



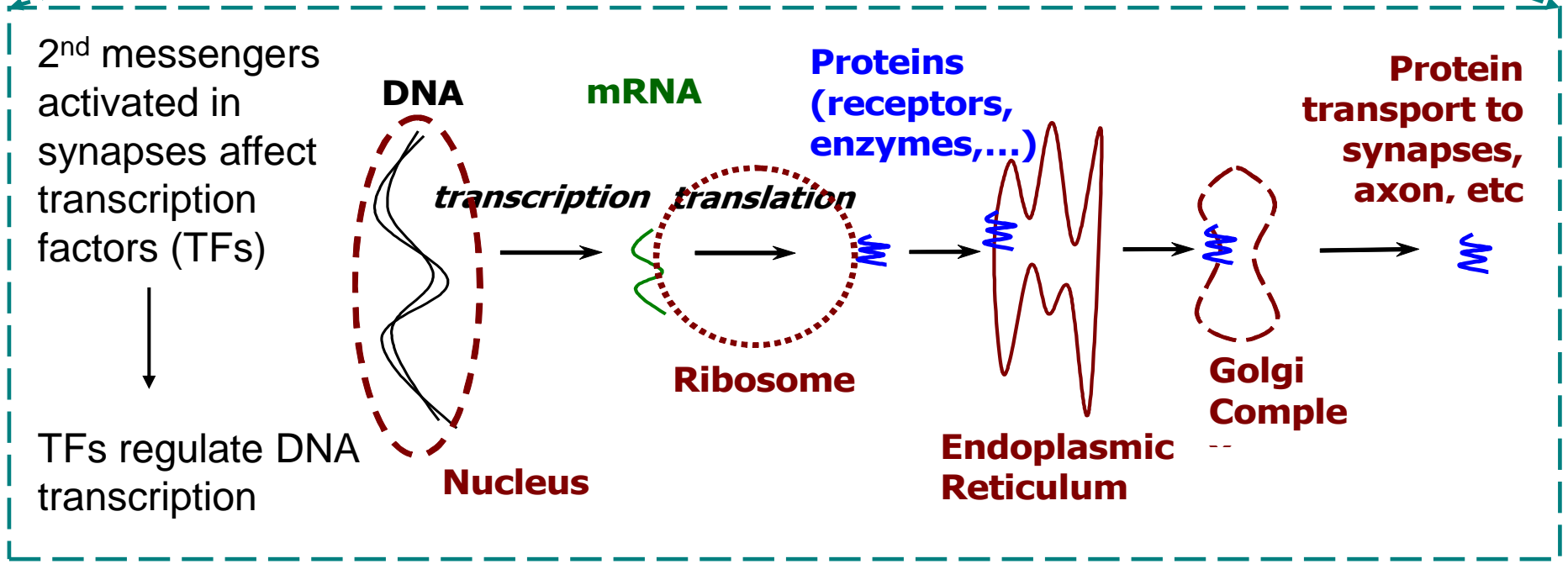
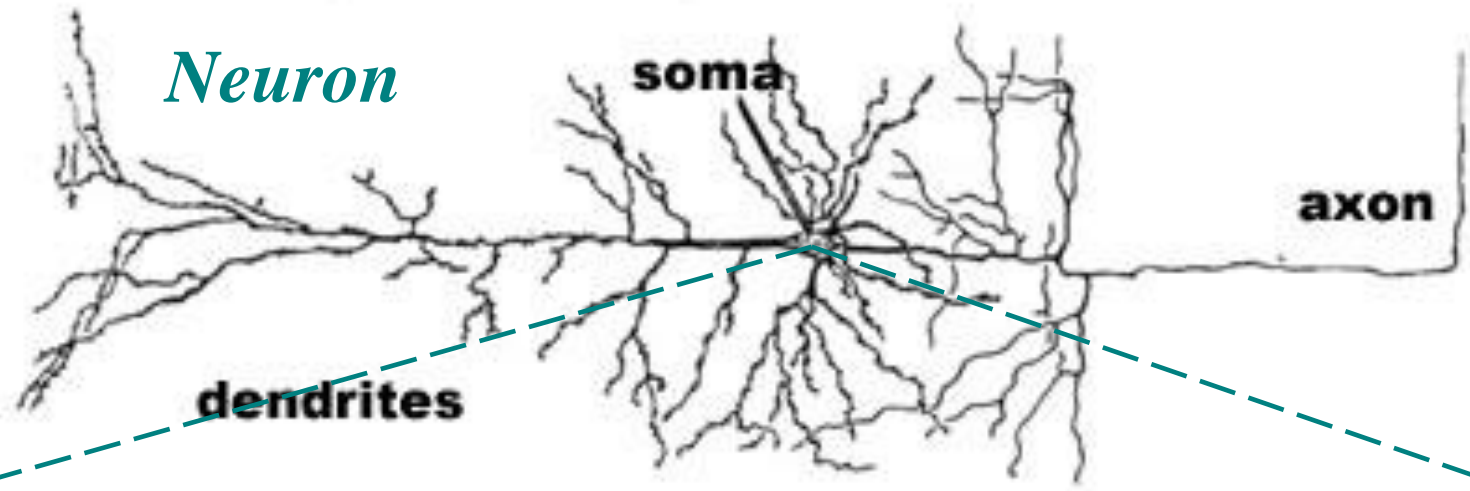
Lubica Benuskova
Nikola Kasabov

