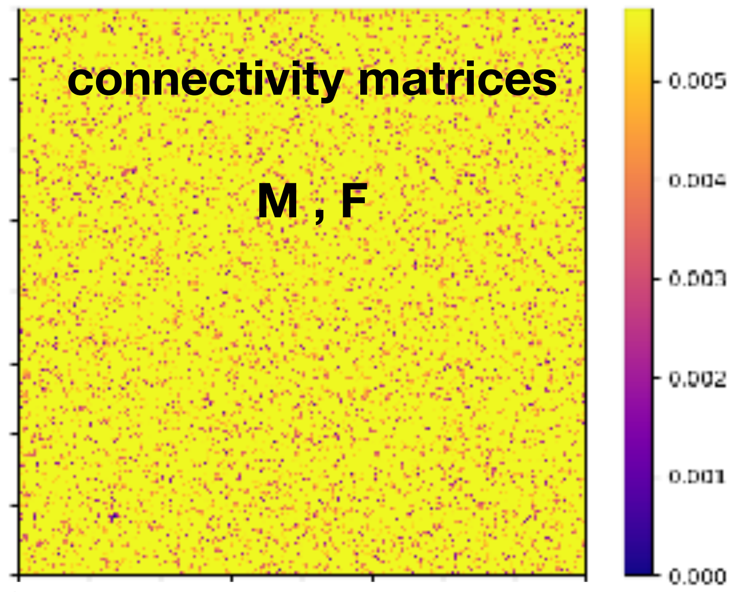


(A. Hutt, J. Lefebvre, D. Hight and H. Kaiser,, Frontiers in Applied Mathematics and Statistics 5:69 (2020))

