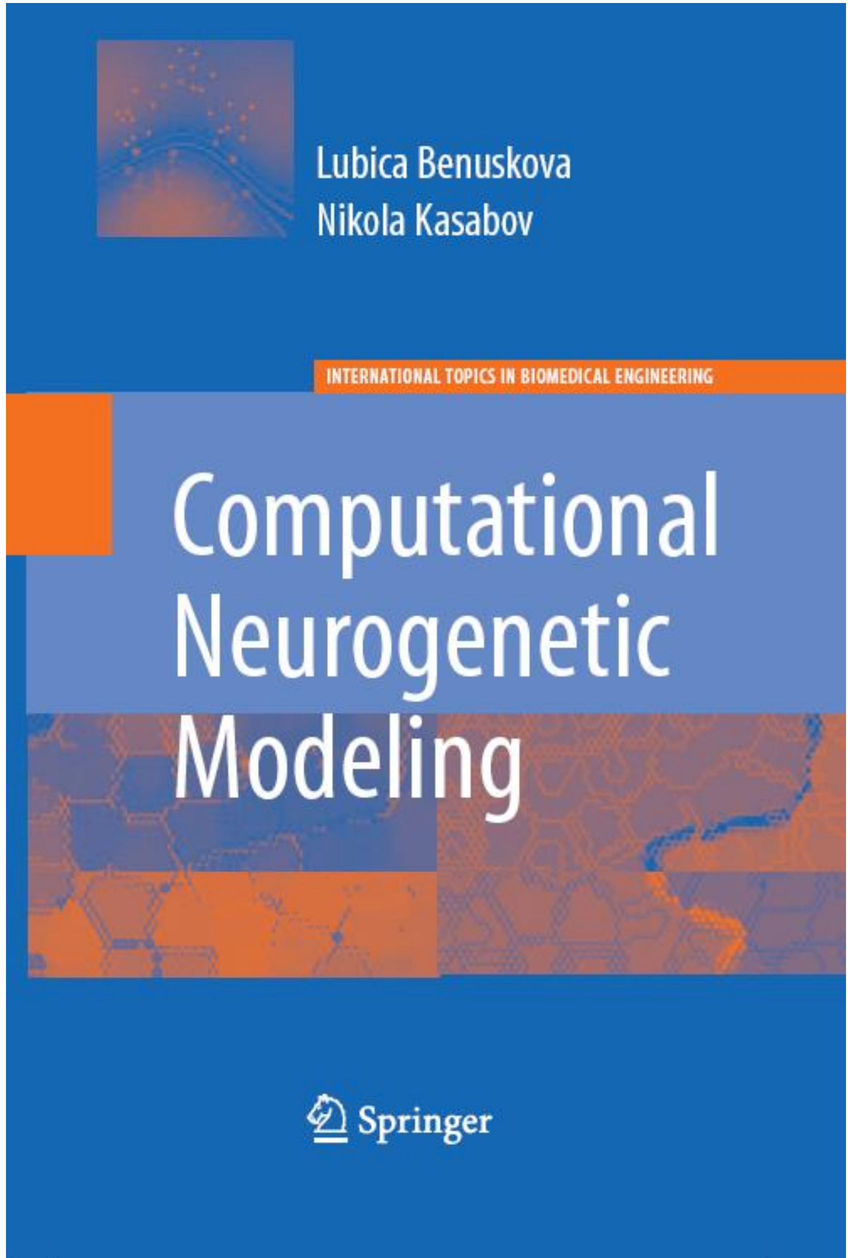
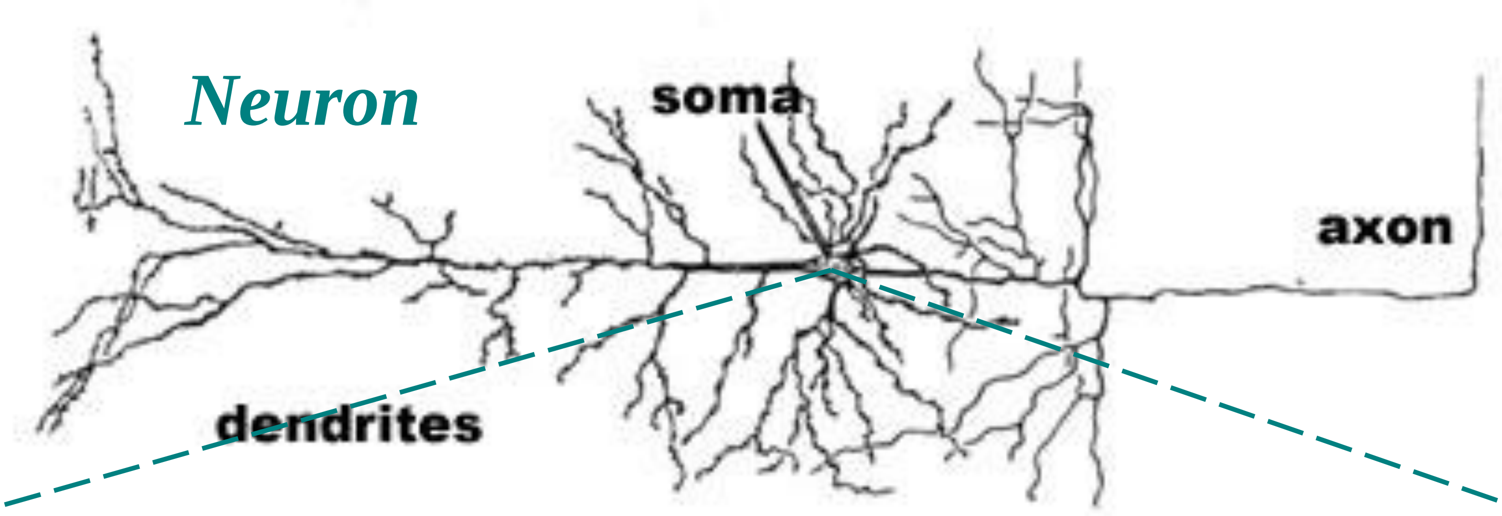

Lubica Benuskova
Nikola Kasabov
INTERNATIONAL TOPICS IN BIOMEDICAL ENGINEERING
Computational Neurogenetic Modeling
Springer

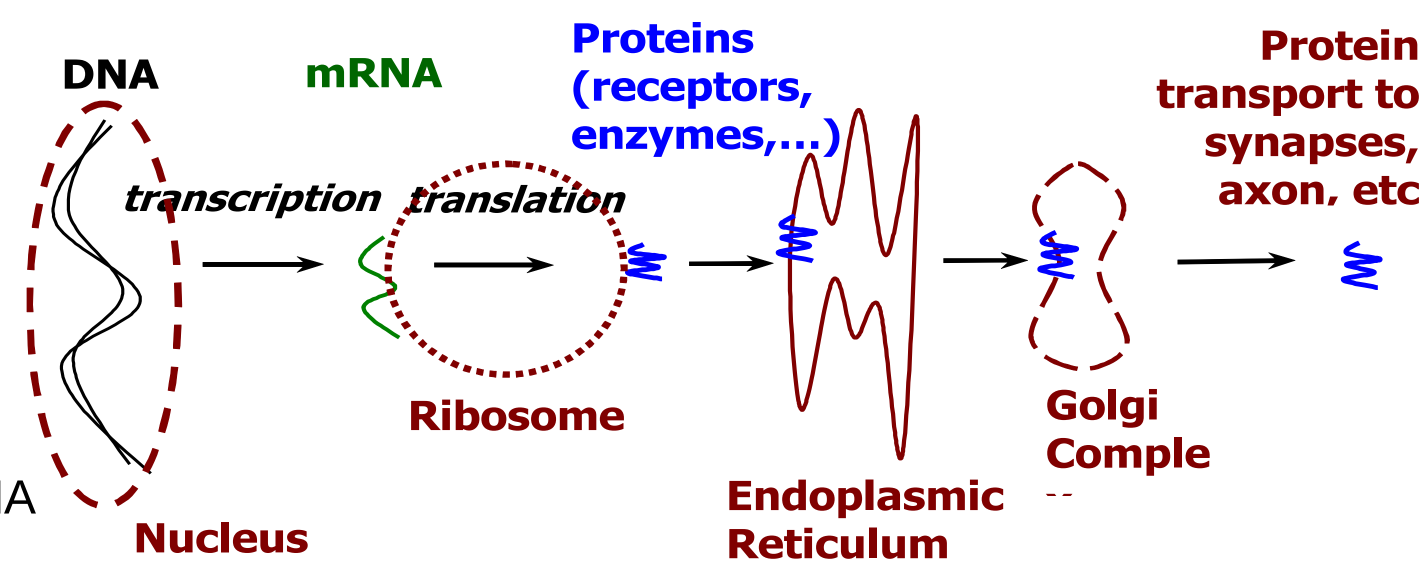
The link of genes to brain functions is through protein synthesis



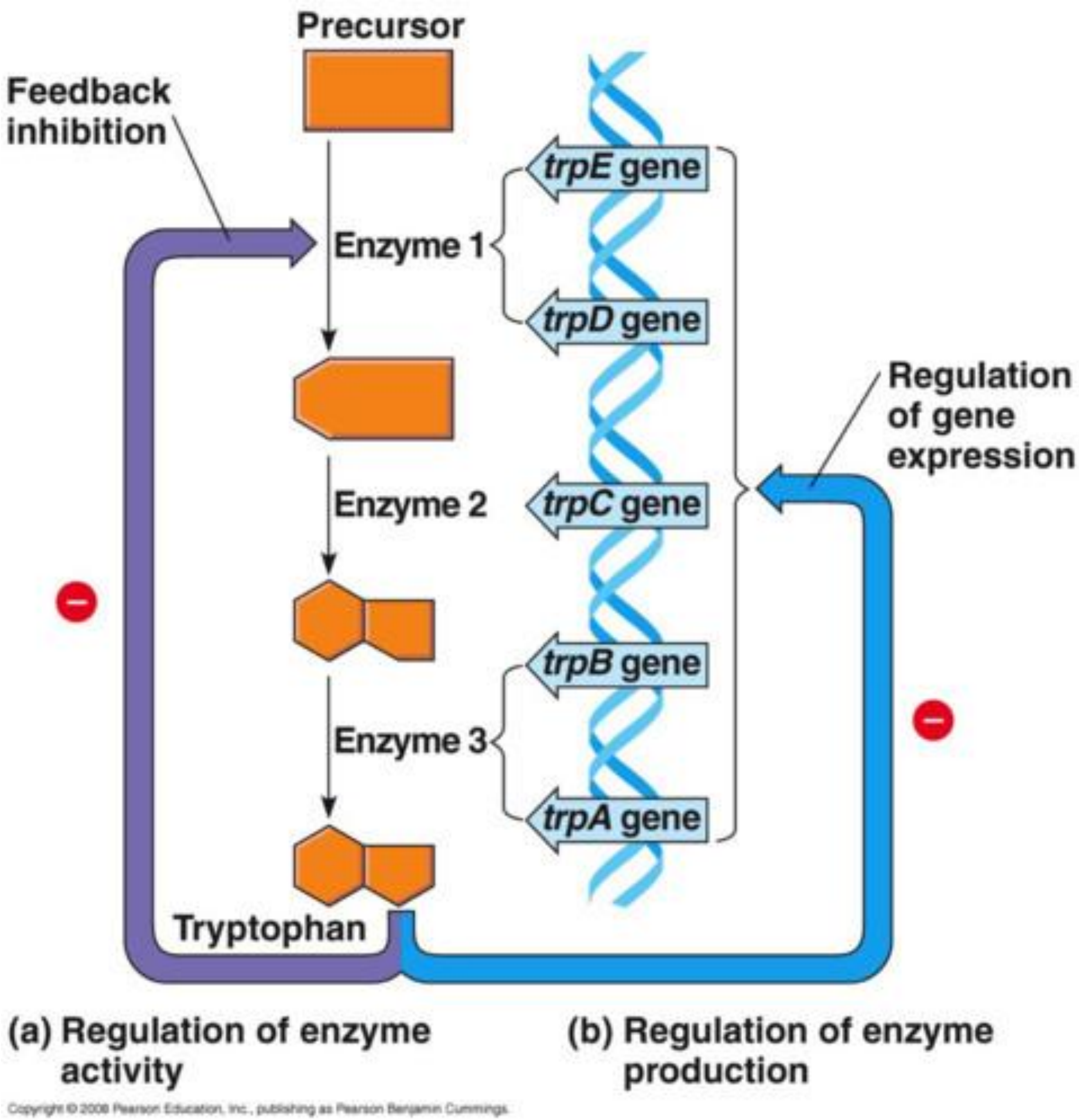
2nd messengers activated in synapses affect transcription factors (TFs)