INTERNATIONAL TOPICS IN BIOMEDICAL ENGINEERING

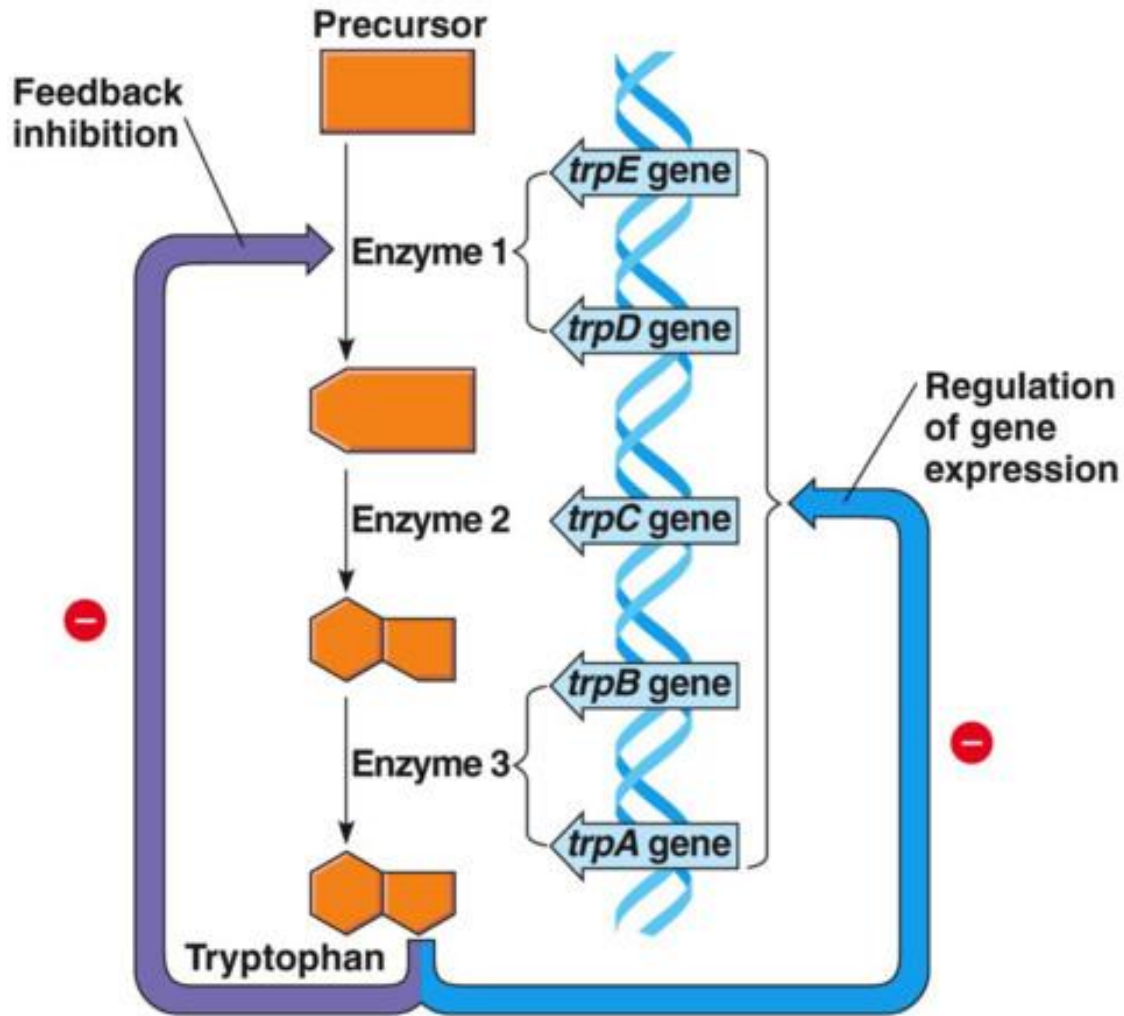
Computational Neurogenetic Modeling

 Springer

The link of genes to brain functions is through protein synthesis



Example of a negative feedback in the GRN

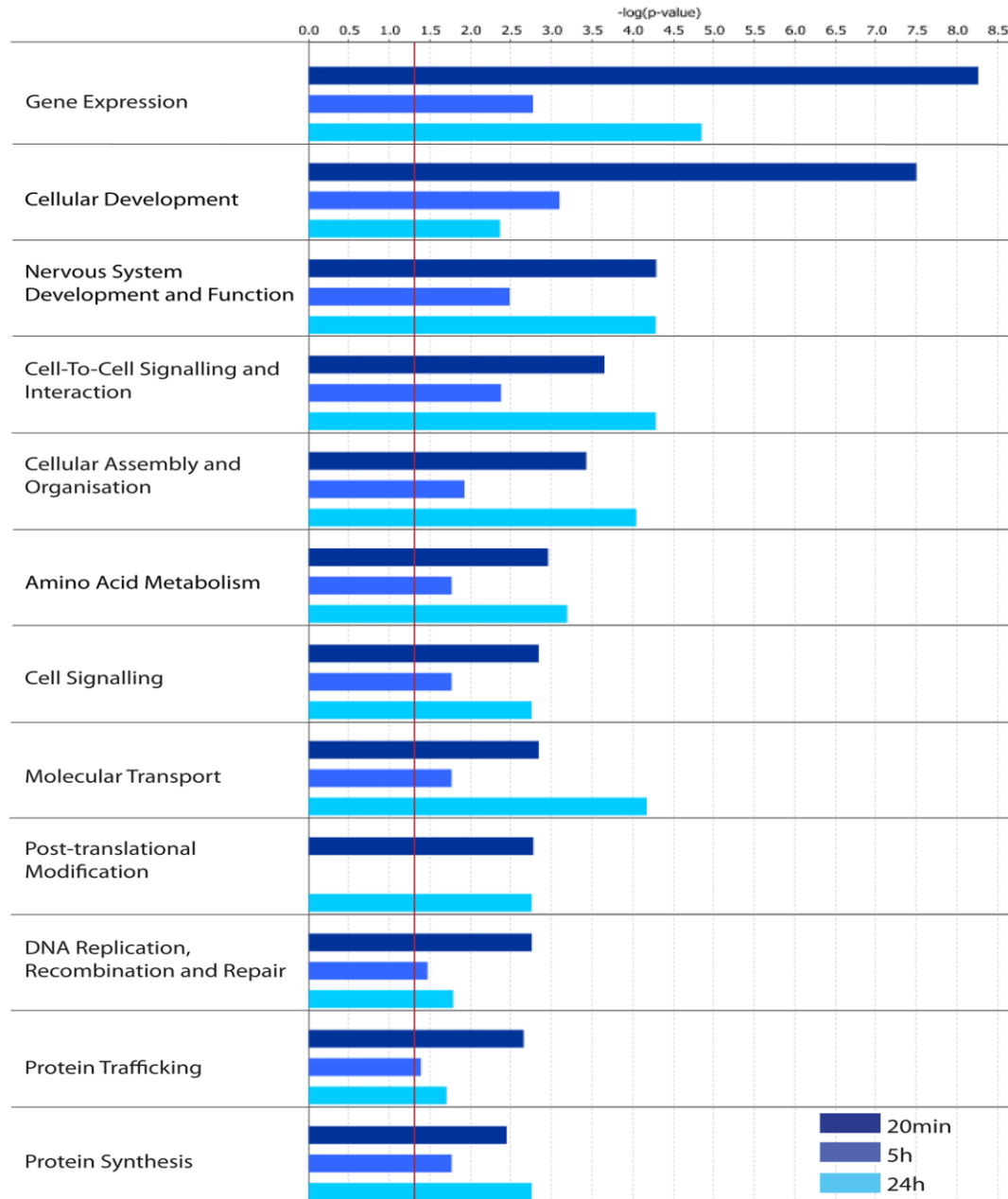


(a) Regulation of enzyme activity

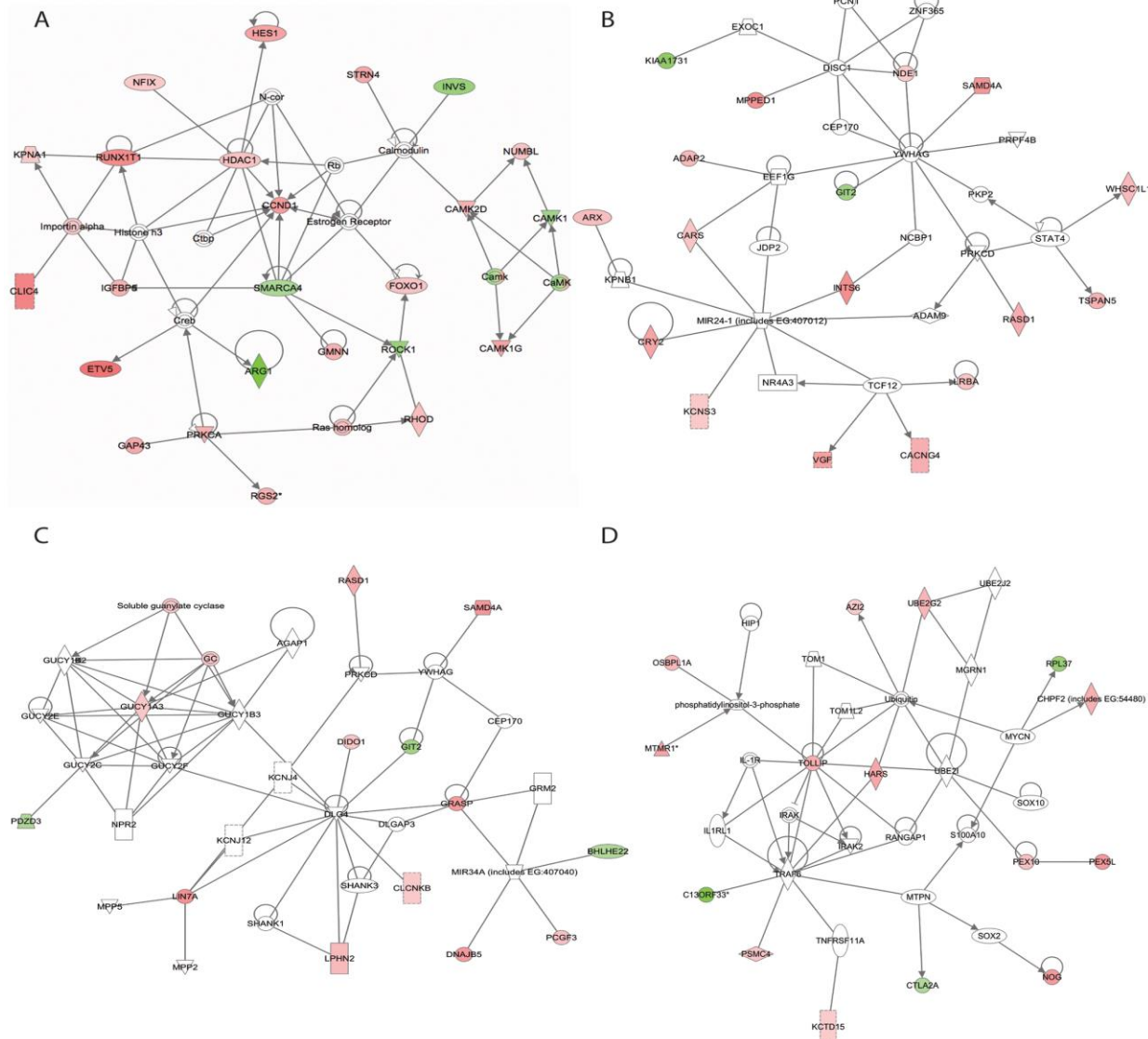
(b) Regulation of enzyme production

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LTP gene regulatory network (GRN) – functions