connection matrices

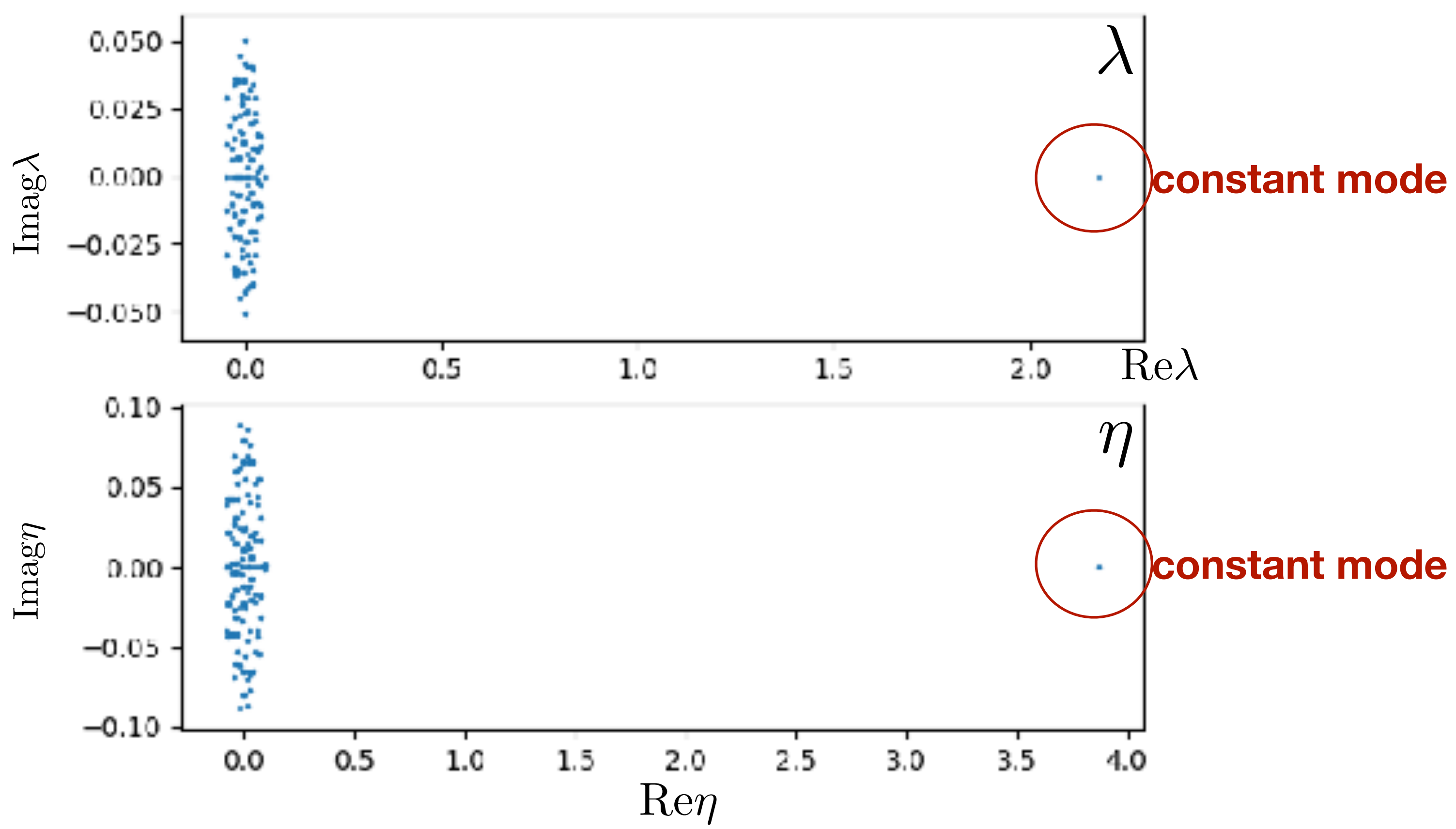


Erdös-Rényi network
with connection probability c=0.95

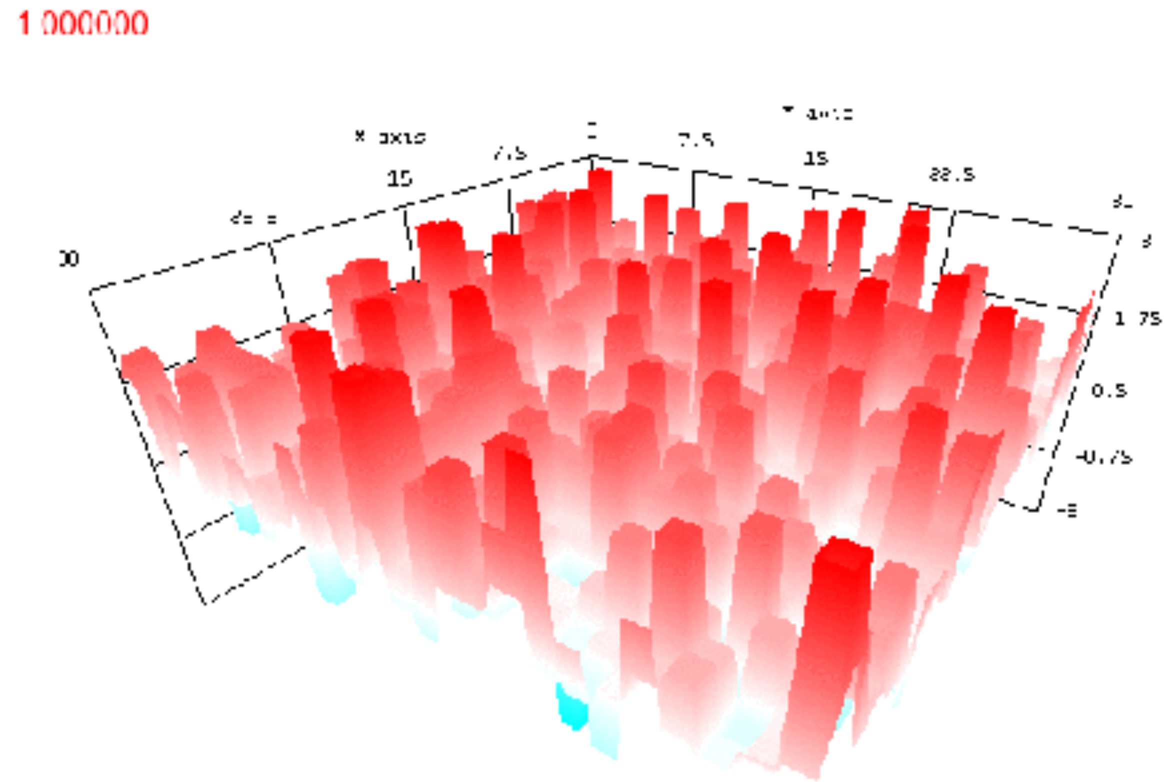


(A. Hutt, J. Lefebvre, D. Hight and H. Kaiser, Frontiers in Applied Mathematics and Statistics 5:69 (2020))

connection kernel spectra

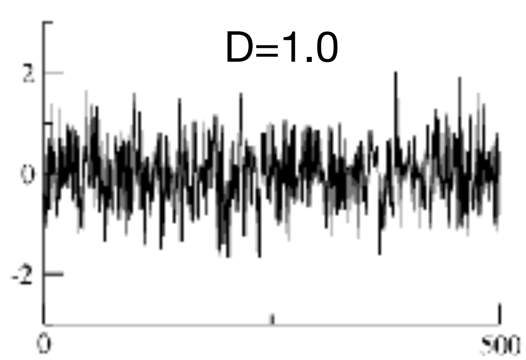


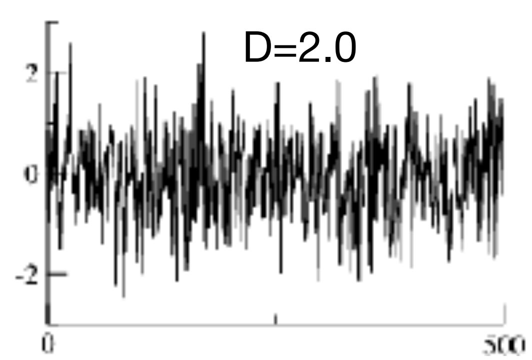
$$\mathbf{v}^t\mathbf{K} = \lambda\mathbf{v}^t \qquad \mathbf{w}^t\mathbf{M} = \eta\mathbf{w}^t$$

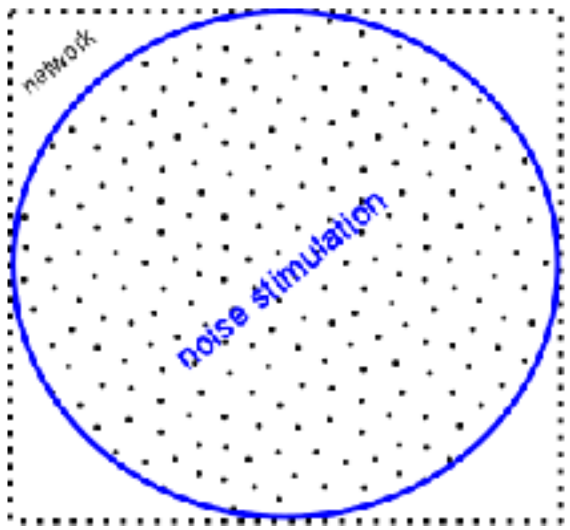


$$\xi_n^{(1)} \sim \mathcal{N}(0, D)$$

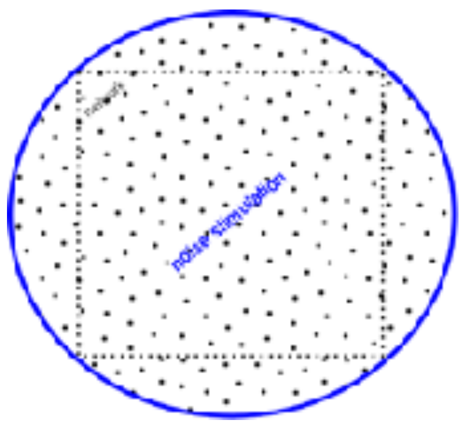
$$\xi_n^{(2)} \sim \mathcal{N}(0, 0.5)$$







analysis:



$$V_n(t) = \bar{V}(t) + v_n(t)$$

$$W_n(t) = \bar{W}(t) + w_n(t)$$

$$\bar{V} = \frac{1}{N}\sum_{n=1}^{N} V_n \ , \ \bar{W} = \frac{1}{N}\sum_{n=1}^{N} W_n$$

mean field dynamics:

$$\hat{L}\bar{V} = FS_1(\bar{V}) - MS_2(\bar{W}) + I_1$$
$$\hat{L}\bar{W} = -FS_2(\bar{W}) + MS_1(\bar{V}) + I_2$$

$$\hat{L}w_n = \xi_n^{(2)}(t)$$
$$\hat{L}v_n = \xi_n^{(1)}(t)$$

Ornstein-Uhlenbeck process

stationary probability density:

$$\rho_v = \mathcal{N}(0, D)$$

$$\rho_w = \mathcal{N}(0, 0.5)$$

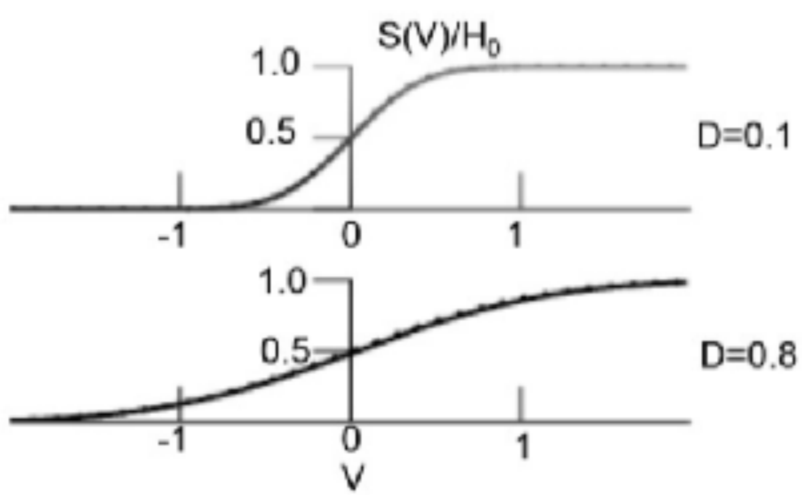
if $E[FH(\bar{V} + v)] \approx E[F] \cdot E[H(\bar{V} + v)]$