↓

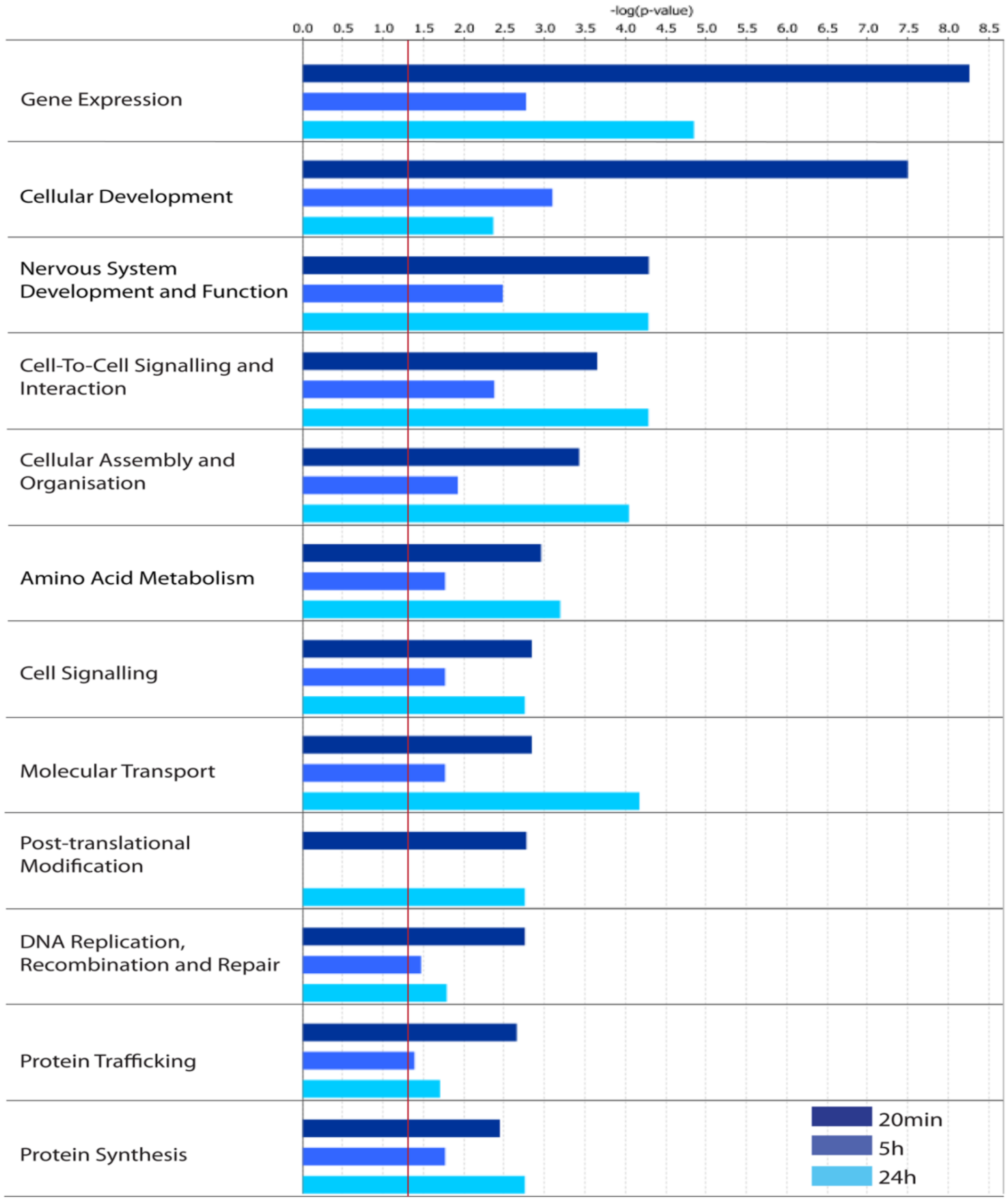
TFs regulate DNA transcription



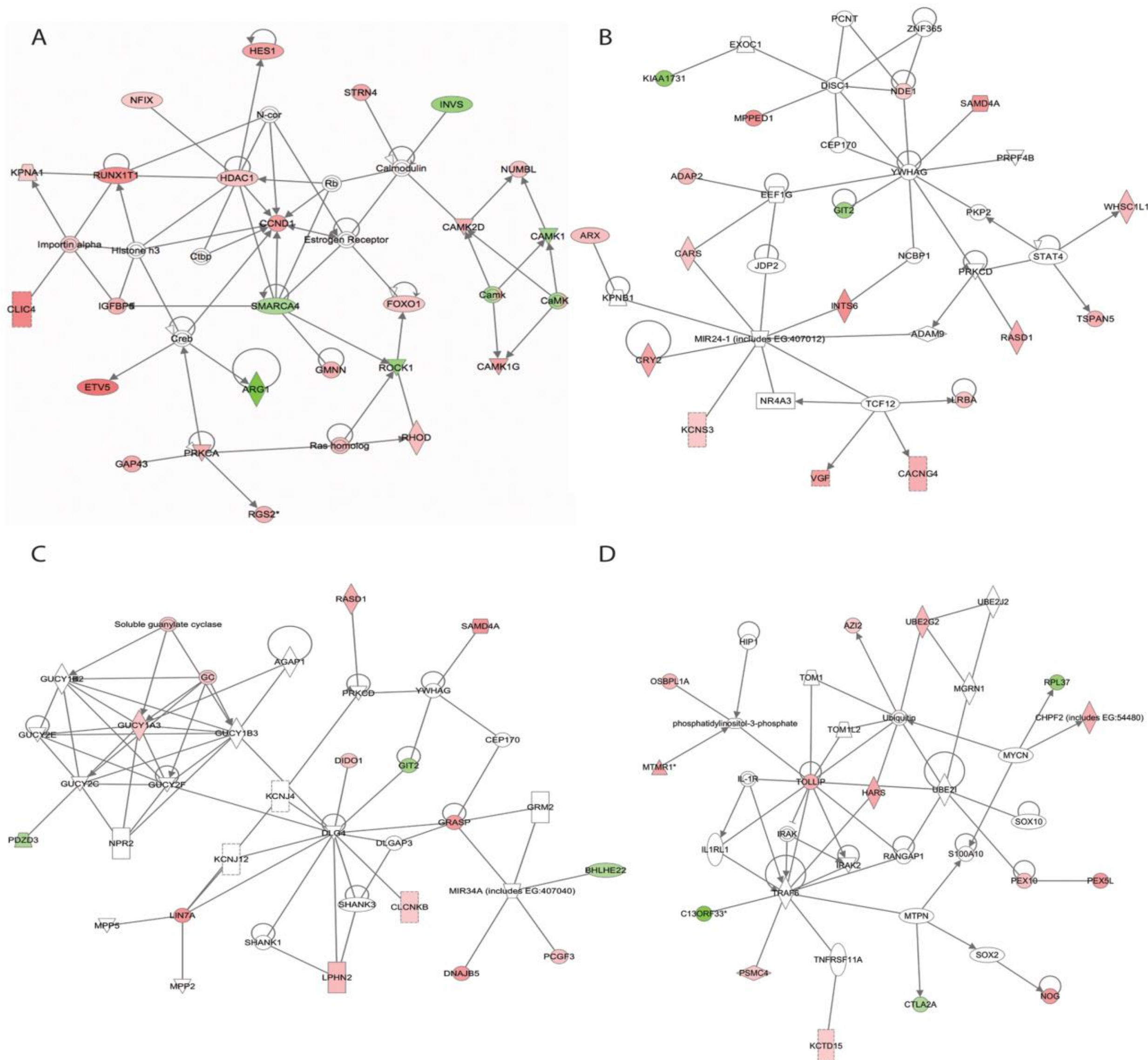
Example of a negative feedback in the GRN