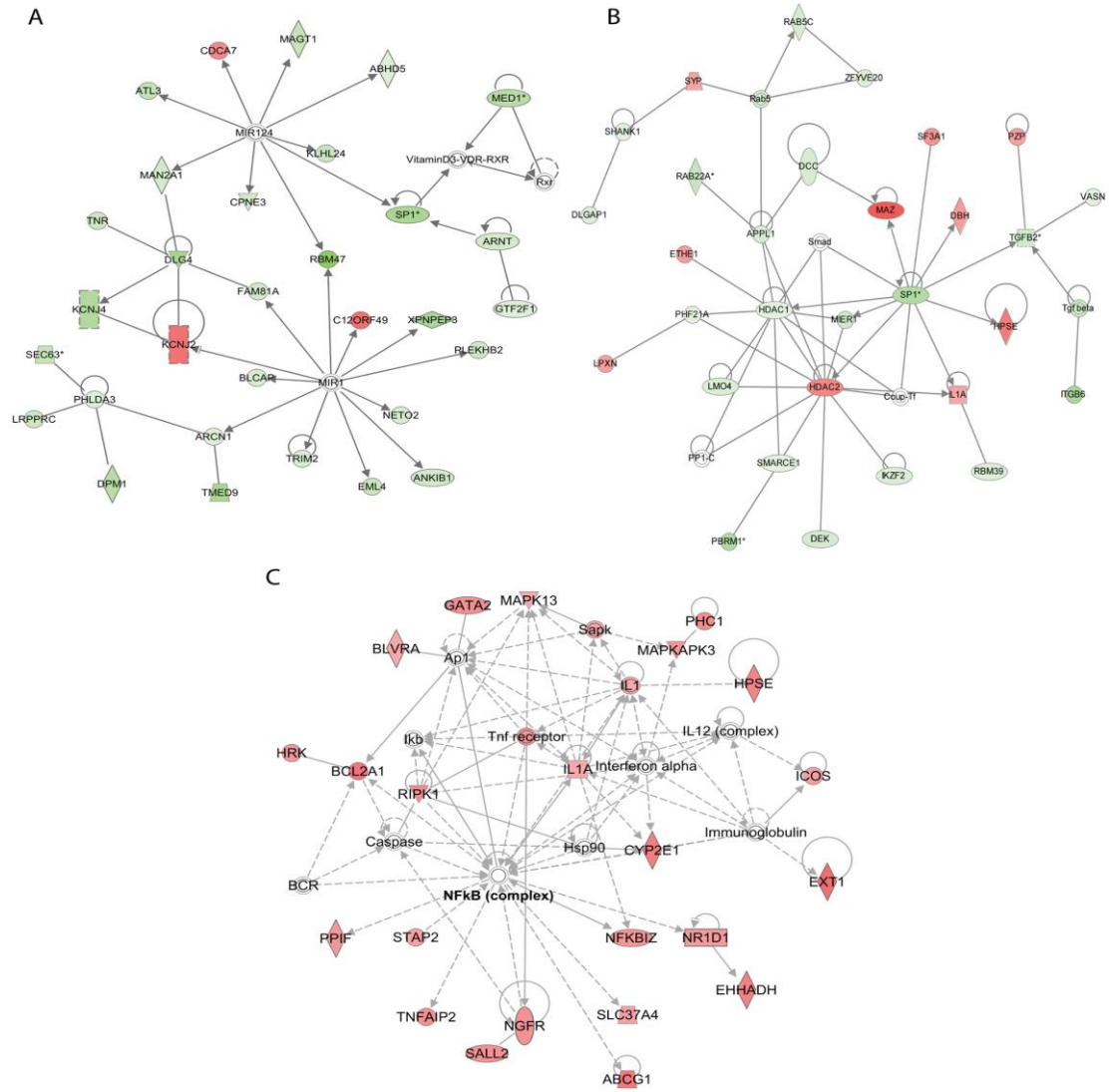


LTP gene regulatory network (GRN) – after 5 hrs



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

LTP gene regulatory network (GRN) – after 24 hrs

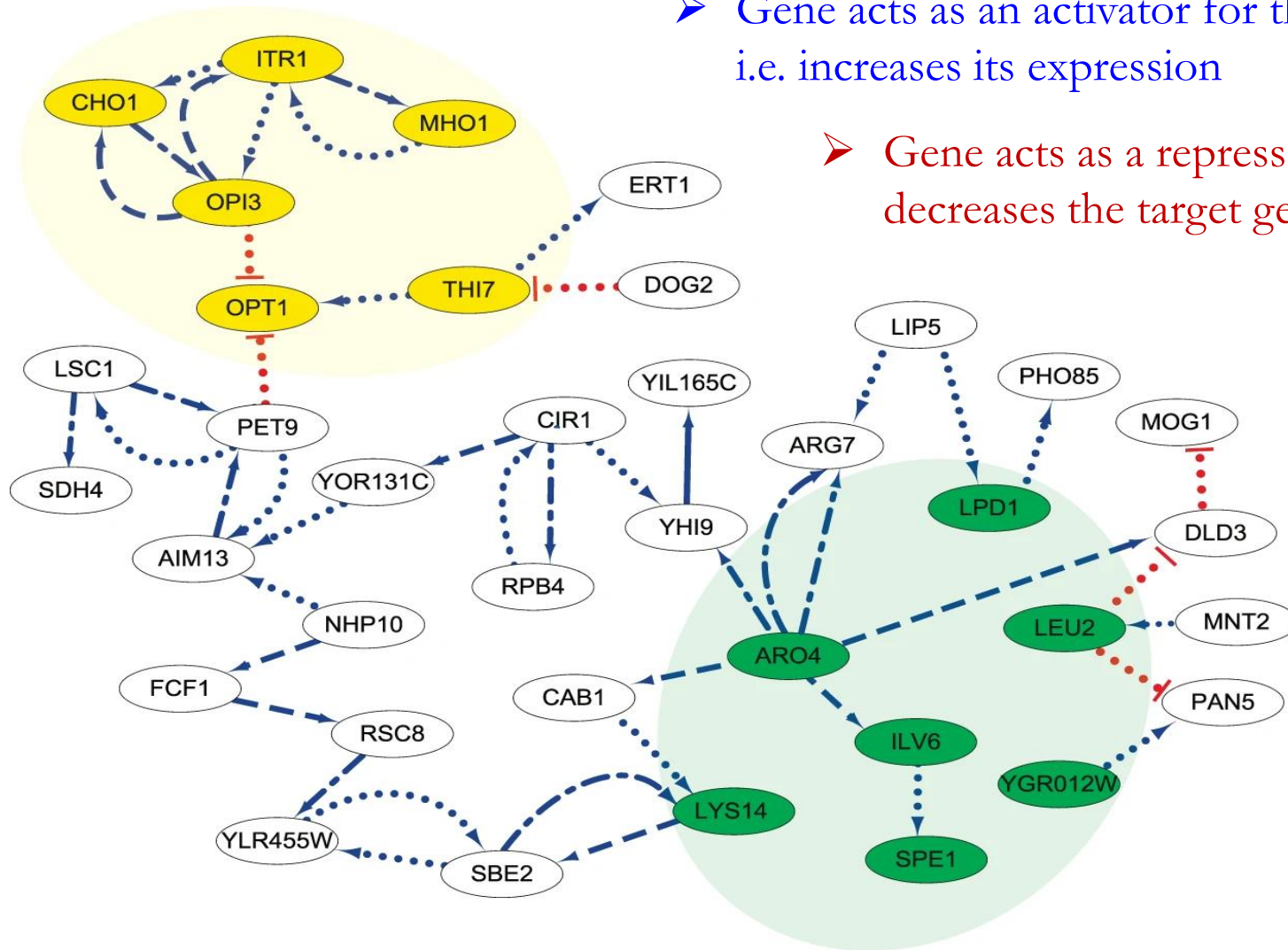


• Source: Ryan et al., Hippocampus, 2011 & PLoS One, 2012)

Yeast gene regulatory network (GRN)

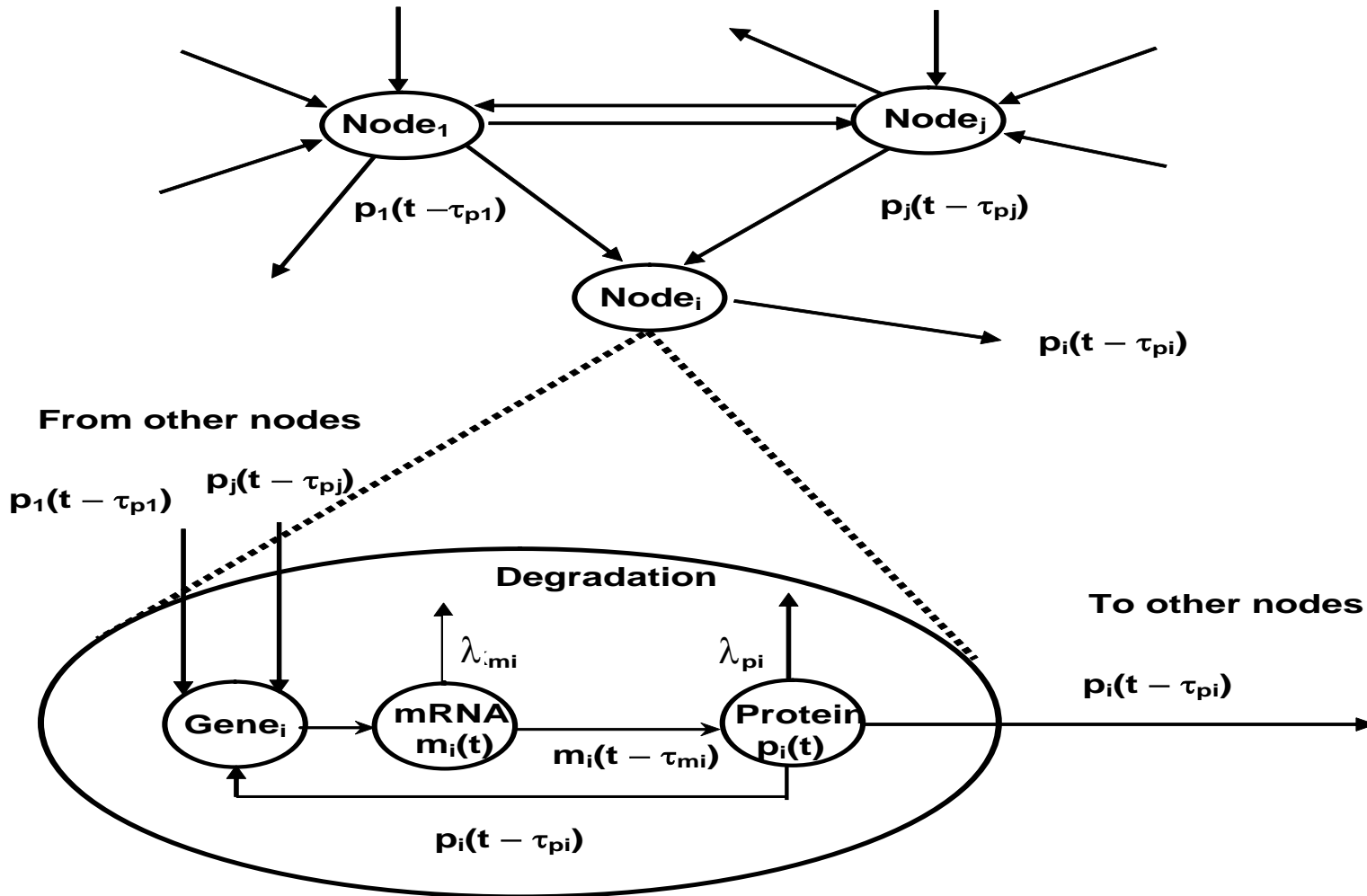
➤ Gene acts as an activator for the target gene, i.e. increases its expression