(A. Hutt, J. Lefebvre, D. Hight and H. Kaiser,, Frontiers in Applied Mathematics and Statistics 5:69 (2020))

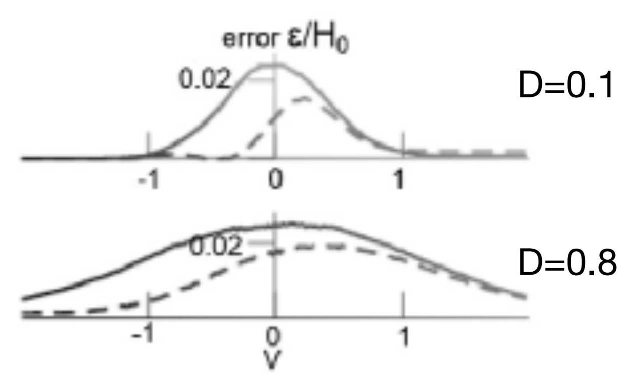
additive noise tunes transfer function

$$S_1(\bar{V}) = \int_{-\infty}^{\infty} h_1(\bar{V}+v)\rho_v(v)dv \qquad \rho_v = \mathcal{N}(0, D)$$

$$S_2(\bar{W}) = \int_{-\infty}^{\infty} h_2(\bar{W}+w)\rho_w(w)dw \qquad \rho_w = \mathcal{N}(0, 0.5)$$



the stronger the noise,
the more flat is the transfer function



low noise (D=0.4)

high noise (D=0.8)

$\bar{V}(t)$ 1.30 1.25

-0.4 -0.6

350 400 time [s]

350 400 time [s]

power spectrum

power 60 30 high low

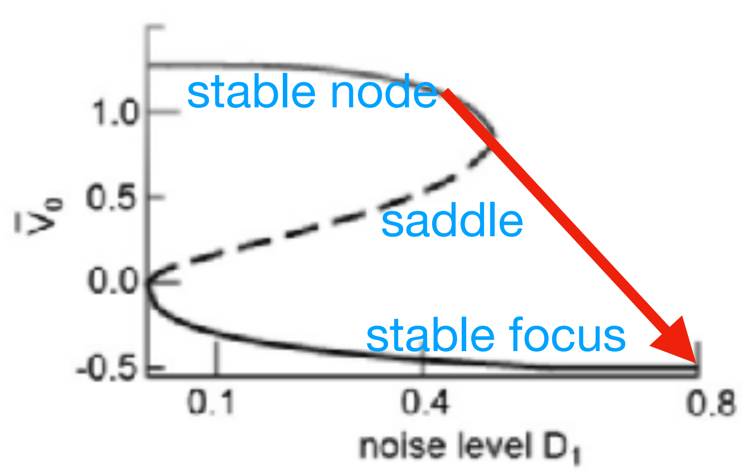
0.5 1.0 1.5 2.0 frequency [Hz]

phase coherence

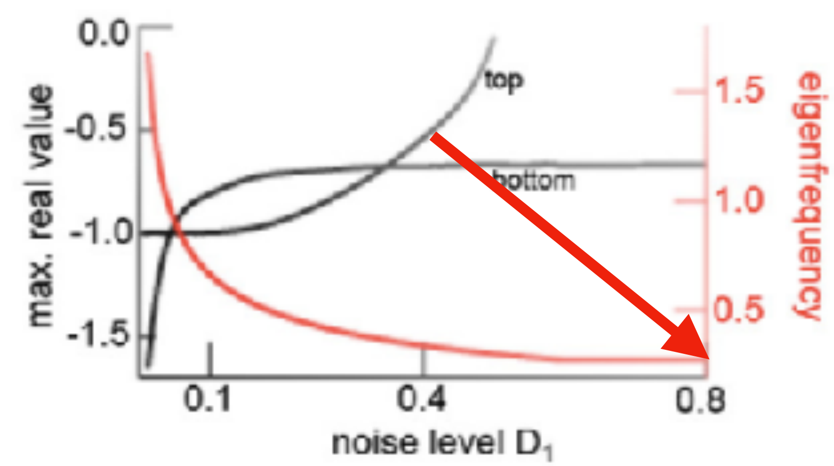
gPLV 0.06 0.03 high low

0.5 1.0 1.5 2.0 frequency [Hz]