LTP gene regulatory network (GRN) – functions

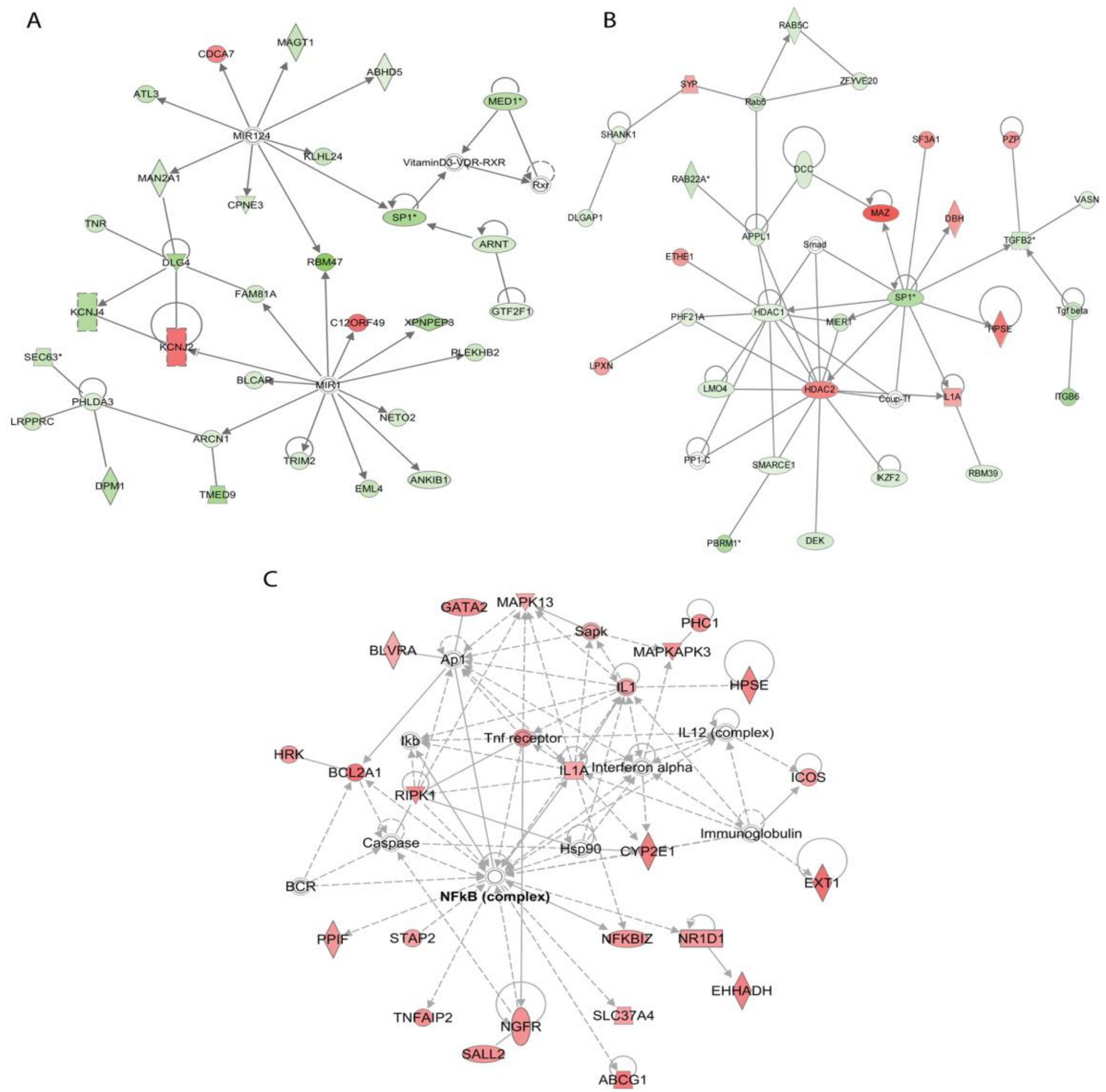


LTP gene regulatory network (GRN) – after 5 hrs



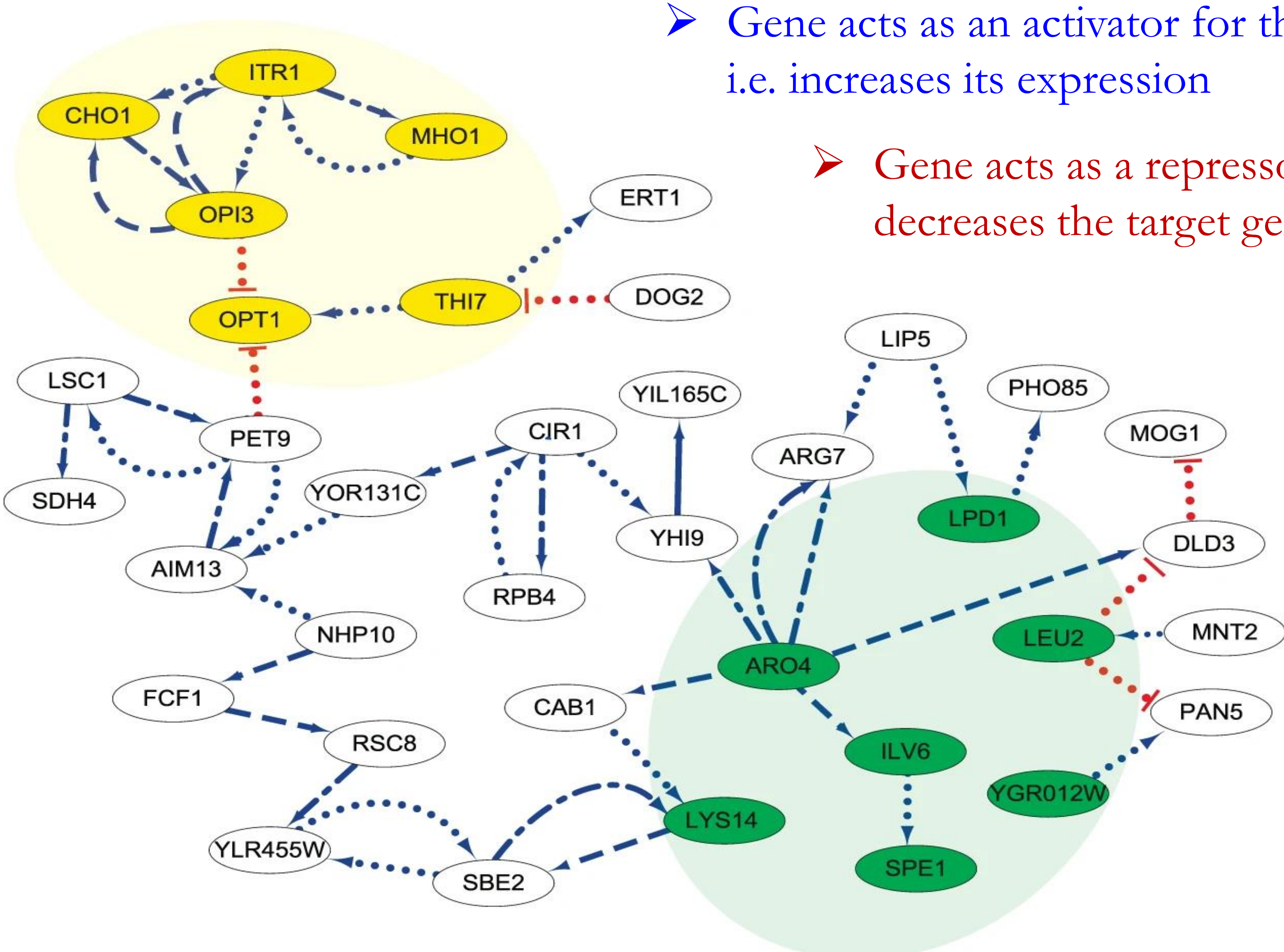
- Source: Ryan et al., Hippocampus, 2011 & PLoS One, 2012)

LTP gene regulatory network (GRN) – after 24 hrs



- Source: Ryan et al., Hippocampus, 2011 & PLoS One, 2012)

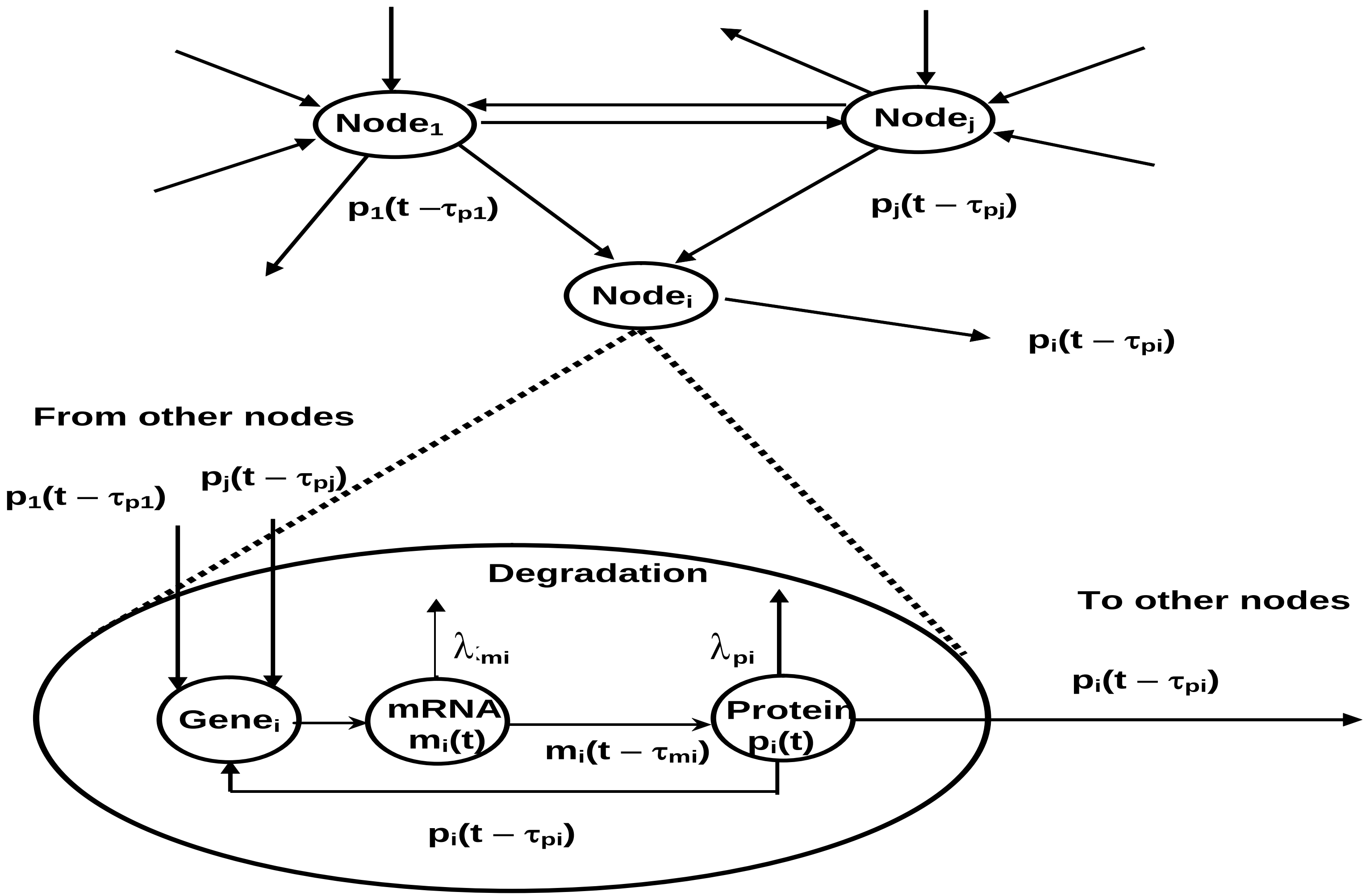
Yeast gene regulatory network (GRN)



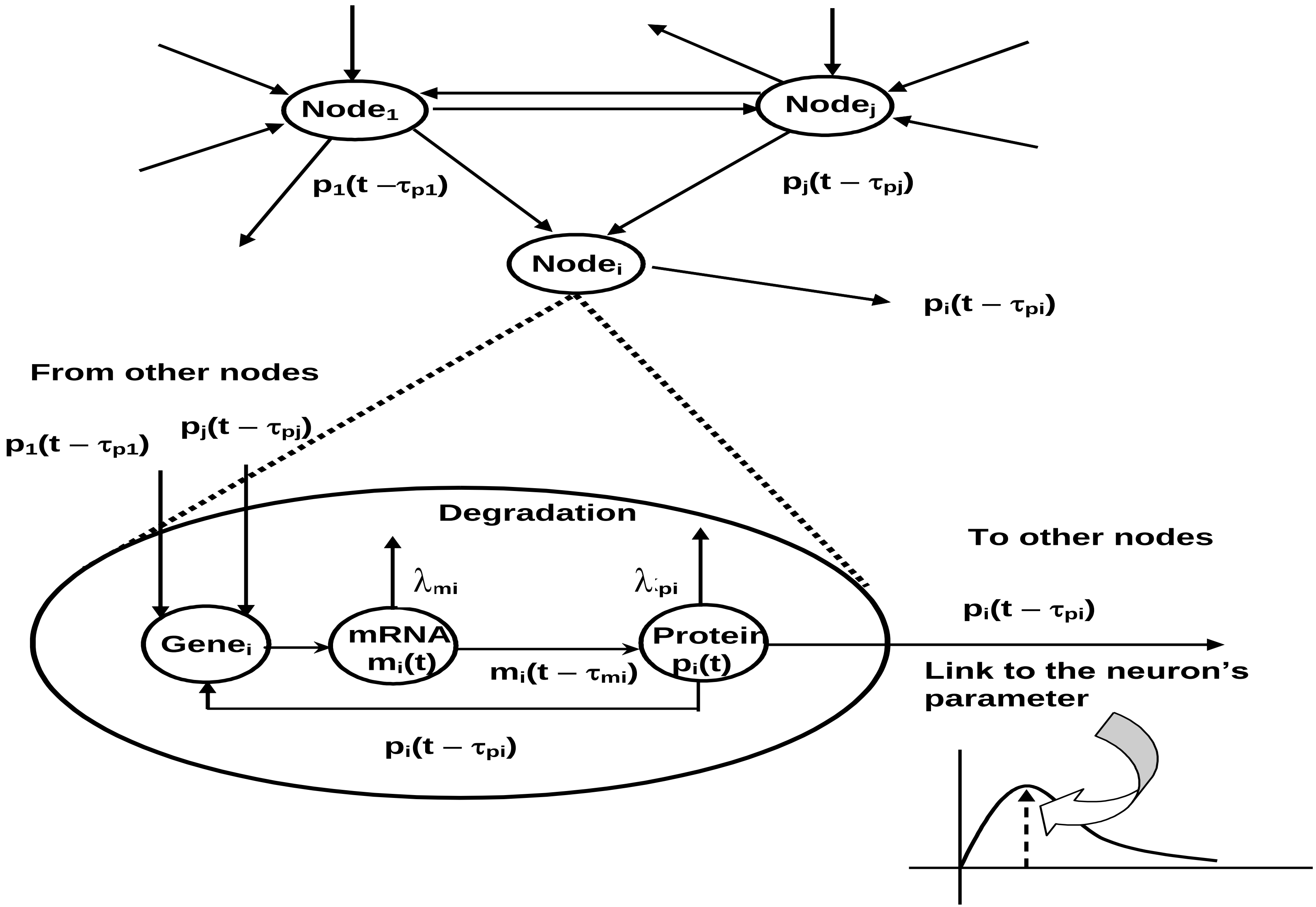
- ➢ Gene acts as an activator for the target gene, i.e. increases its expression
  - ➢ Gene acts as a repressor, i.e. decreases the target gene expression