➤ Gene acts as a repressor, i.e. decreases the target gene expression

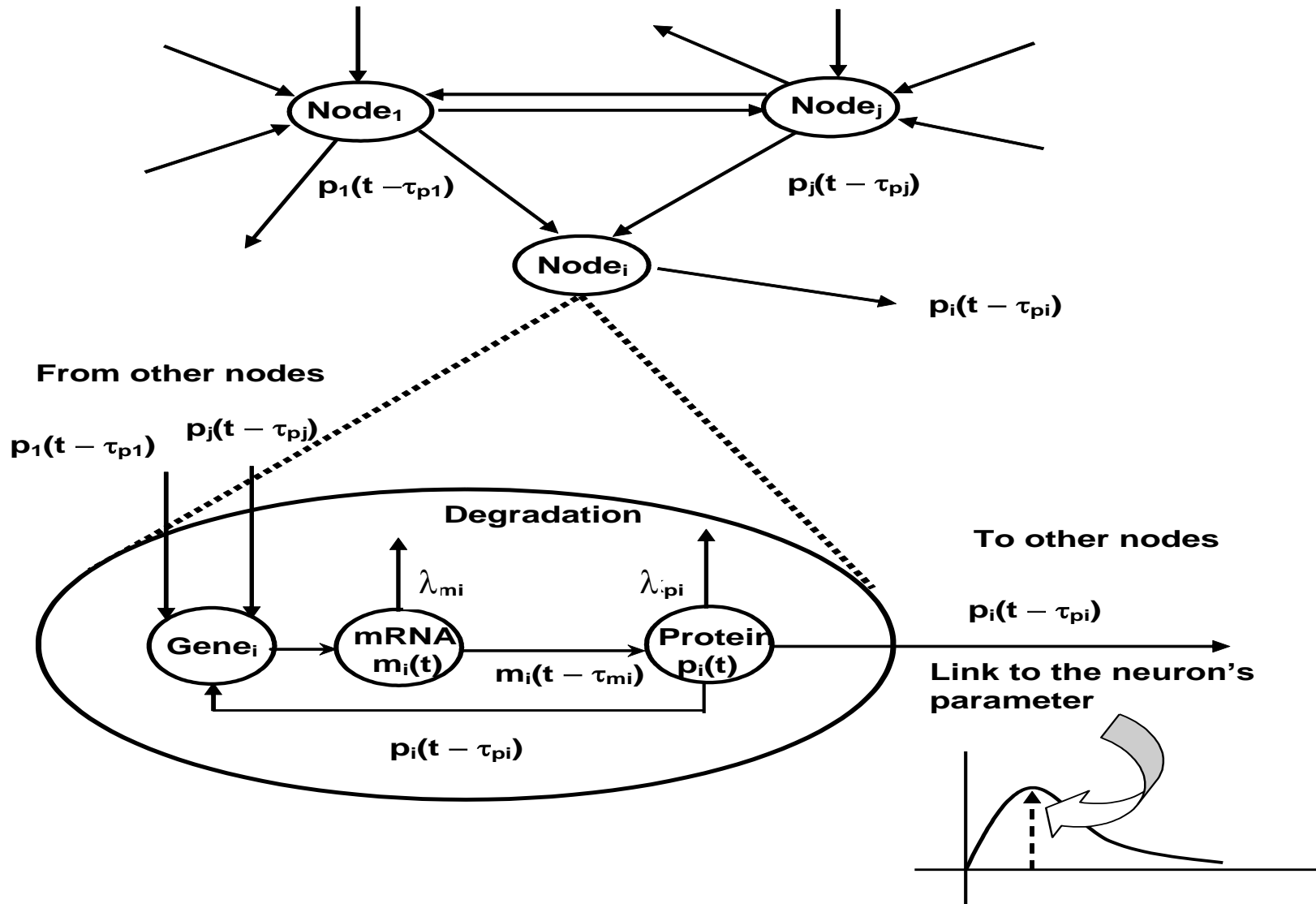


• Source: Inferring GRN in yeast (Chen et al., Sci. Rep., 2019)

GRN: towards mathematical model



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



System of differential equations

mRNA levels

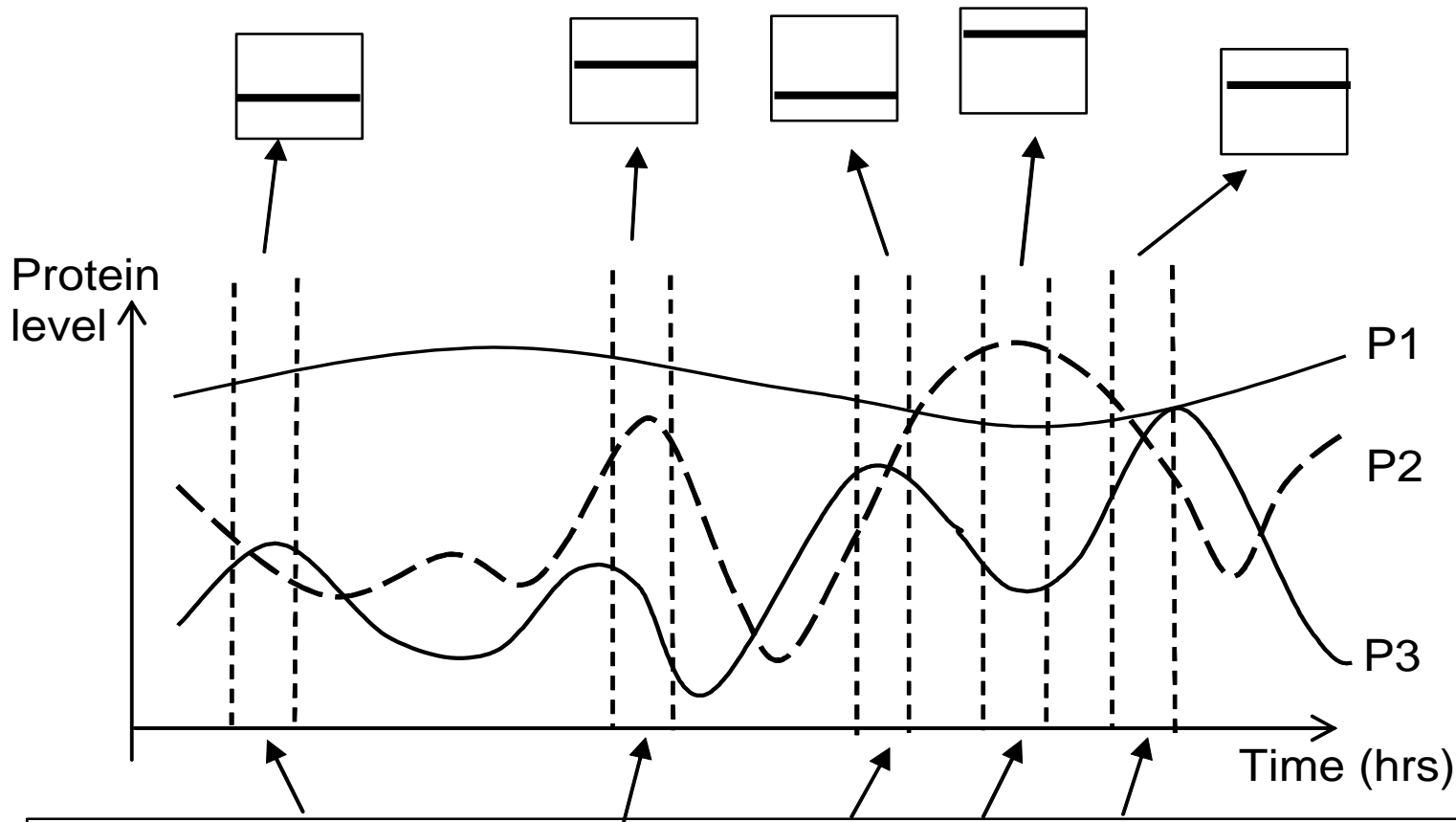
$$\frac{dm_i}{dt} = A_{m_i} \sigma_{m_i} \left(\sum_{j=1}^n \underbrace{w_{ij}}_{\text{coefficients of the GRN interaction matrix}} p_j(t - \tau_{p_j}) + \underbrace{\sum_{k=1}^K v_{ik} x_k(t - \tau_{x_k}) + b_{m_i}}_{\text{External factors (hormones, drugs,...)}} \right) - \lambda_{m_i} m_i(t)$$

Protein levels

$$\frac{dp_i}{dt} = A_{p_i} \sigma_{p_i} \left(m_i(t - \tau_{m_i}) + \underbrace{\sum_{k=1}^{K'} u_{ik} y_k(t - \tau_{y_k}) + b_{p_i}}_{\text{External factors (hormones, drugs,...)}} \right) - \lambda_{p_i} p_i(t)$$