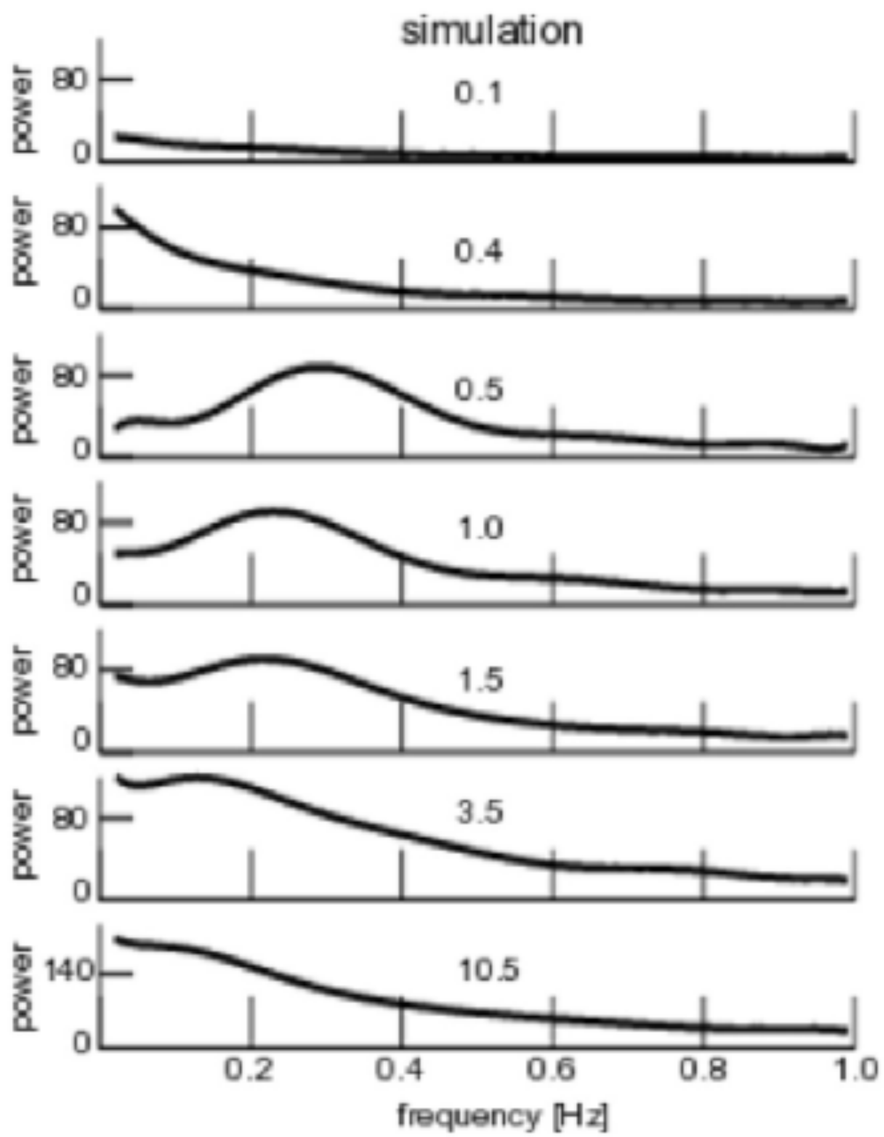
equilibrium



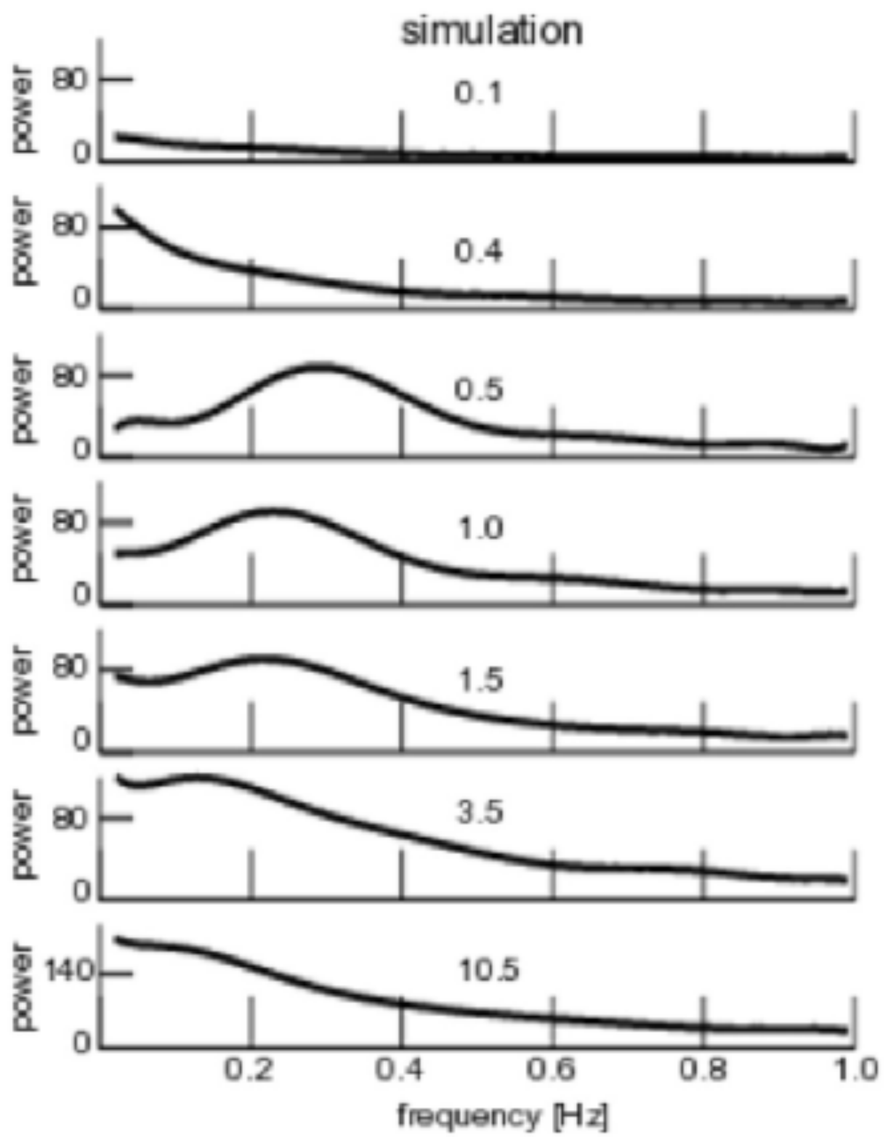
linear Lyapunov exponent



link to coherence resonance



link to coherence resonance

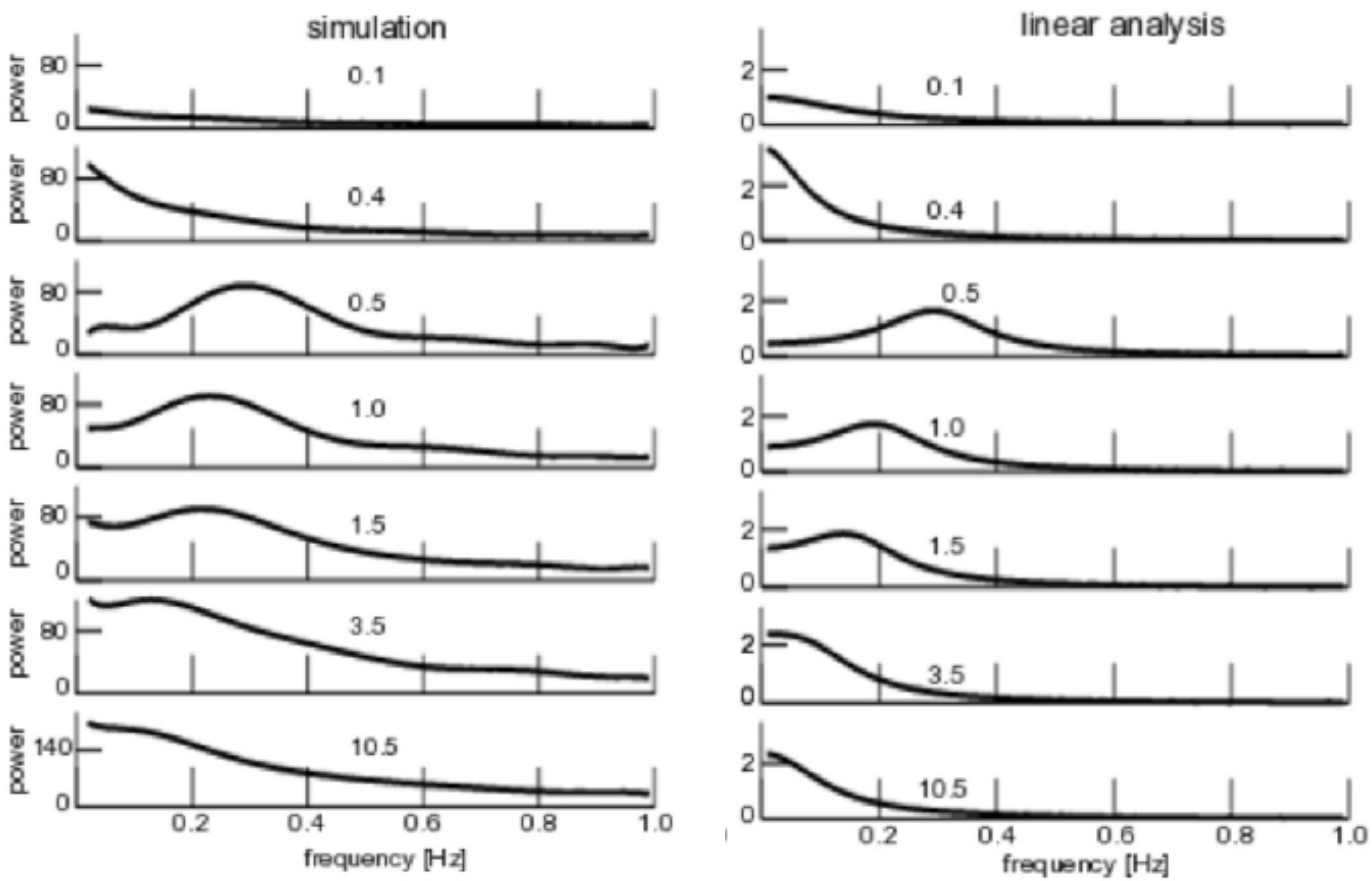


analytical linear power spectrum

$$\mathbf{L} = \begin{pmatrix} -1 + FS_1'(\bar{V}_0) & -MS_2'(\bar{W}_0) \\ MS_1'(\bar{V}_0) & -1 - FS_2'(\bar{W}_0) \end{pmatrix}$$