- Source: Inferring GRN in yeast (Chen et al., Sci. Rep., 2019)

GRN: towards mathematical model



Principle of CNGM: neural model parameters are linked to protein levels $p_i(t)$



System of differential equations

mRNA levels

w_{ij} coefficients of the GRN interaction matrix

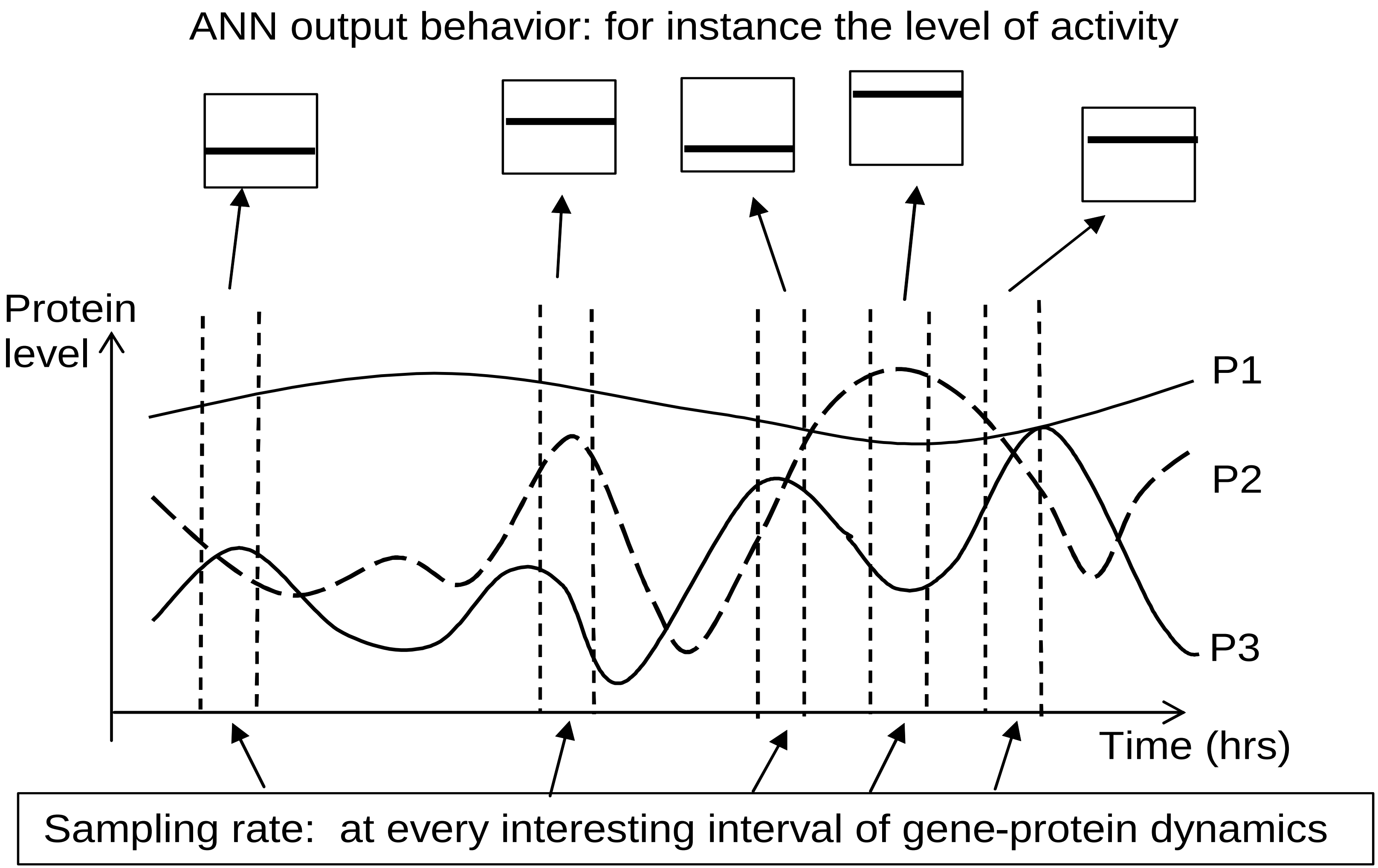
$$\frac{dm_i}{dt} = A_{m_i}\ \sigma_{m_i}\left(\sum_{j=1}^{n} w_{ij} p_j(t-\tau_{p_j}) + \sum_{k=1}^{K} v_{ik} x_k(t-\tau_{x_k}) + b_{m_i}\right) - \lambda_{m_i} m_i(t)$$

Protein levels

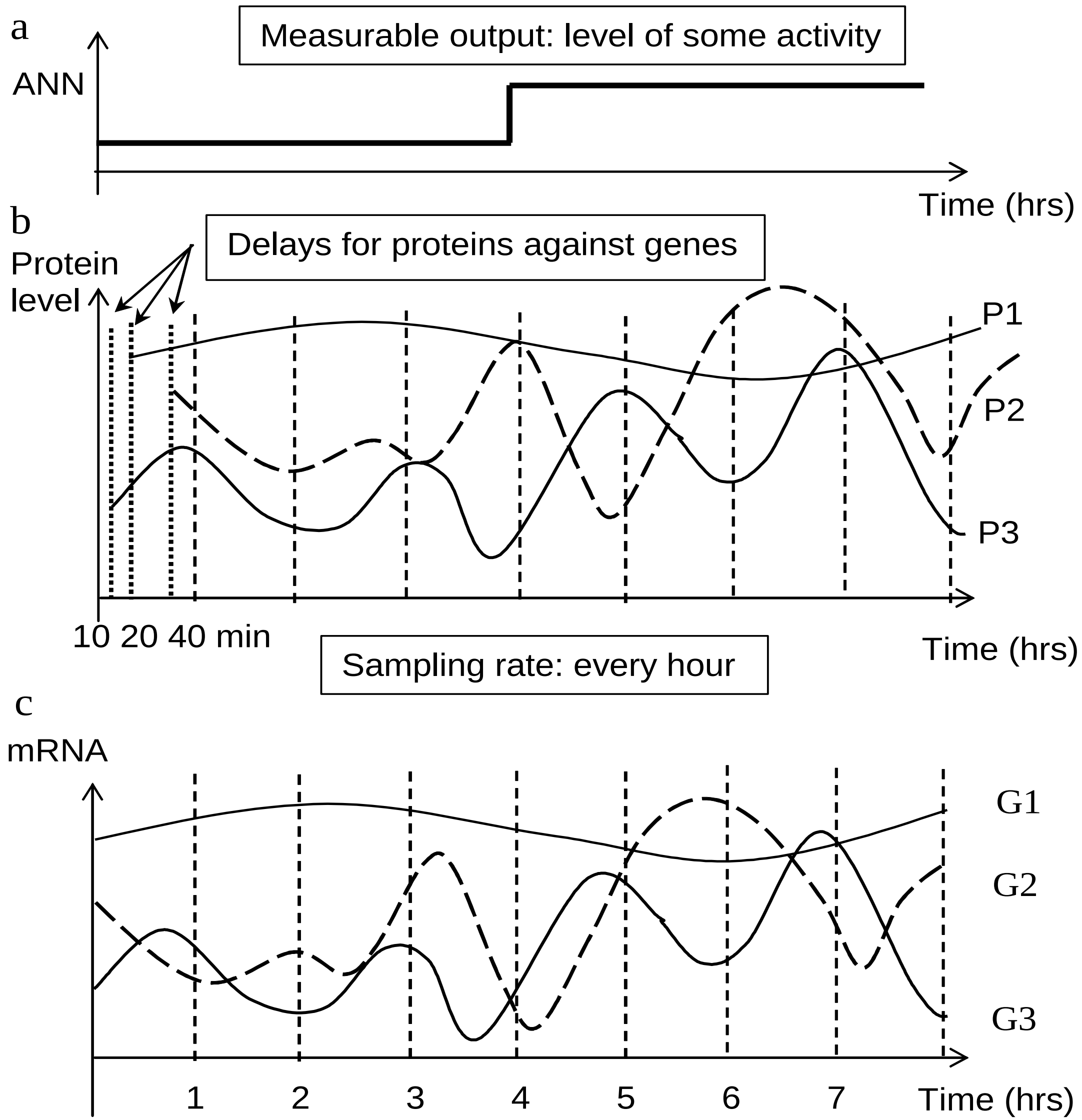
External factors (hormones, drugs,…)

$$\frac{dp_i}{dt} = A_{p_i}\ \sigma_{p_i}\left(m_i(t-\tau_{m_i}) + \sum_{k=1}^{K'} u_{ik} y_k(t-\tau_{y_k}) + b_{p_i}\right) - \lambda_{p_i} p_i(t)$$

Output behaviour of model neurons depends on underlying gene/protein dynamics

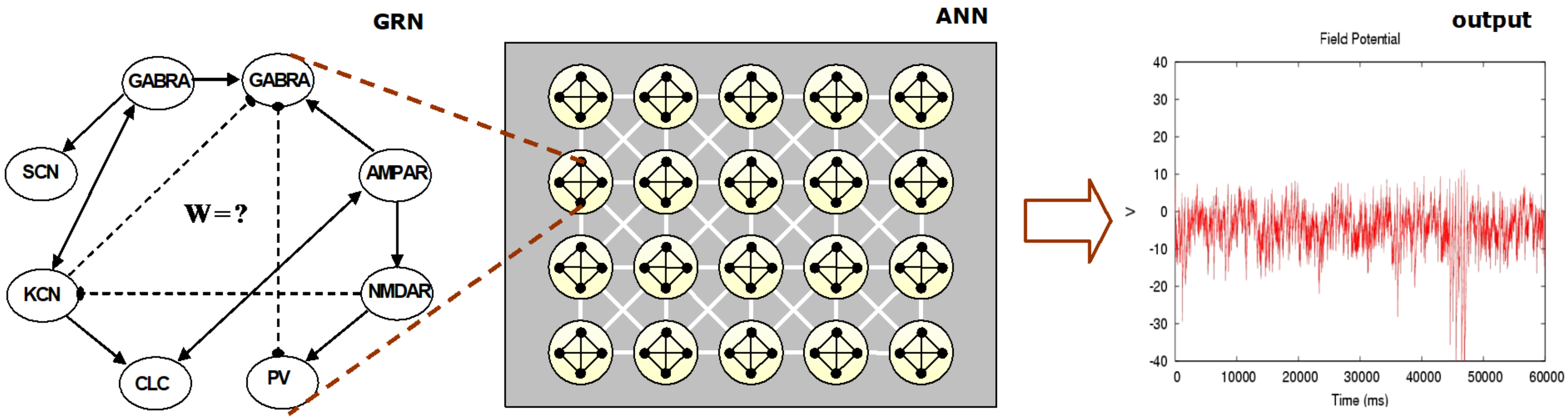


CNGM: three embedded multi-scale dynamic systems



Example: electrical activity

Question: which gene interactions lead to the desired spectral characteristics of Local Field Potential?