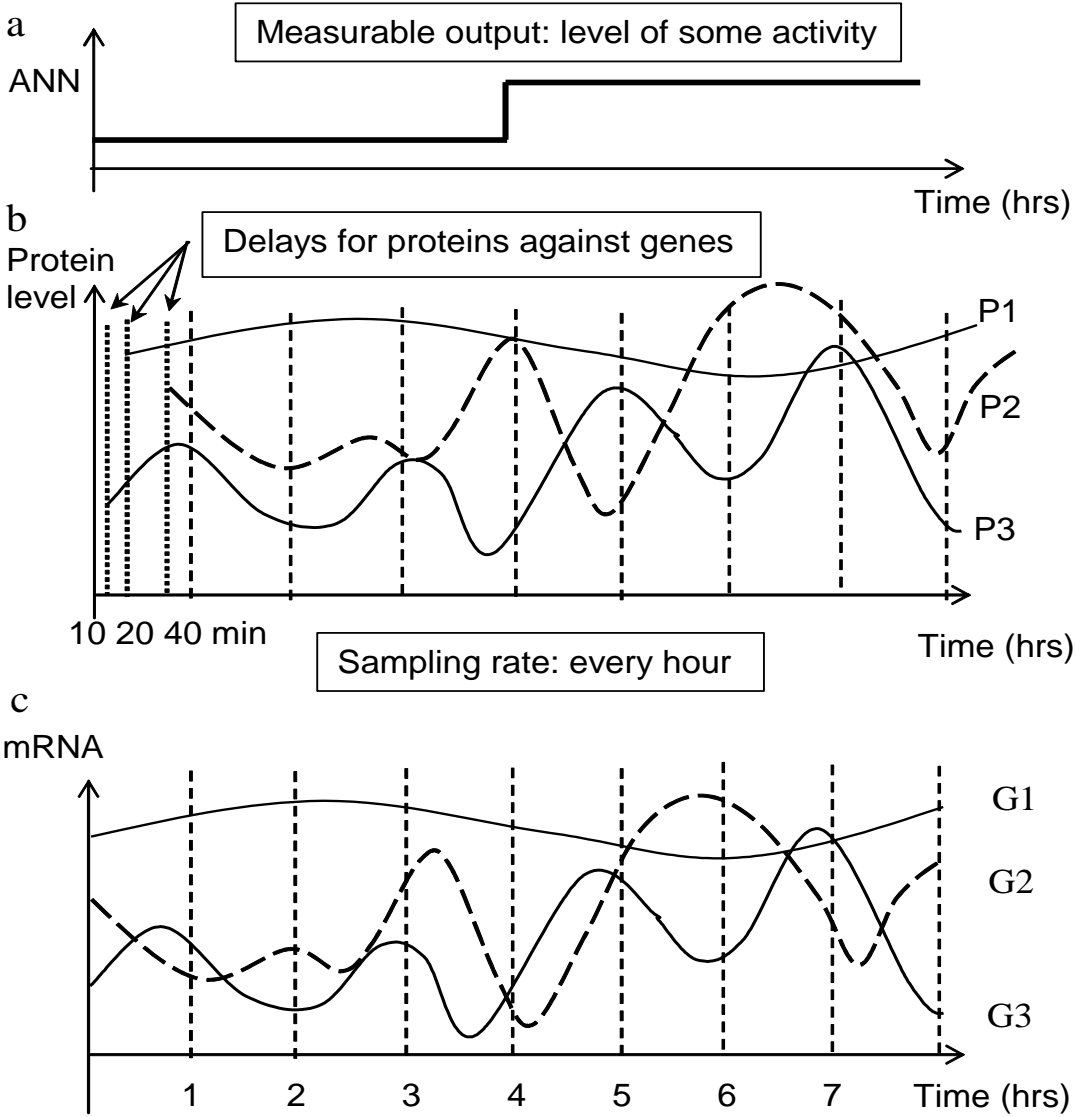
Output behaviour of model neurons depends on underlying gene/protein dynamics

ANN output behavior: for instance the level of activity



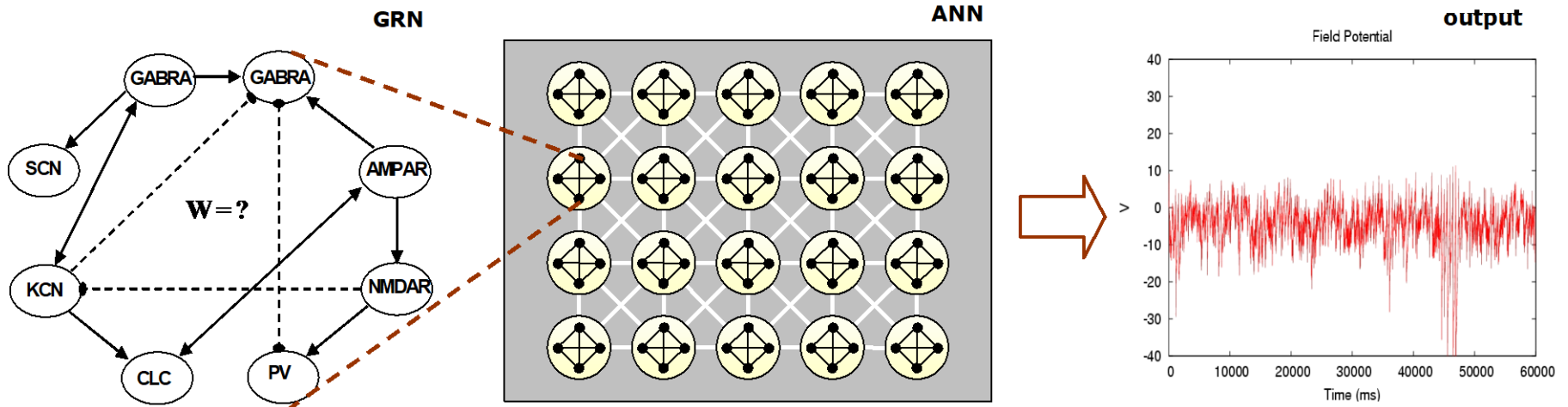
Sampling rate: at every interesting interval of gene-protein dynamics

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

Model ANN

ANN output LFP

Abstract connections W

Gene-protein regulatory network model

mRNA levels

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

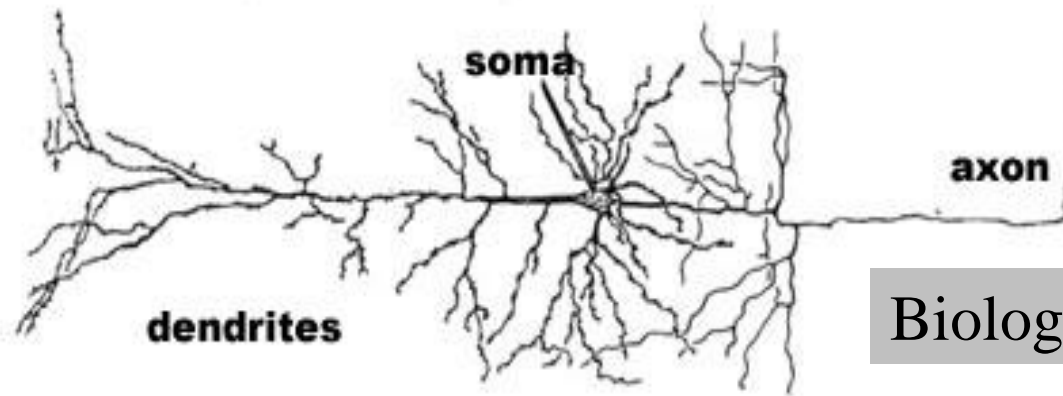
Protein levels

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

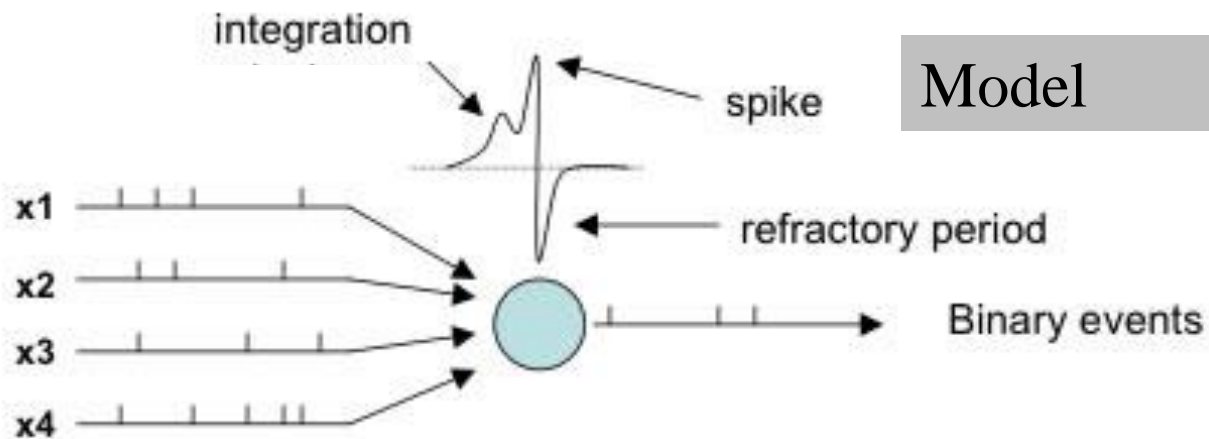
Values of neuronal parameters will depend on levels of proteins p

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

Neuron model



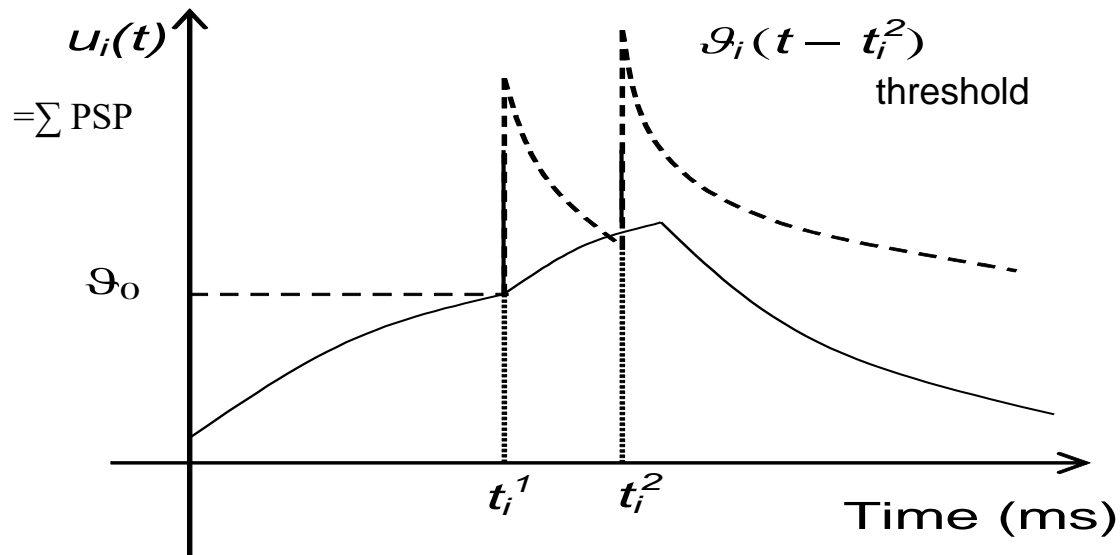
Biological neuron



Model

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

Spiking neuron model



Spike
Response
Model

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

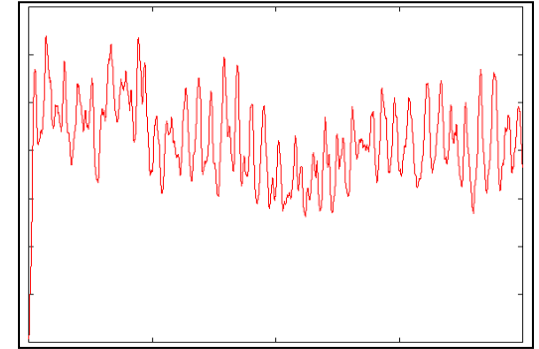
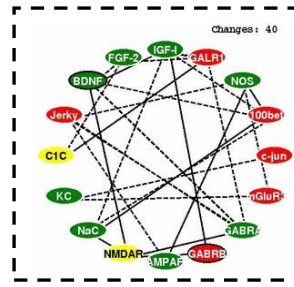
type = fast excitation, slow_excitation, fast_inhibition, slow_inhibition