$$R(\nu) = \frac{D_0(L_{22}^2 + L_{12}^2 + 4\pi^2\nu^2)}{4\pi^2(L_{11} + L_{22})^2\nu^2 + (det\mathbf{L} - 4\pi^2\nu^2)^2}$$

link to coherence resonance



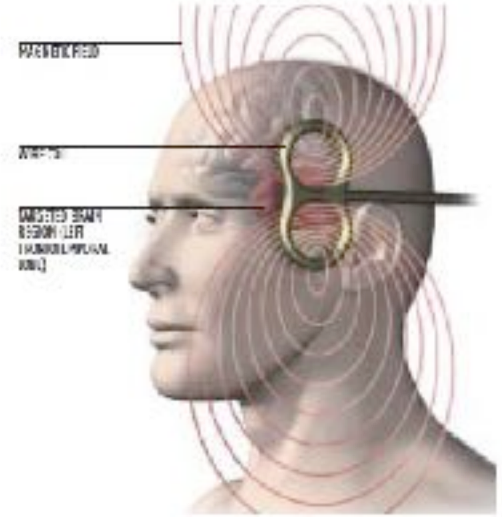
Outline

clinical cases

short-term projects

long-term projects

what are analog drugs and digital drugs ?



Alzheimer disease medication
(*F. Blanc, iCube Strasbourg*) ⟷ rTMS

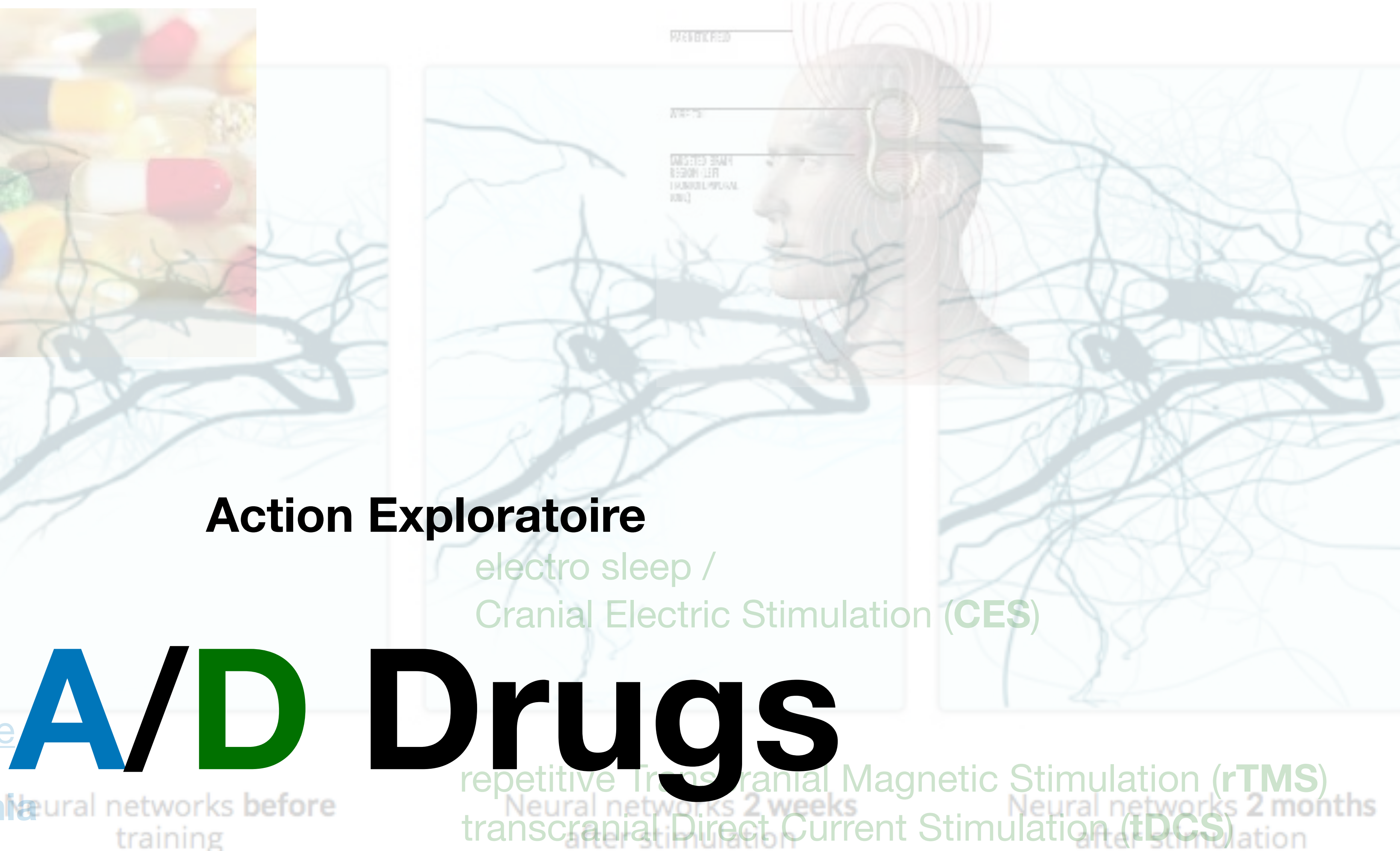
<u>psychodelic drugs</u>
inducing trance
LSD, mescaline ⟷ binaural beats (*digital drug*)