Gene regulatory network

Abstract connections **W**

Model ANN

ANN output LFP

Gene-protein regulatory network model

mRNA levels

$$\frac{dm_i}{dt} = A_{m_i}\ \sigma_{m_i}\left(\sum_{j=1}^{n} w_{ij} p_j(t-\tau_{p_j}) + b_{m_i}\right) - \lambda_{m_i} m_i(t)$$

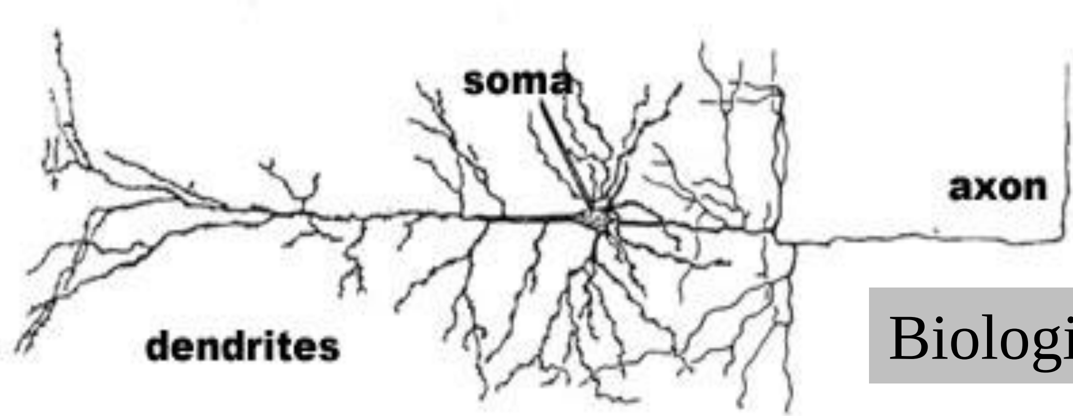
Protein levels

$$\frac{dp_i}{dt} = A_{p_i}\ \sigma_{p_i}\left(m_i(t-\tau_{m_i}) + b_{p_i}\right) - \lambda_{p_i} p_i(t)$$

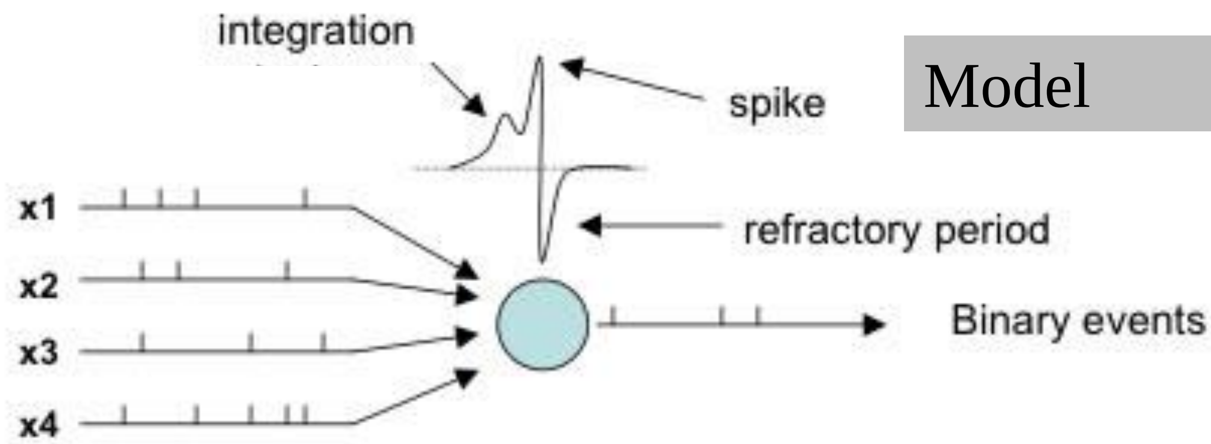
Values of neuronal parameters will depend on levels of proteins *p*

$$P_j(t) = P_j(0)\, p_j(t)$$

Neuron model



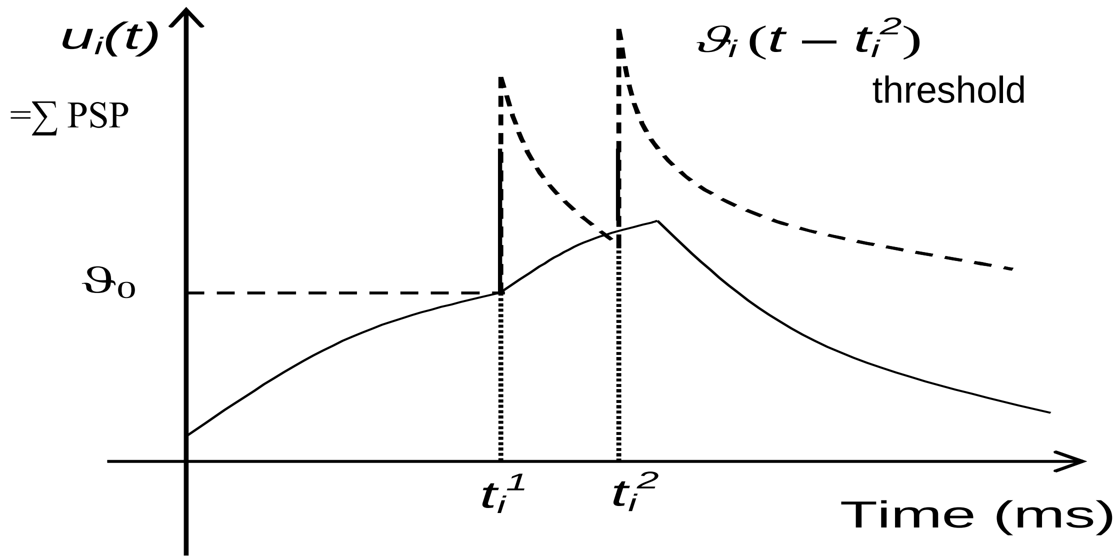
Biological neuron



Model

Values of neuron model paramaters will be linked to the levels of proteins (like receptors and ion channels)

Spiking neuron model



Spike Response Model

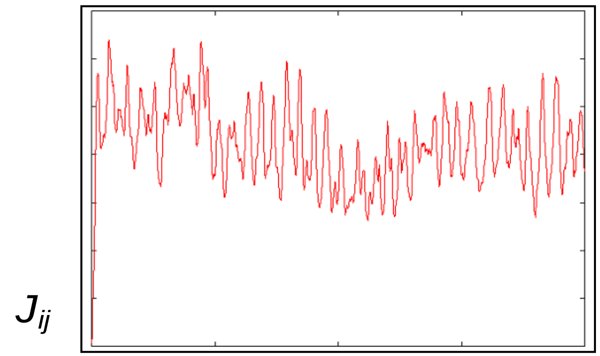
$$PSP_{ij}^{type}(t - t_j - \Delta_{ij}^{ax}) = A^{type}\left(\exp\left(-\frac{t - t_j - \Delta_{ij}^{ax}}{\tau_{decay}^{type}}\right) - \exp\left(-\frac{t - t_j - \Delta_{ij}^{ax}}{\tau_{rise}^{type}}\right)\right)$$

type = fast excitation, slow_excitation, fast_inhibition, slow_inhibition

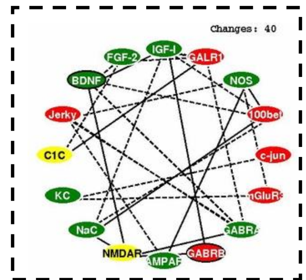
Neural network model of cerebral cortex with input from thalamus