Neural network model of cerebral cortex with input from thalamus

OUTPUT : Local Field Potential

$$\text{LFP}(t) = \sum u_i(t) \approx \text{EEG} = \sum \text{LFP}(t)$$

The same GRN in each neuron

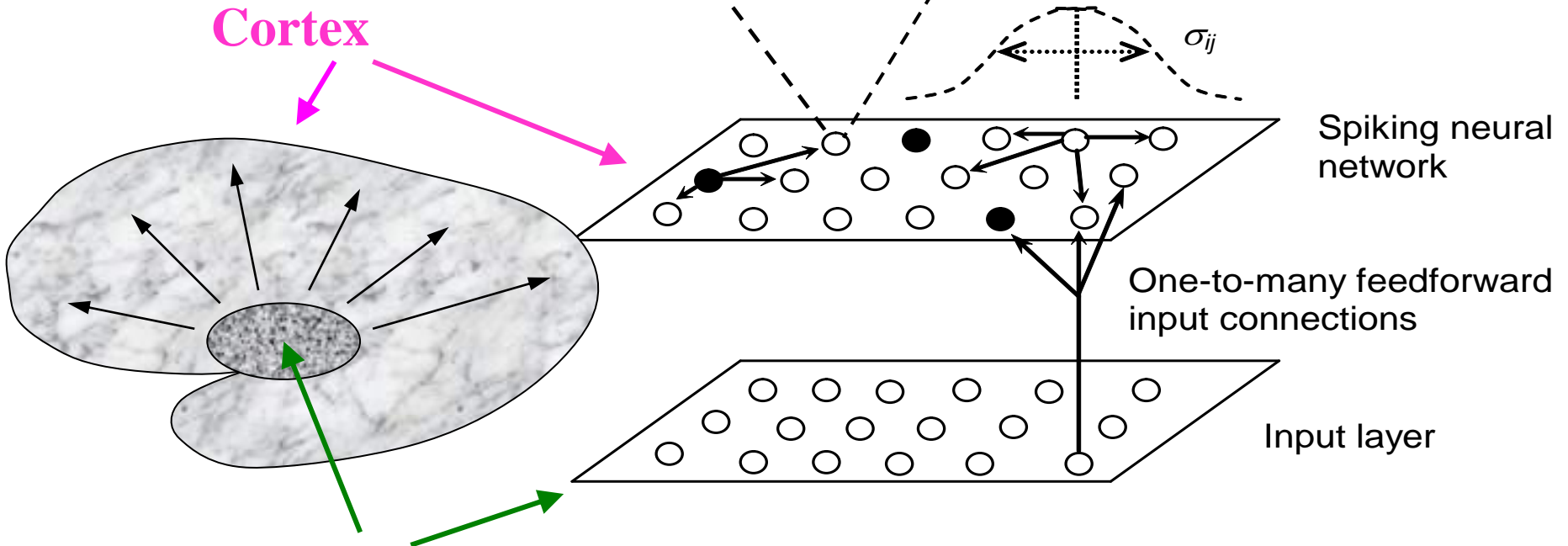


J_{ij}

σ_{ij}

Cortex

Thalamus



Credits: Simei Gomes Wysoski

Neuro Genetic Model

File Edit View New Parameters Help

Signal Analysis
File Name: eeg_quiroga.txt
Run

Spiking Neural Network
Run

Neuro Genetic Model
 ◆ New gene matrix [W]
 ◆ Existent gene matrix [W]
 ◆ New gene value G(0)
 ◆ Existent gene value G(0)
 ◆ Linear
 ◆ Non Linear
 Run
 Clean log Mapping graph

Step by step Visualization
 GRN changes in time
 No. of changes: 200
 View

Optimization
 To be optimized
 Neuron Parameters view
 GRN Weights view
 Genes Initial Values view
 Genetic Algorithm Run

Set of solutions
 Dir In: /all_result
 Run Fitness Thres: 0.2
 Number solutions: 0

Testing epileptic constraints
 Dir out: /epileptic_result
 Run

Knowledge Discovery Statistical Analysis
 Dir: /all_result
 Run Number of files: 0

Output Graphs
 all_spikes.ps
 Close

Parameters Editor

3.000000	Amplitude Fast Excitation
5.000000	Tau Rise Fast Excitation
6.000000	Tau Decay Fast Excitation
1.500000	Amplitude Slow Excitation
45.000000	Tau Rise Slow Excitation
75.000000	Tau Decay Slow Excitation
0.500000	Amplitude Fast Inhibition
1.000000	Tau Rise Fast Inhibition
7.000000	Tau Decay Fast Inhibition
4.000000	Amplitude Slow Inhibition
65.000000	Tau Rise Slow Inhibition
145.000000	Tau Decay Slow Inhibition
20.000000	Threshold (theta)
45.000000	Threshold time constant
4.000000	Number of times (k) of threshold
0.150000	Proportion of Inhibitory neurons
0.017000	Probability of External Firing
4.000000	Amplitude External peak (w)

File Name: /neu_par.ini

Continuous Gene Protein Regulatory Network
 GPRN SNN for a time interval
 From: 0 To: 1 sec Run