anaesthetic drugs
(D. Hight, University Hospital Bern) ⟷ ??

?? ⟷ 

analytical/digital drug

analytical	digital
sleep drugs	electro sleep / Cranial Electric Stimulation (**CES**)
drugs to relieve	
schizophrenia	repetitive Transcranial Magnetic Stimulation (**rTMS**)
major depression	transcranial Direct Current Stimulation (**tDCS**)
Alzheimer disease	transcranial Alternating Current Stimulation (**tACS**)
psychodelic drugs inducing trance	binaural beats
anaesthetic drugs	??
??	television viewing in children



Action Exploratoire

A/D Drugs

(2020-2023)

sleep drugs

drugs to relieve

schizophrenia

major depression

Alzheimer disease

psychodelic drugs

inducing trance

anaesthetic drugs

??

electro sleep /
Cranial Electric Stimulation (**CES**)

repetitive Transcranial Magnetic Stimulation (**rTMS**)

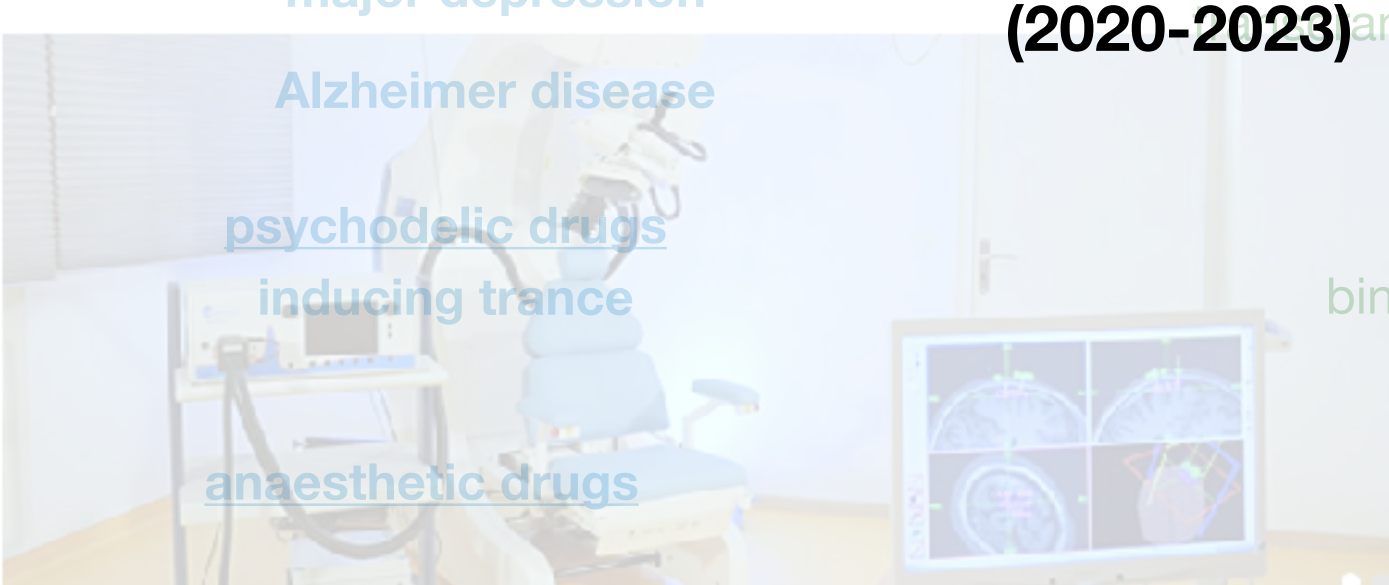
transcranial Direct Current Stimulation (**tDCS**)

transcranial Alternating Current Stimulation (**tACS**)

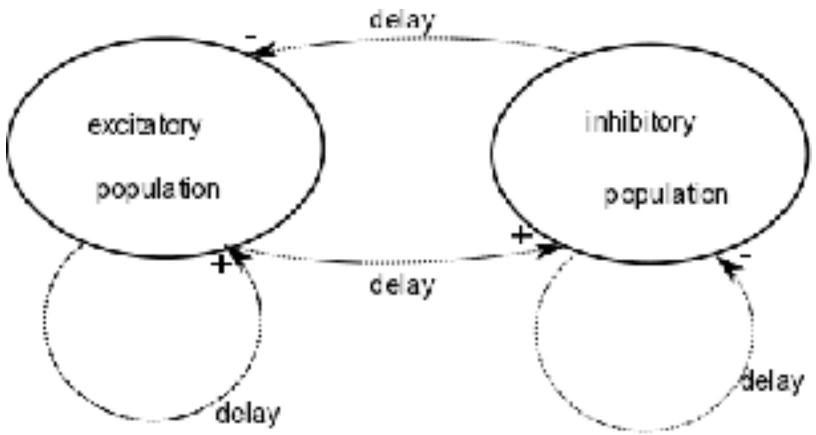
binaural beats

??