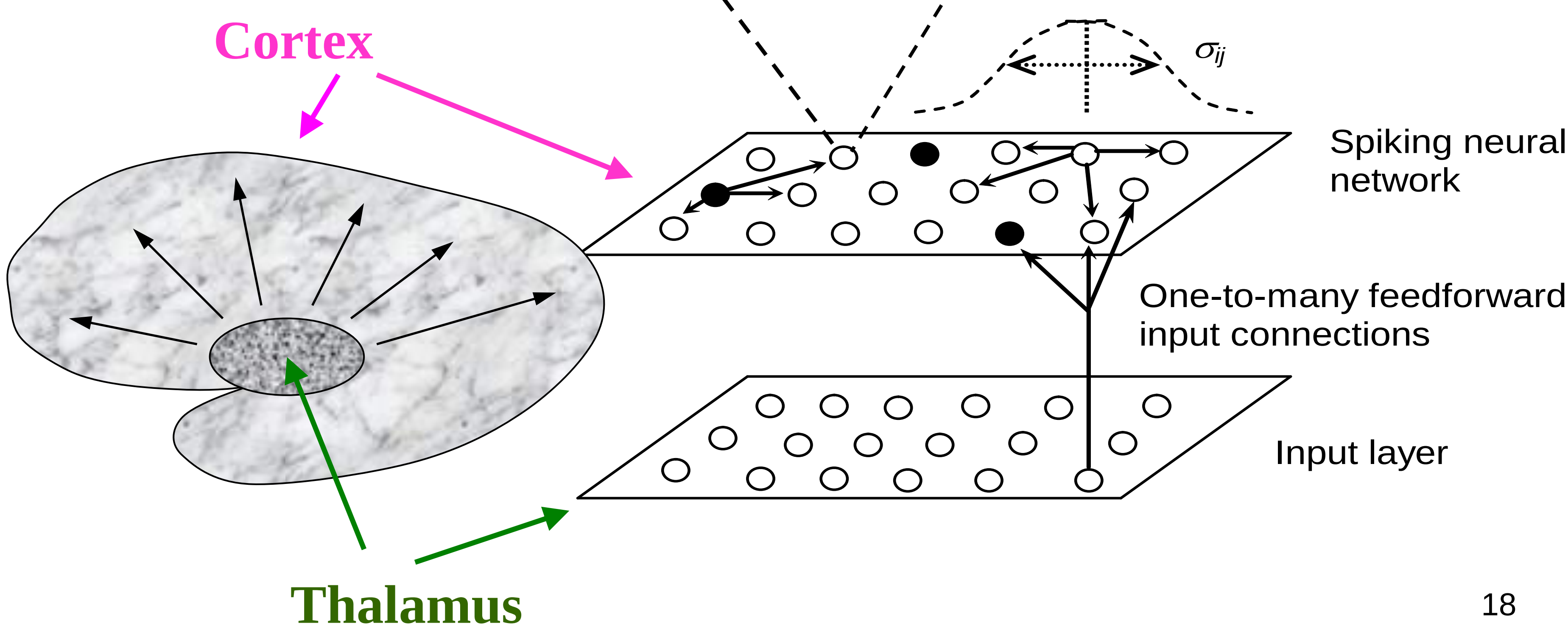
OUTPUT : Local Field Potential

$$LFP(t) = \sum u_i(t) \approx EEG = \sum LFP(t)$$



The same GRN in each neuron





Credits: Simei Gomes Wysoski

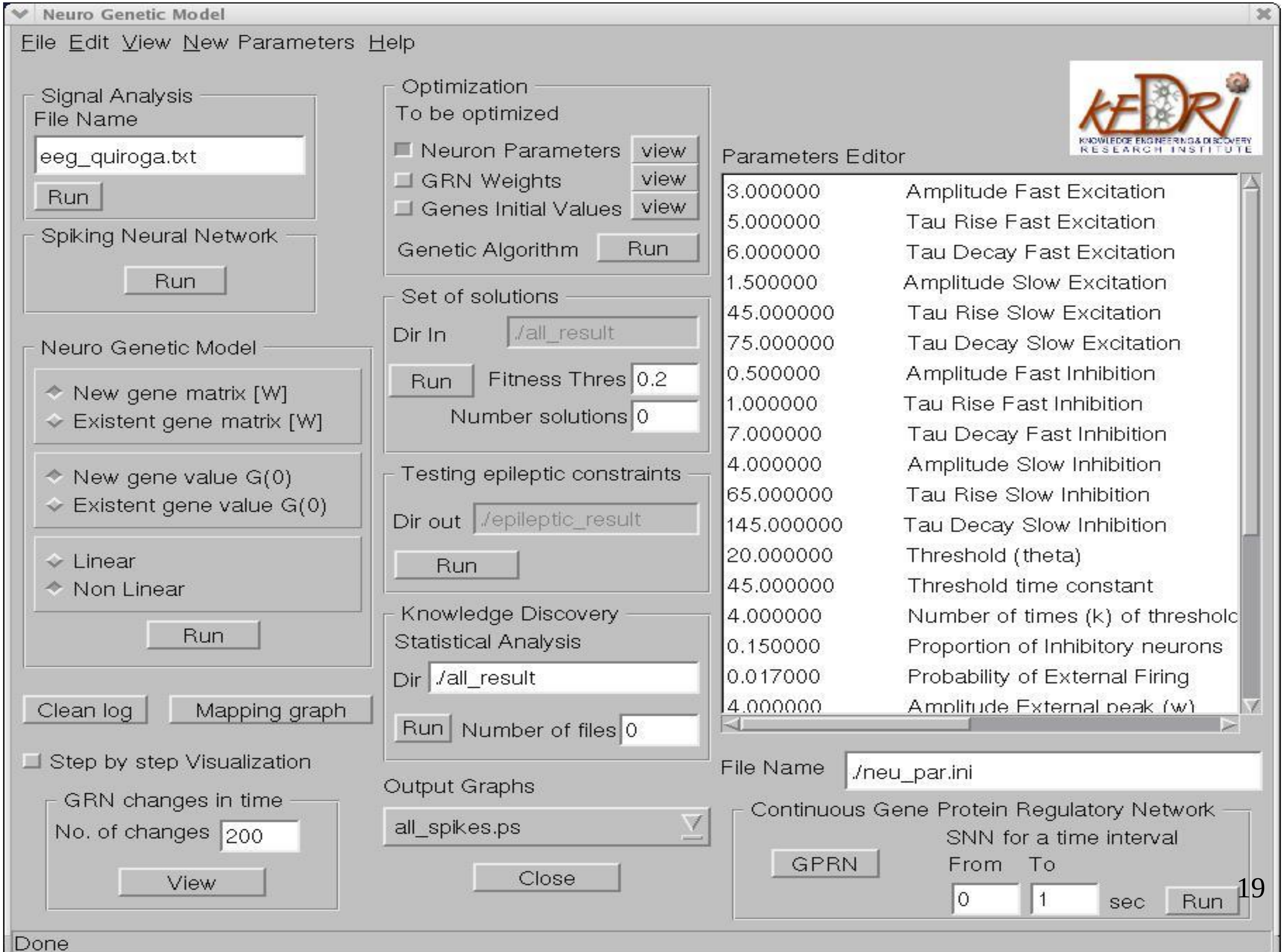


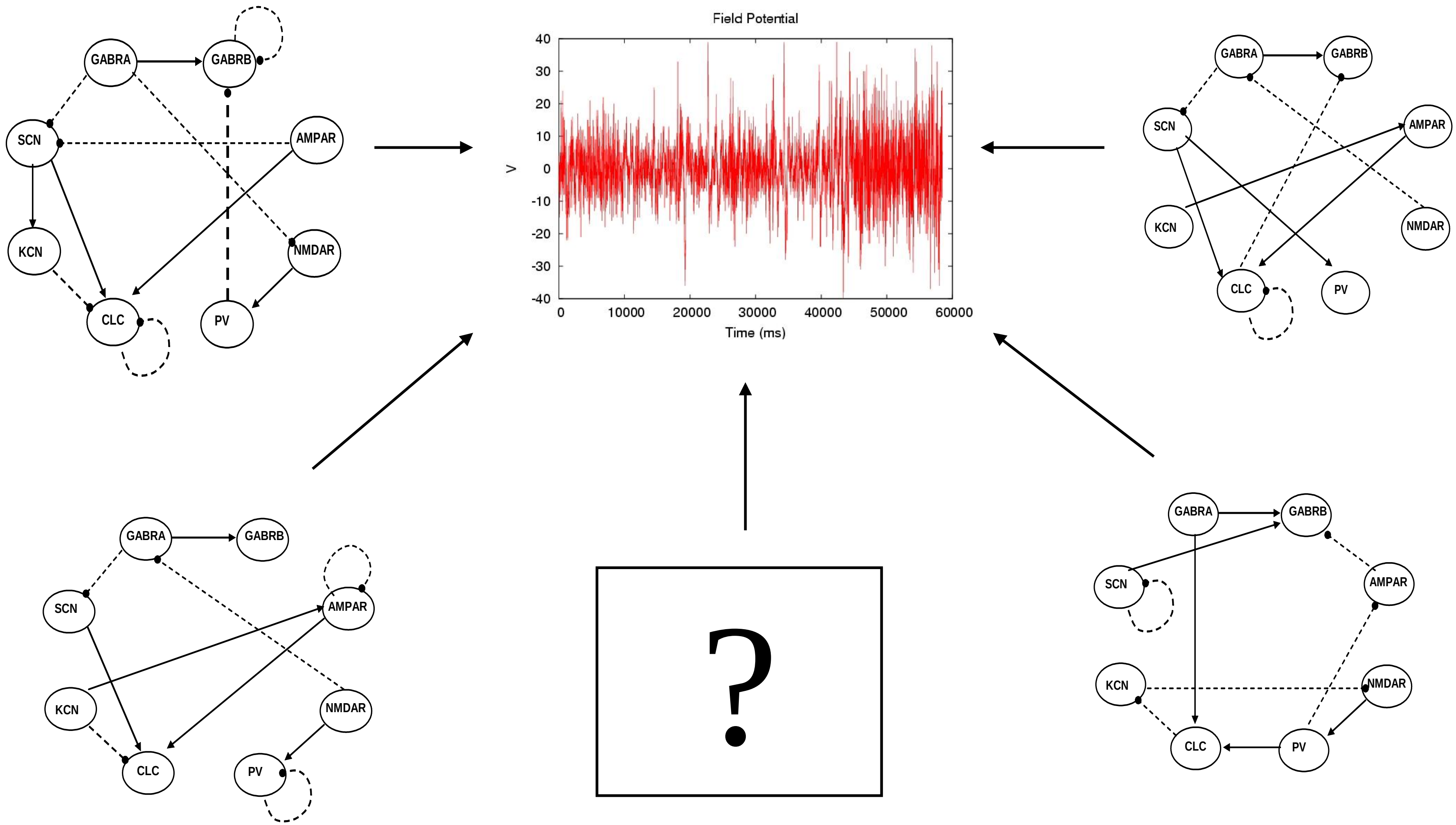
Table of neuron parameters

NEURON'S PARAMETERS	PROTEIN	RANGE of INTIAL VALUES
Fast excitation: Amplitude rise / decay time constants (ms)	AMPAR	0.5 – 3.0 1–5 / 5–10
Slow excitation: Amplitude rise / decay time constants (ms)	NMDAR	0.5 – 4.0 10–50 / 30–50
Fast inhibition: Amplitude rise / decay time constants (ms)	GABRA	4 – 8 5–10 / 20–30
Slow inhibition: Amplitude rise / decay time constants (ms)	GABRB	5 – 10 20–80 / 50–150
Resting firing threshold, decay time constant (ms)	SCN	17 – 25 5 – 50

Table of network parameters

SNN PARAMETER	VALUE
Number of neurons	120
Proportion of inhibitory neurons	0.2
Probability of external (thalamic) fiber firing	0.015
Peak/sigma of external input (TC) weight	5 / 1
Peak/sigma of lateral excitatory weights	10 / 4
Peak/sigma of lateral inhibitory weights	40 / 6
Probability of connection	0.5
Unit delay in excitatory/inhibitory spike propagation	1 / 2 ms

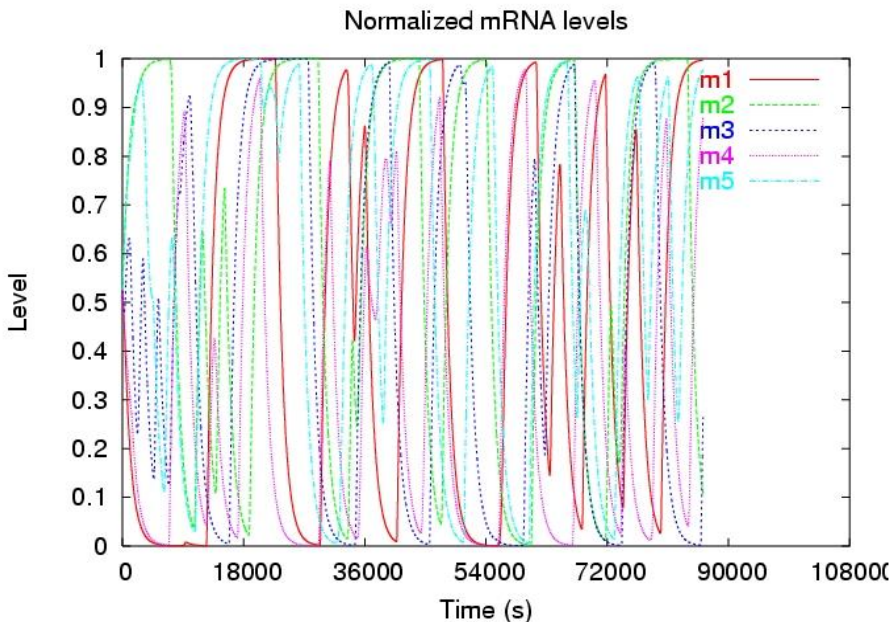
Question: which gene interactions lead to the desired spectral characteristics of LFP/EEG?

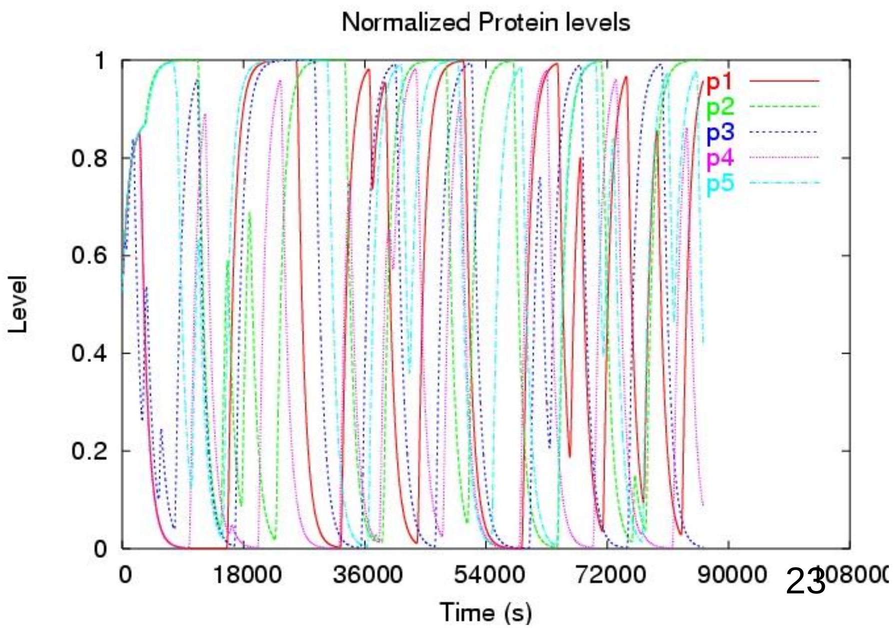


Toy example

- We generated an artificial gene interaction matrix W leading to a complex gene and protein dynamics over 24 hrs (only 5 genes/proteins)

- These were "genetic variables" for AMPAR (fast excitation), NMDAR (slow excitation, GABRA (fast inihibition), GABRB (slow inhibition), SCN (Firing threshold)