Done

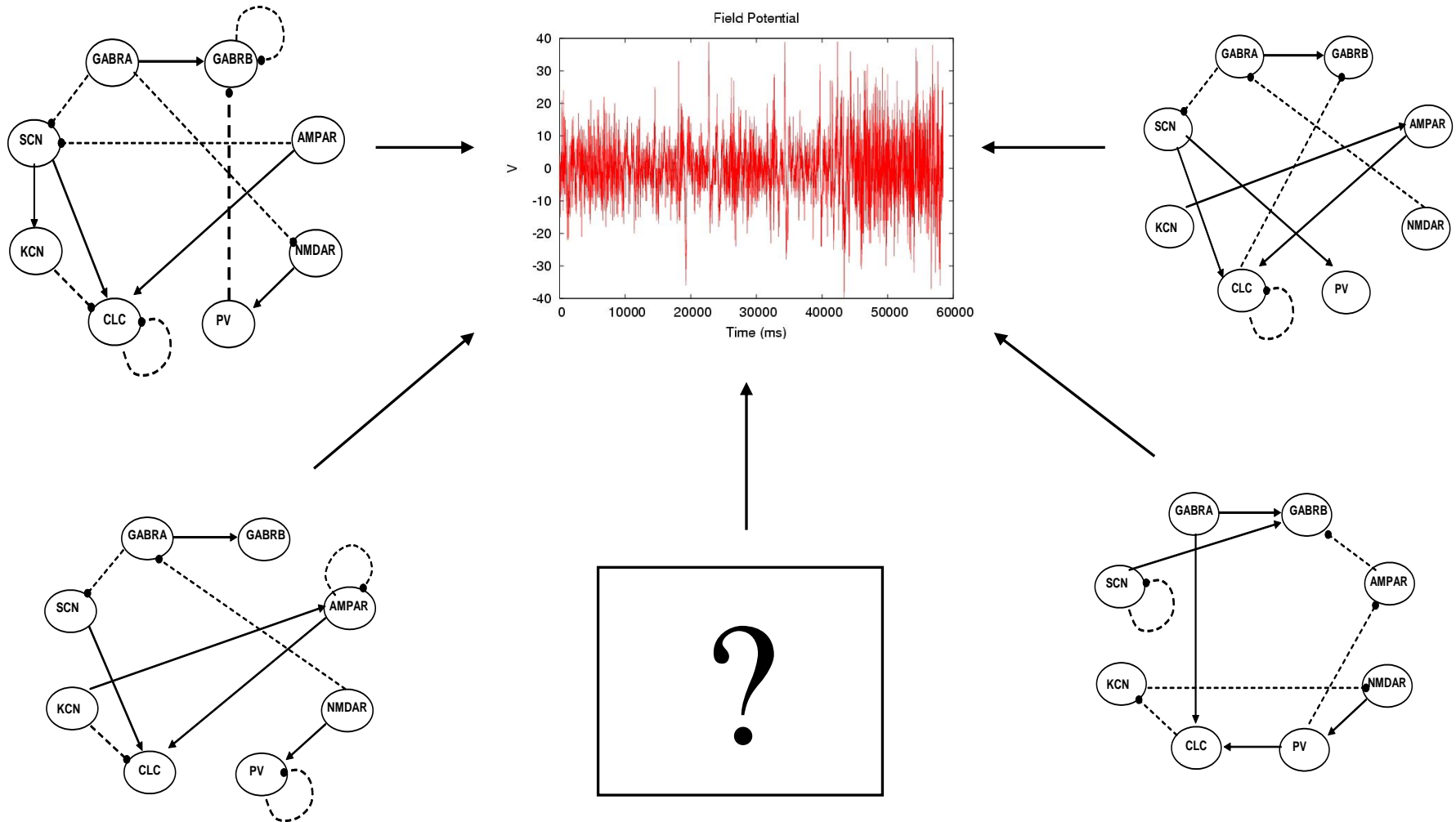
Table of neuron parameters

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

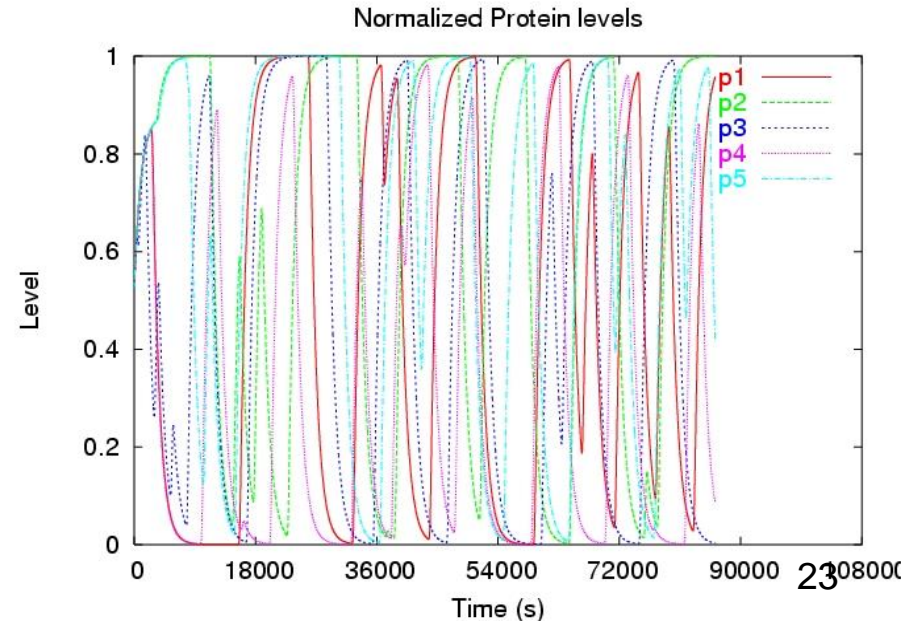
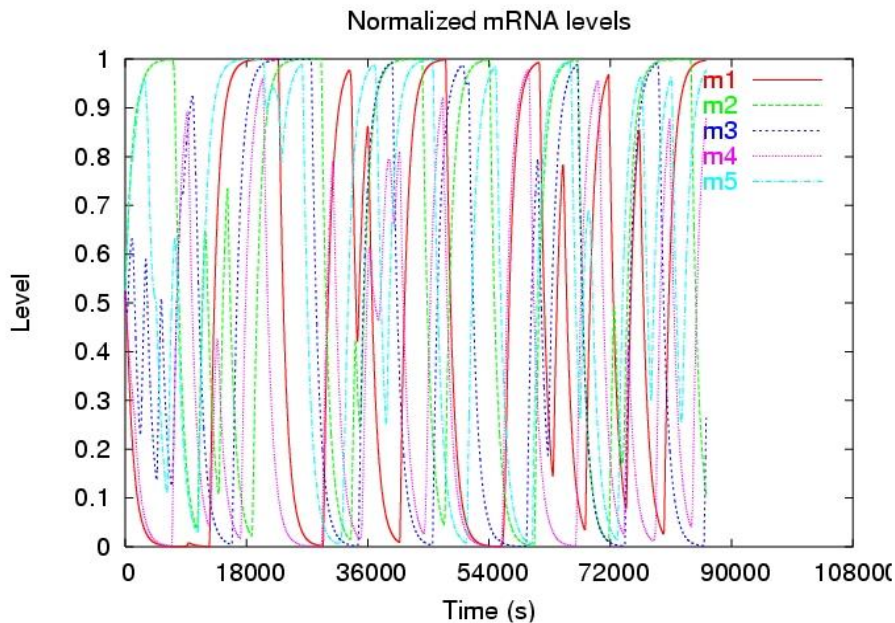
SNN PARAMETER	VALUE
Number of neurons	120
Proportion of inhibitory neurons	0.2
Probability of external (thalamic) fiber firing	0.015
Peak/sigma of external input (TC) weight	5 / 1
Peak/sigma of lateral excitatory weights	10 / 4
Peak/sigma of lateral inhibitory weights	40 / 6
Probability of connection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

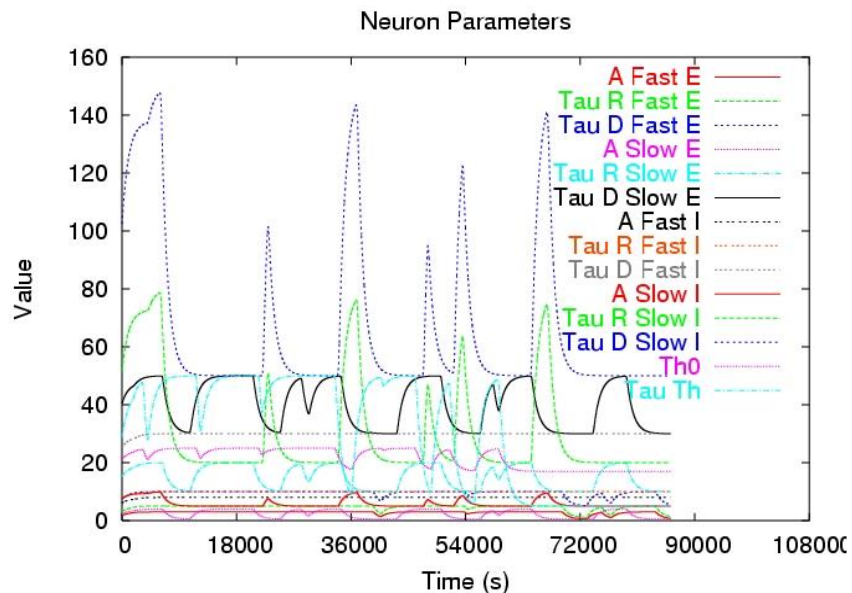
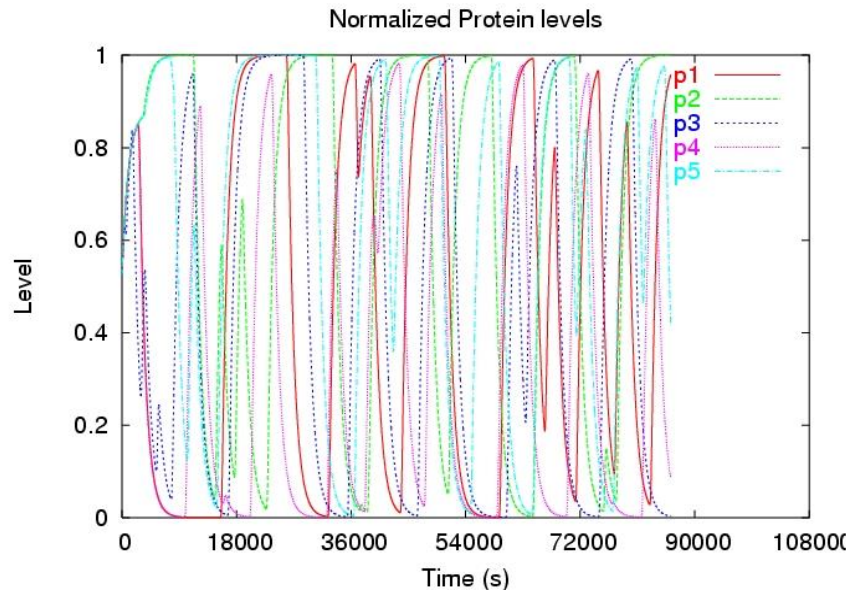
- We generated an artificial gene interaction matrix W leading to a complex gene and protein dynamics over 24 hrs (only 5 genes/proteins)
- These were “genetic variables” for AMPAR (fast excitation), NMDAR (slow excitation), GABRA (fast inhibition), GABRB (slow inhibition), SCN (Firing threshold)