television viewing in children



first application



reduced cortico-thalamic model

$$\alpha_e^{-1}\frac{dU_e}{dt} = -U_e + bV_e + \overline{W}_{e\to e}F_e[U_e(t-\tau)] + \overline{W}_{i\to e}F_i[U_i(t-\tau)] + I_e$$

$$\alpha_i^{-1}\frac{dU_i}{dt} = -U_i + bV_i + \overline{W}_{e\to i}F_e[U_e(t-\tau)] + \overline{W}_{i\to i}F_i[U_i(t-\tau)] + I_i$$

$$a_e^{-1}\frac{dV_e}{dt} = -V_e + U_e$$

$$a_i^{-1}\frac{dV_i}{dt} = -V_i + U_i,$$

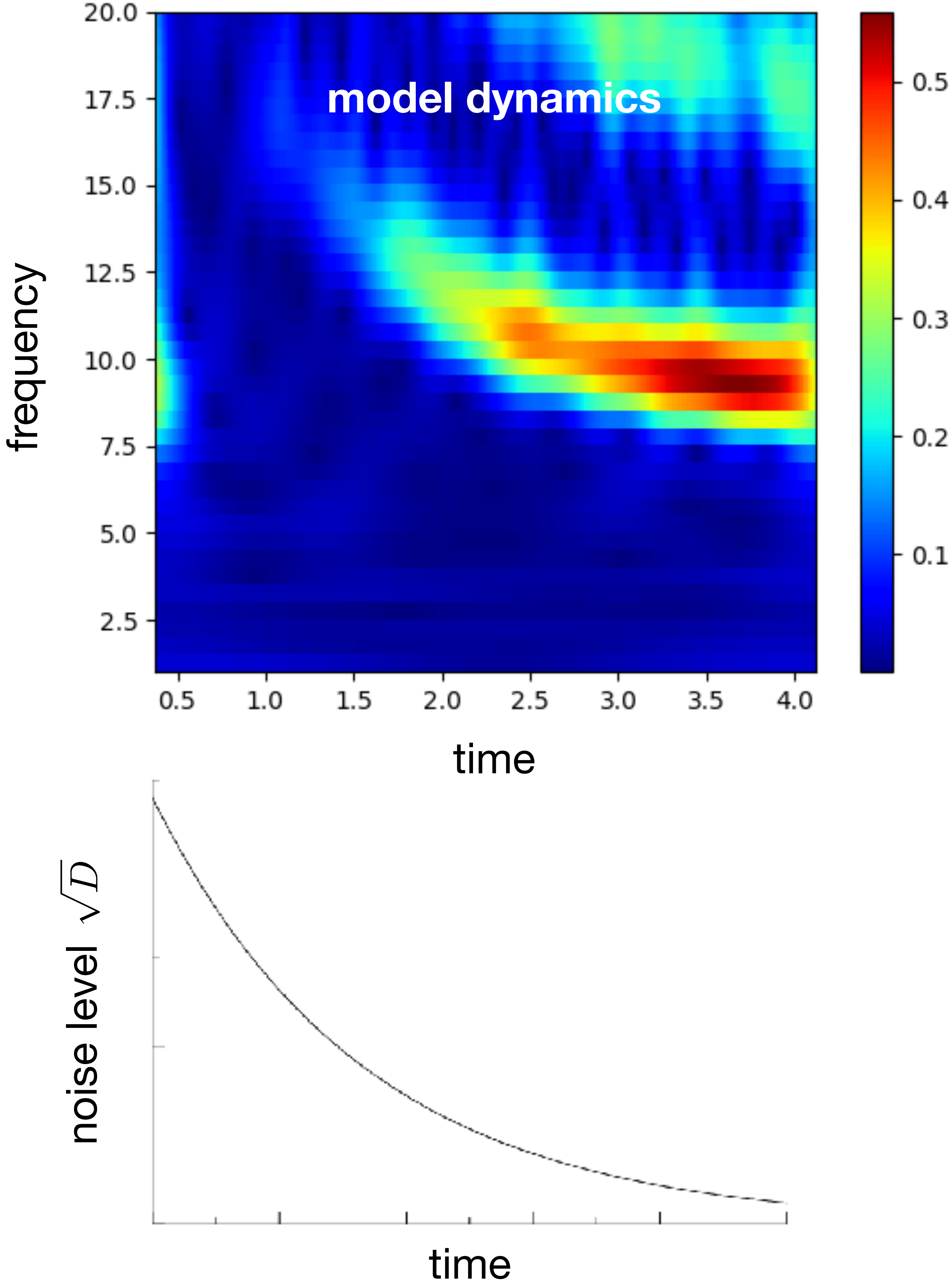
mathematical model

$$F_k[U] = \frac{1}{2}\left[1 + \mathrm{erf}\left(\frac{U-h}{\sigma_k\sqrt{2}}\right)\right],$$

$$A = \sqrt{2\pi}\,\frac{a+\lambda_+}{\lambda_+ - \lambda_-}, \qquad B = -\sqrt{2\pi}\,\frac{a+\lambda_-}{\lambda_+ - \lambda_-}$$

$$\sigma_k = -\sqrt{2}D\left(\frac{A^2}{2\lambda_+} + \frac{2AB}{\lambda_+ + \lambda_-} + \frac{B}{2\lambda_-}\right)$$

$$\lambda_\pm = \left(-a_k - \alpha_k \pm \sqrt{(a_k - \alpha_k)^2 + 4ba_k\alpha_k}\right)\Big/2$$



model dynamics
frequency
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
time
0.5
0.4
0.3
0.2
0.1
noise level $\sqrt{D}$
time

question:

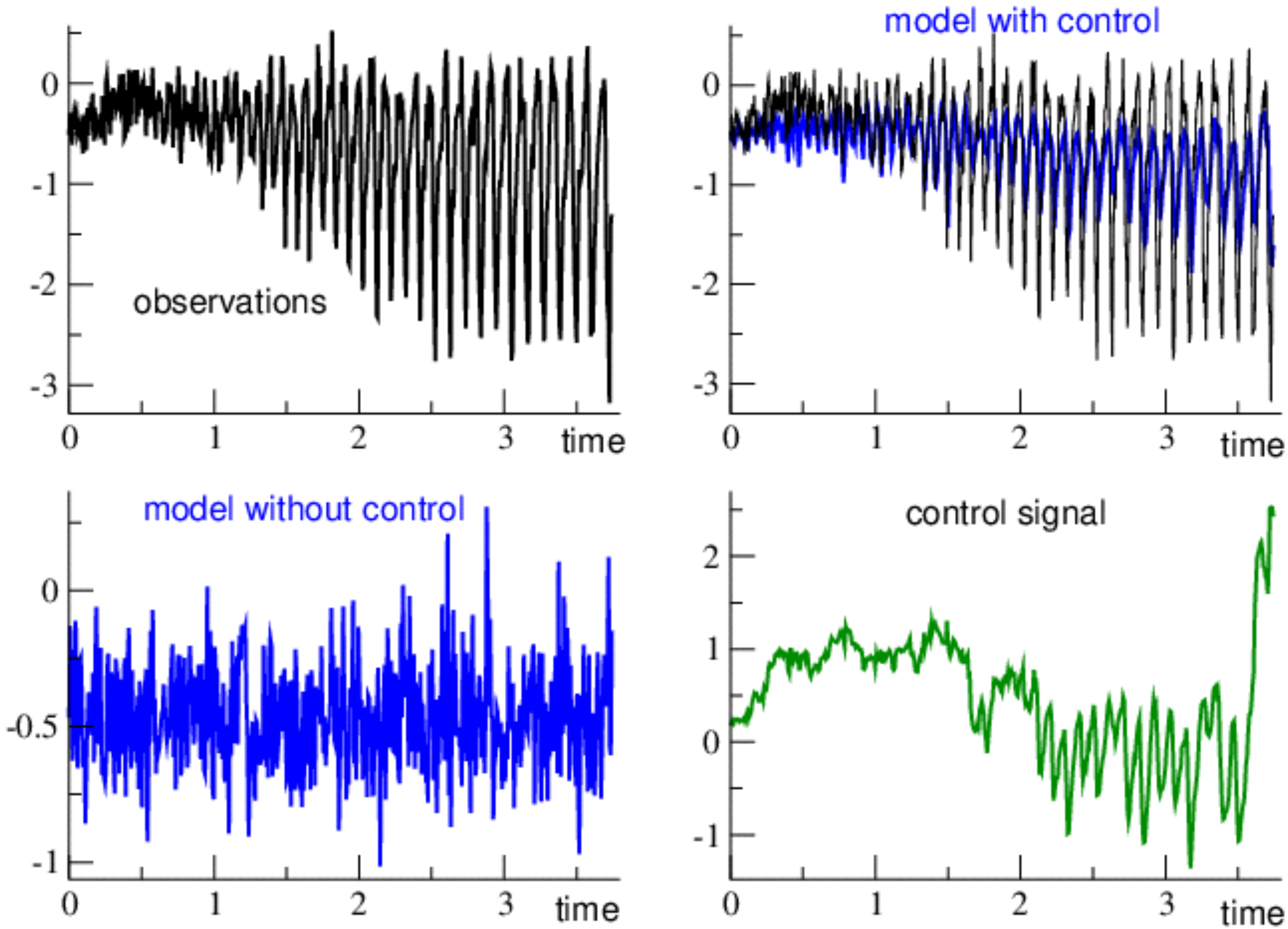
can we stimulate a system in such a way,

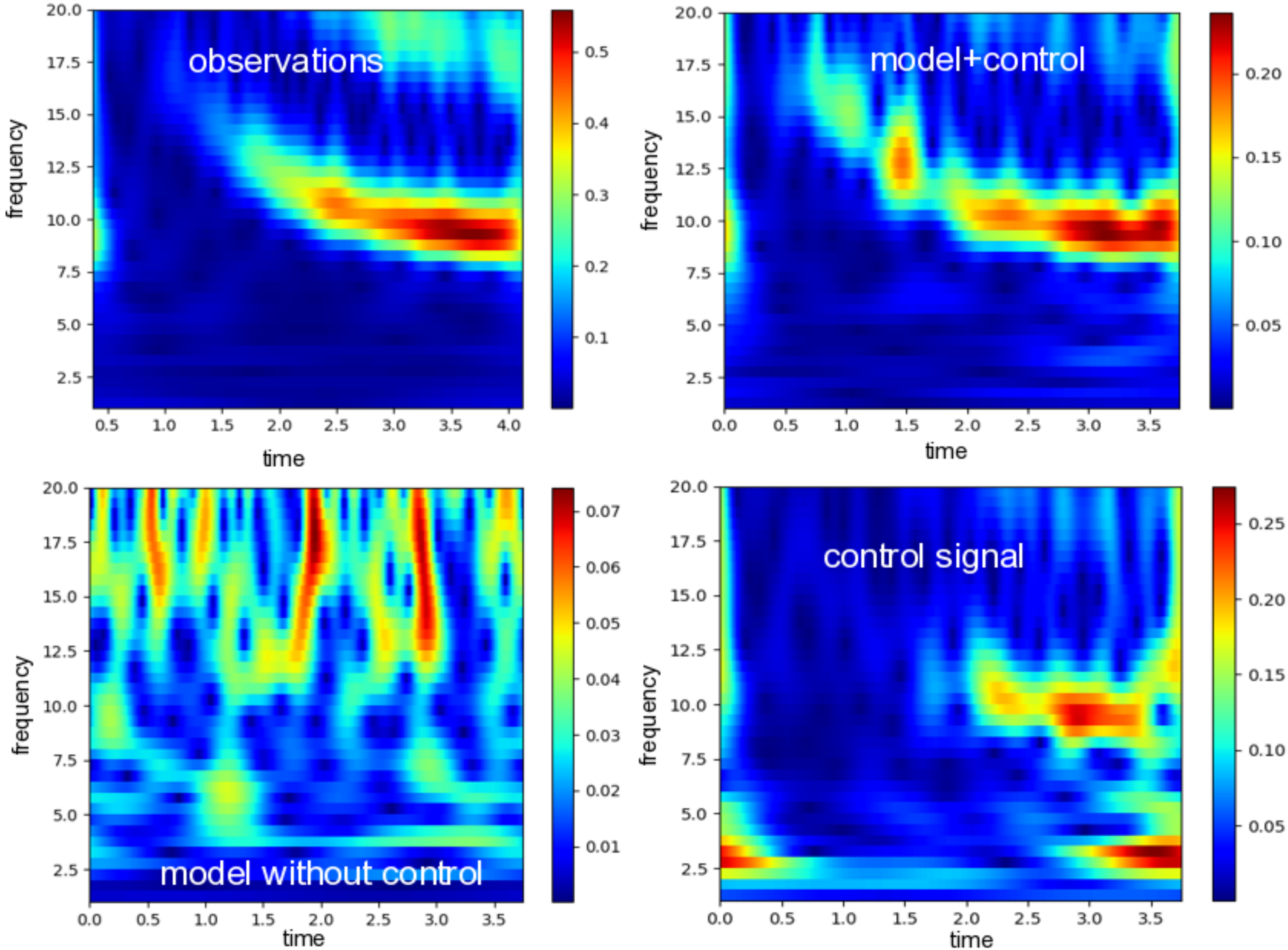
that the system evolves similar to observed data ?

implementation:

- estimate external input I_e optimally that
  model dynamics is controlled by observations

- apply ensemble Kalman filter (LETKF)


observations
model with control
model without control
control signal
time
time
time
time
0
-1
-2
-3
0
-0.5
-1
2
1
0
-1
0
1
2
3



observations
model+control
model without control
control signal
frequency
time

Interpretation:

- external stimulus controls system
    - model dynamics resembles observations
        - controlled system without anaesthesia effect resembles system with anaesthesia effect
            - transformation from
              system under anaesthesia (analog drug)
              to
              system under control (digital drug)

A/D drug transformation


Thank you for your attention