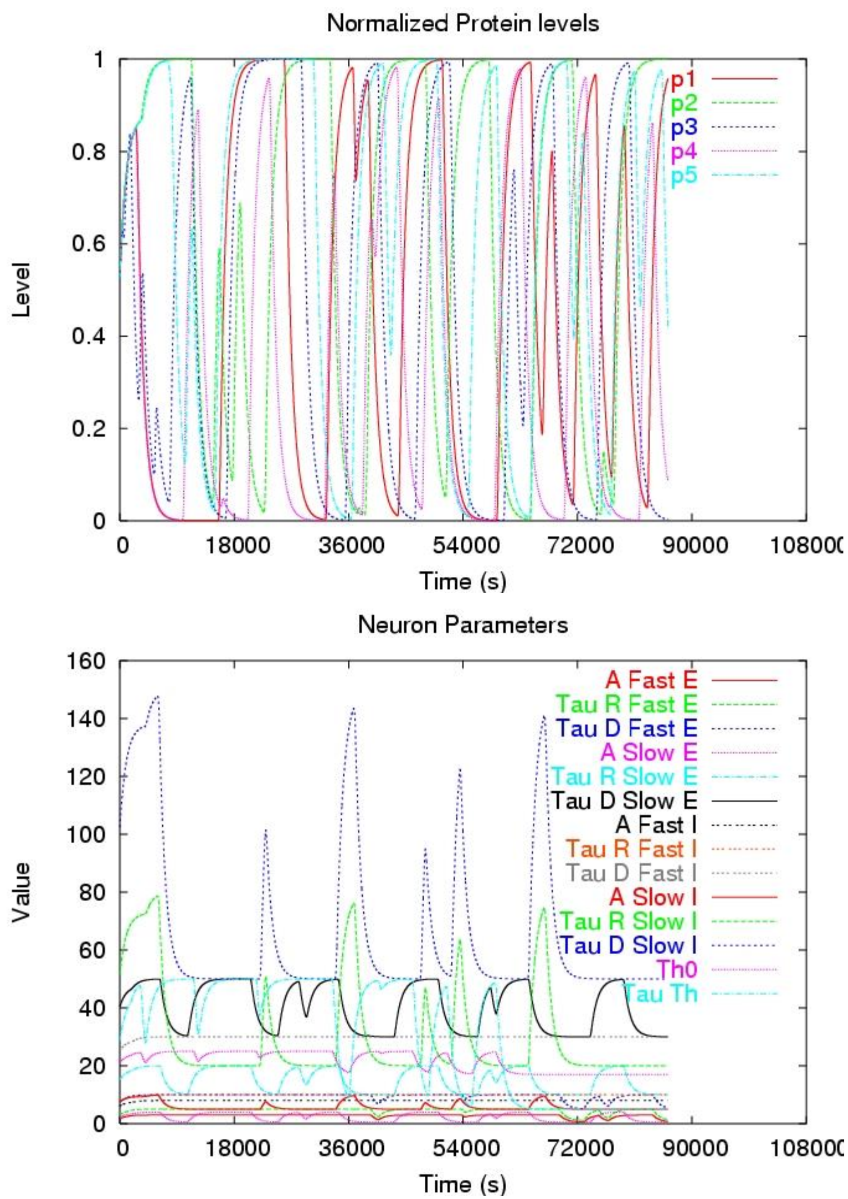




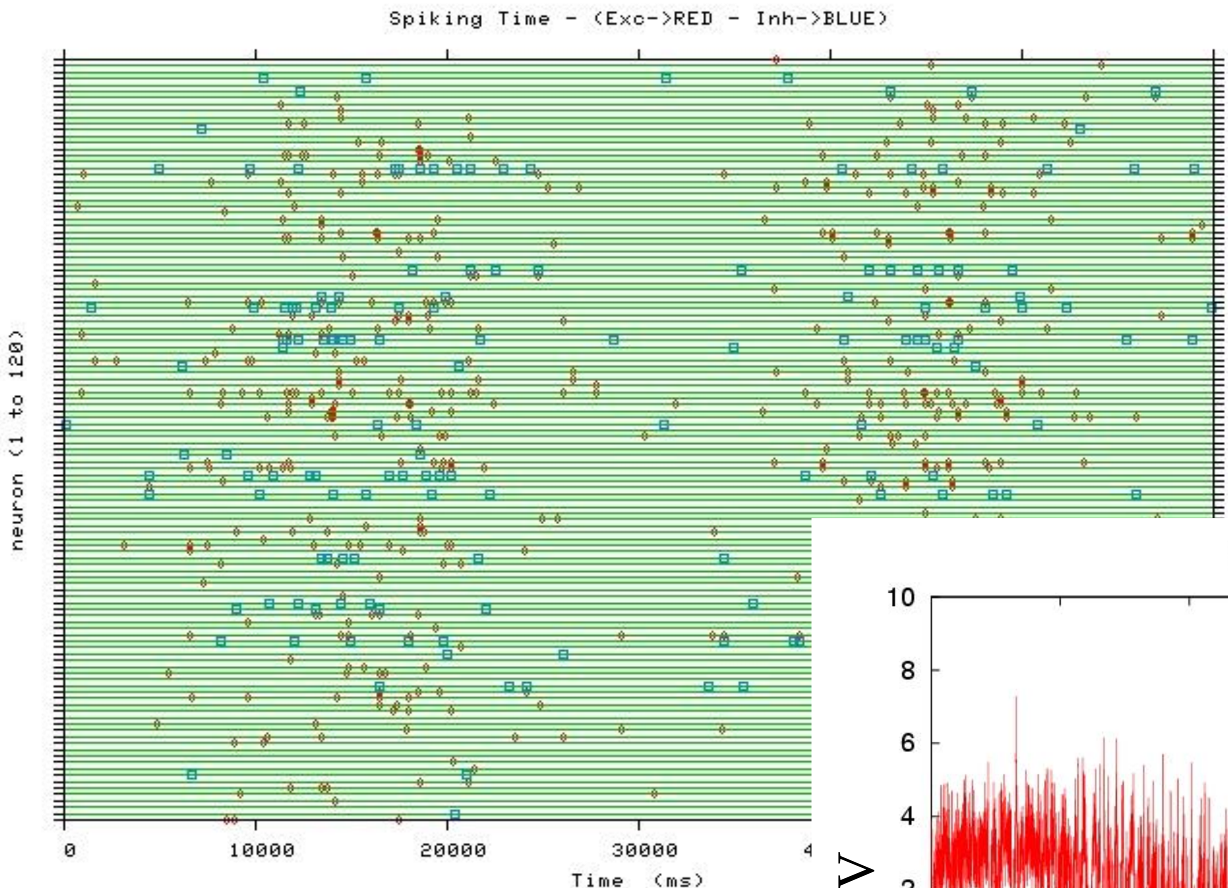
Toy example: complete genome

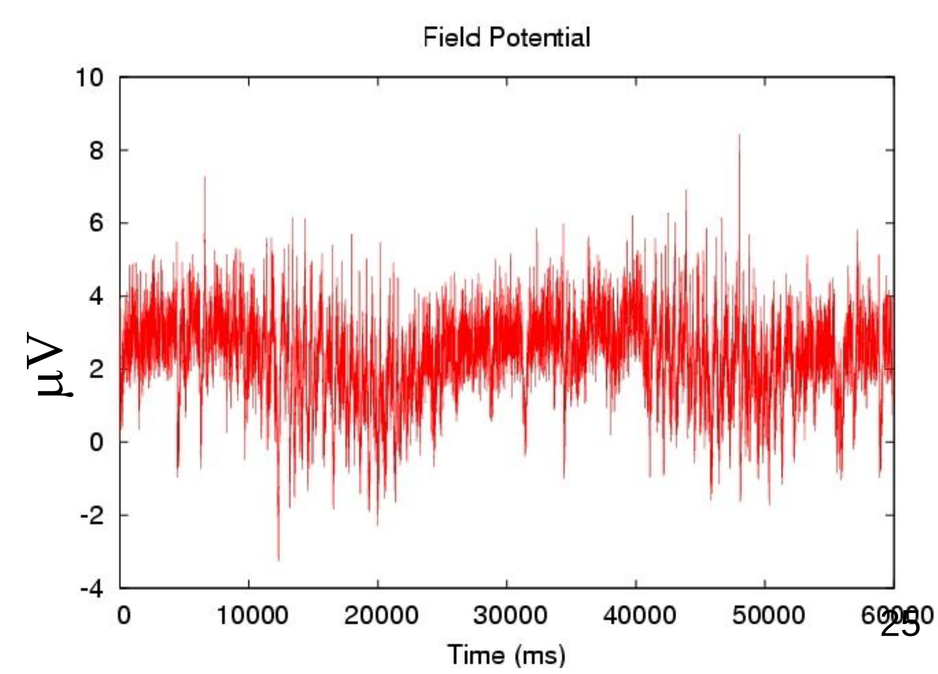
Value of parameter is proportional to the level of a protein

$$P_j(t) = P_j(0)\, p_j(t)$$

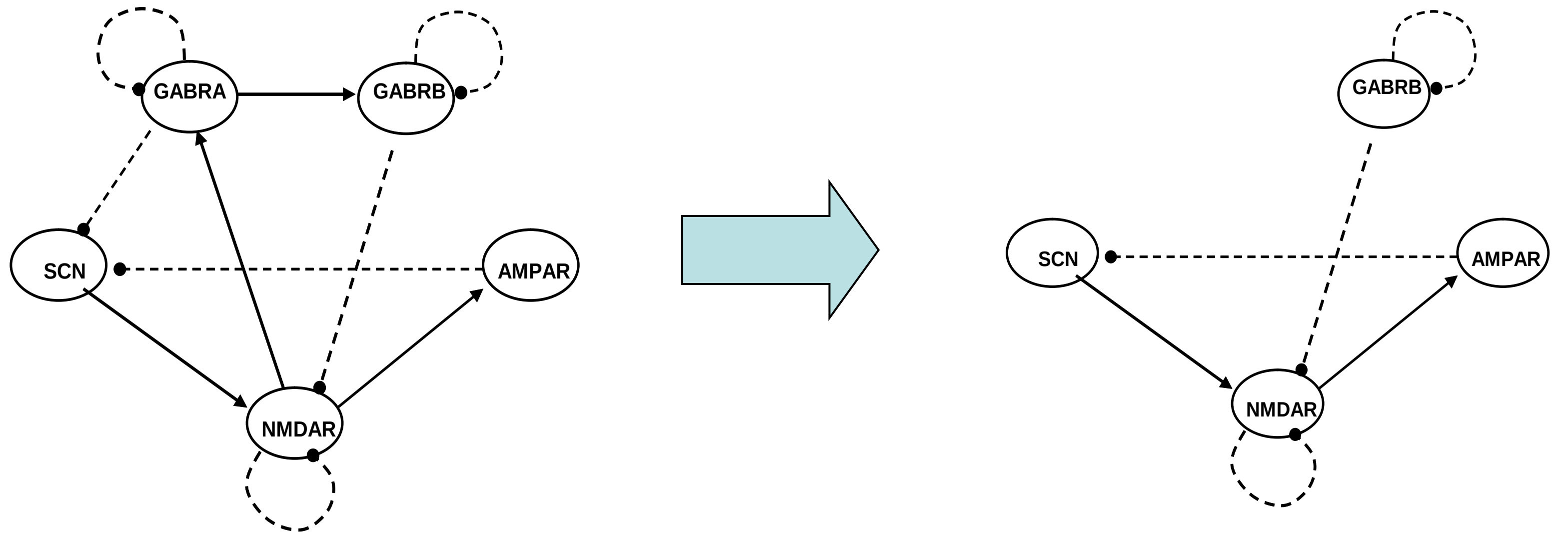


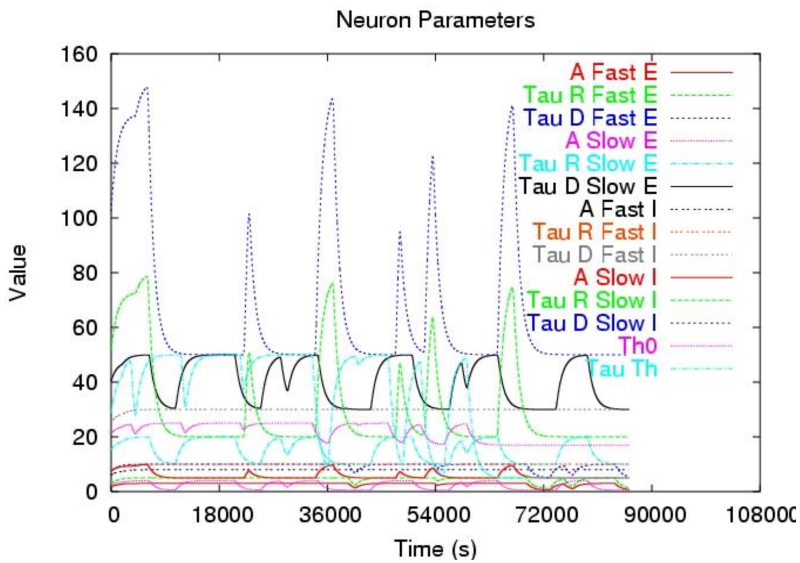
Asynchronous neural activity

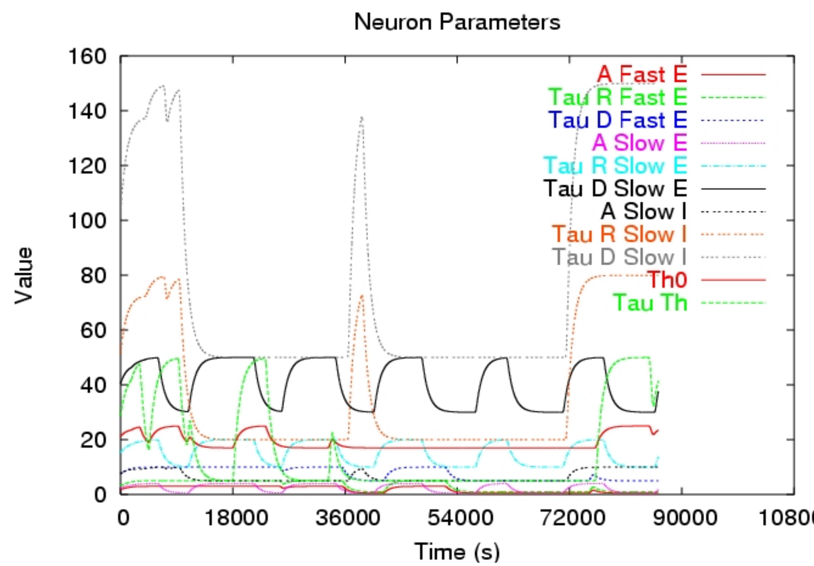




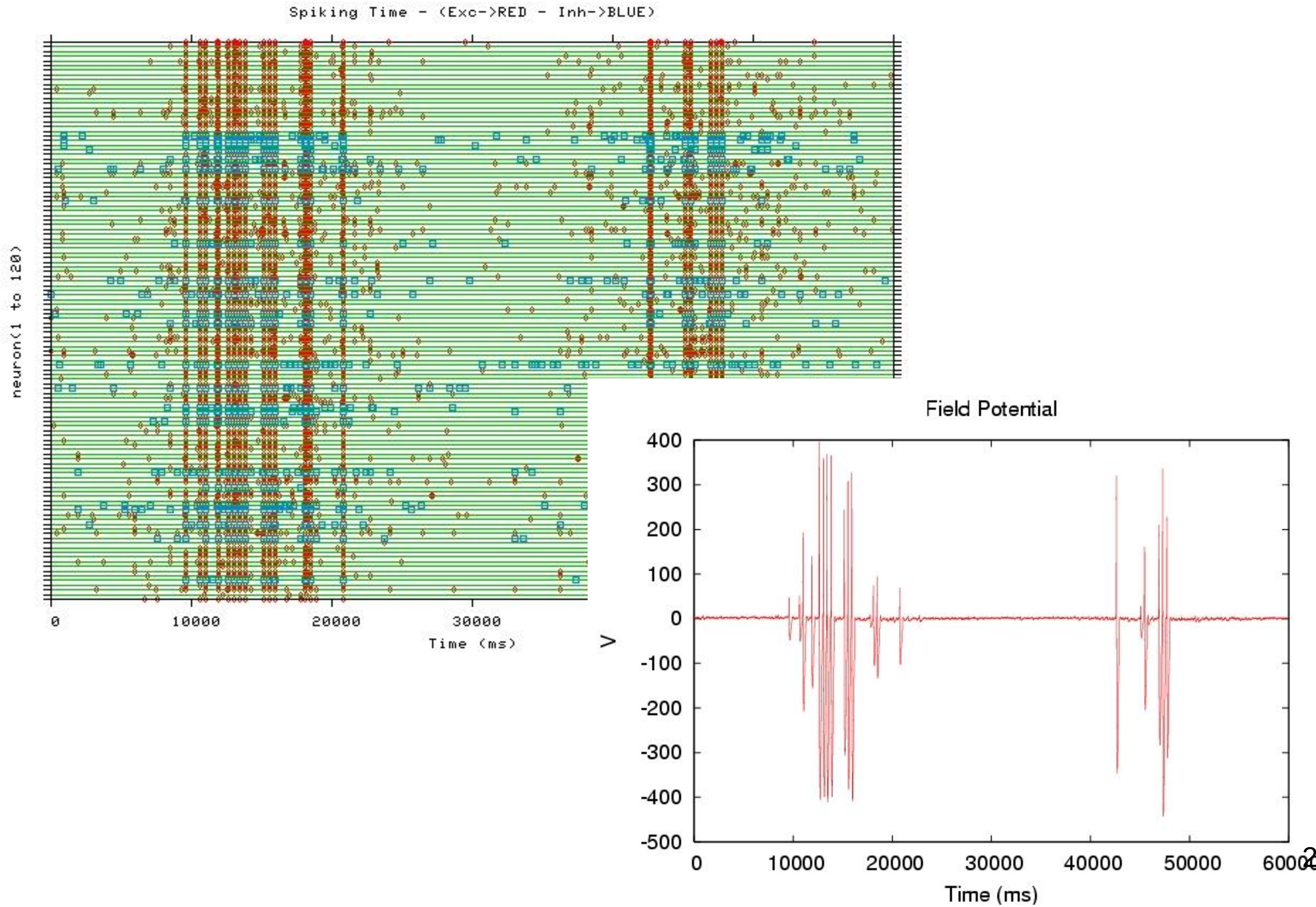
Toy example: GABRA deleted



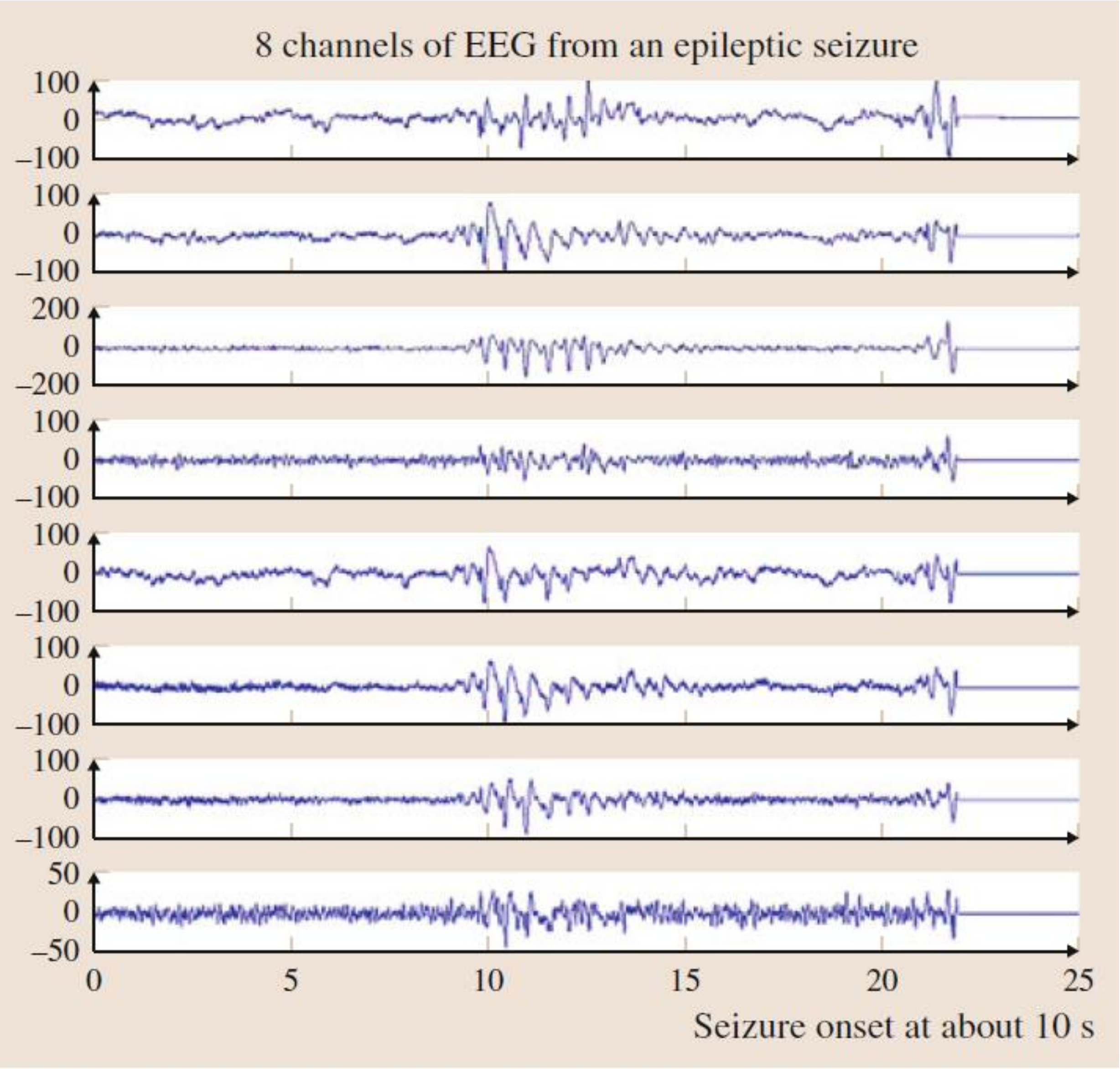




Frequent spontaneous global synchronisations



EEG in CAE



- Recording of eight channels of the normal and epileptic slow-wave discharge (SWD) in childhood absence epilepsy. SWD have large amplitudes and frequency of 2.5–4Hz.

Observations from the toy model

- Coefficients of gene-to-gene interaction were generated randomly. Many random gene-to-gene interactions yielded realistically looking LFP.

- We tested each interaction matrix by deleting the gene variable for GABRA. Some of interaction matrices yielded permanent synchronisation, some produced occasional synchronisations, some produced no synchronisations at al.

- This simple model shows gene mutations/deletions may have no effect on neural dynamics, everything depends on the rest of the GRN interactions and the function of the remaining genes/proteins.

- Or is this result only an artefact related to this simplified model?

Examples of neurogenetic models

- Marnellos G, Mjolsness ED (2003) Gene network models and neural development. In: *Modeling Neural Development*, ed. by A. van Ooyen, MIT Press, Cambridge.
- Smolen P et al. (2004) Simulation of Drosophila circadian oscillations, mutations, and light responses by a model with VRI, PDP-1, and CLK. *Biophysical J.* 86, 2786–2802.
- Benuskova L, Kasabov N (2007) Modeling L-LTP based on changes in concentration of pCREB transcription factor. *Neurocomputing* 70, 2035-2040.
- Benuskova L, Kasabov N (2008) Modeling brain dynamics using computational neurogenetic approach. *Cognitive Neurodynamics* 2(4), 319-334.
- Benuskova L, Kasabov N (2014) Computational neurogenetic modeling: gene-dependent dynamics of cortex and idiopathic epilepsy. In: N. Kasabov (Ed), *Springer Handbook of Bio-/Neuroinformatics*, Springer-Verlag, Berlin/Heidelberg.
- Nido GS, Ryan MM, Benuskova L, Williams JM (2015) Dynamical properties of gene regulatory networks involved in LTP. *Front. Mol. Neuroscience* 8:42.