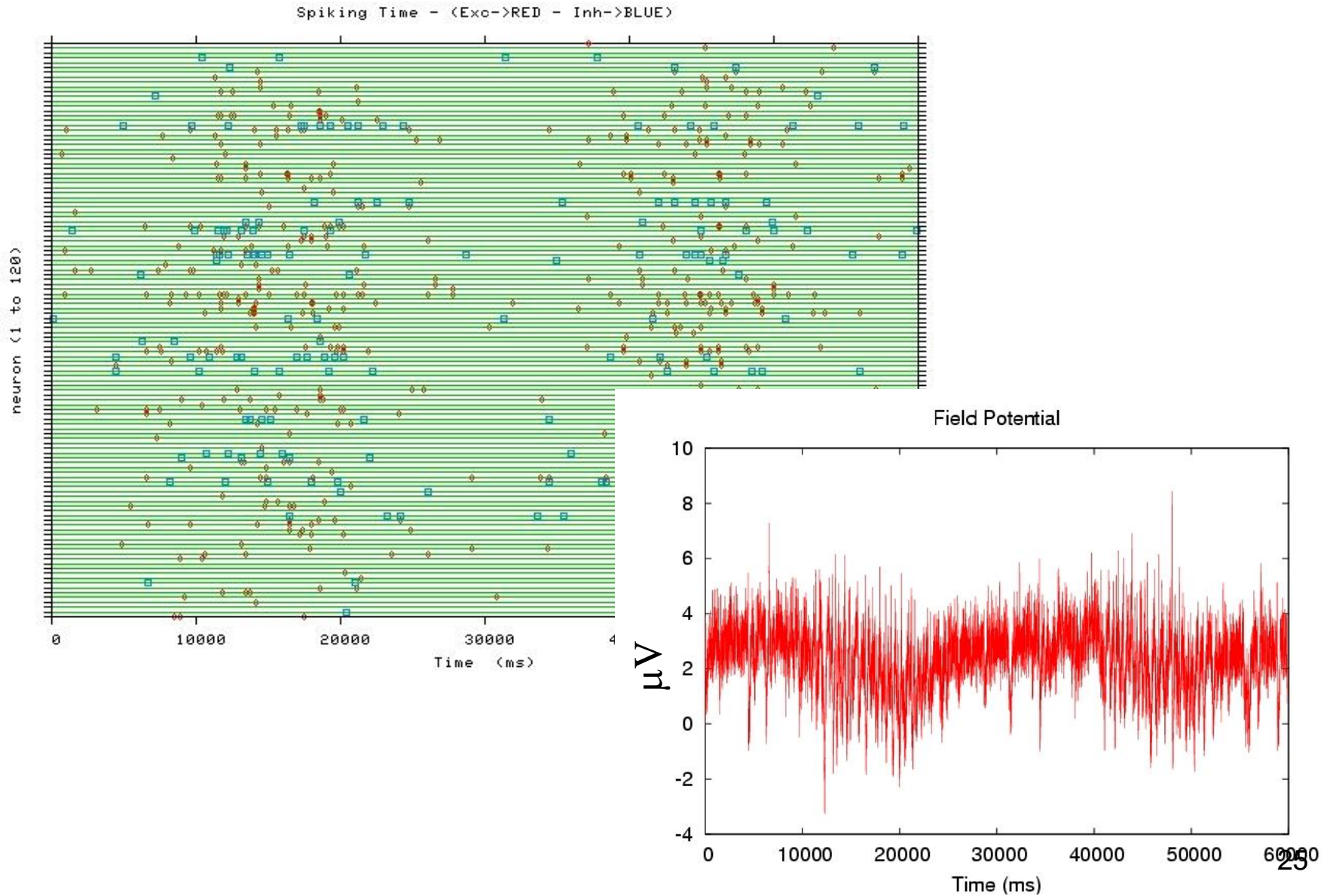
Toy example: complete genome

Value of parameter is proportional to the level of a protein

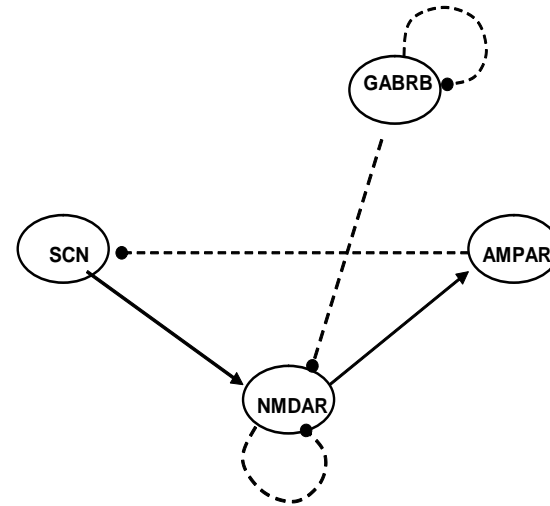
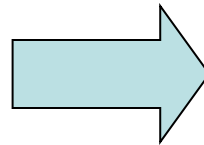
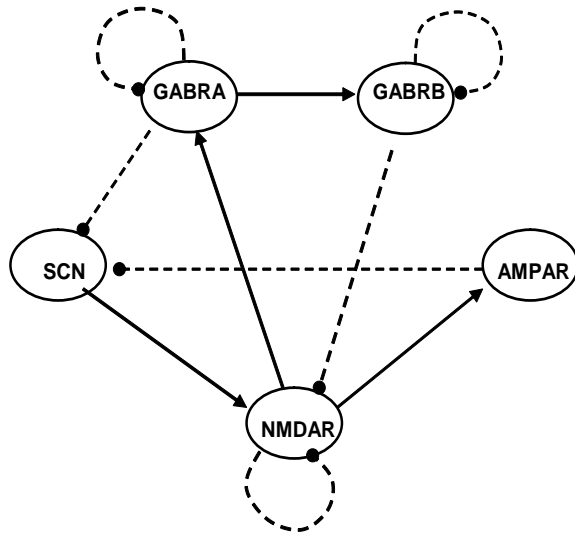
$$P_j(t) = P_j(0) p_j(t)$$



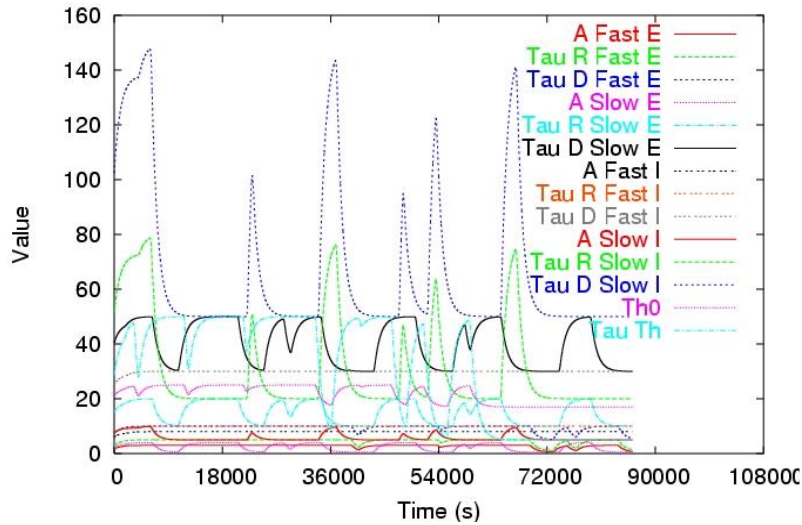
Asynchronous neural activity



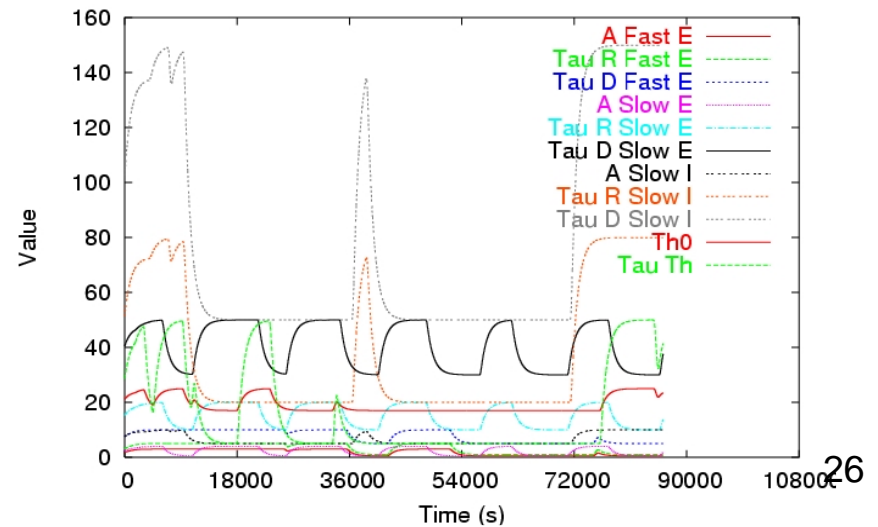
Toy example: GABRA deleted



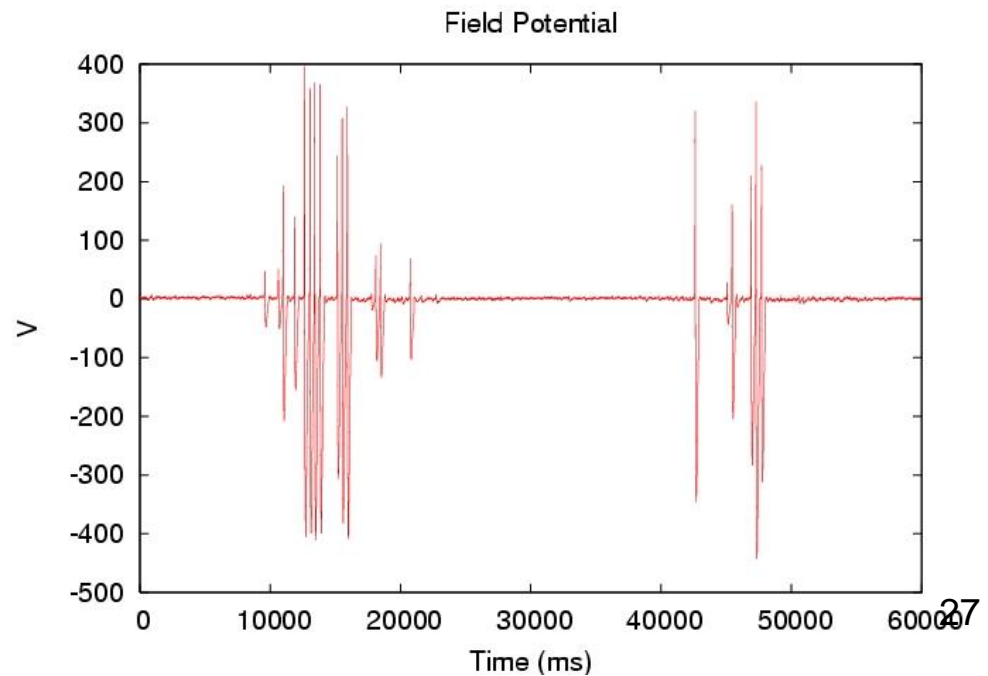
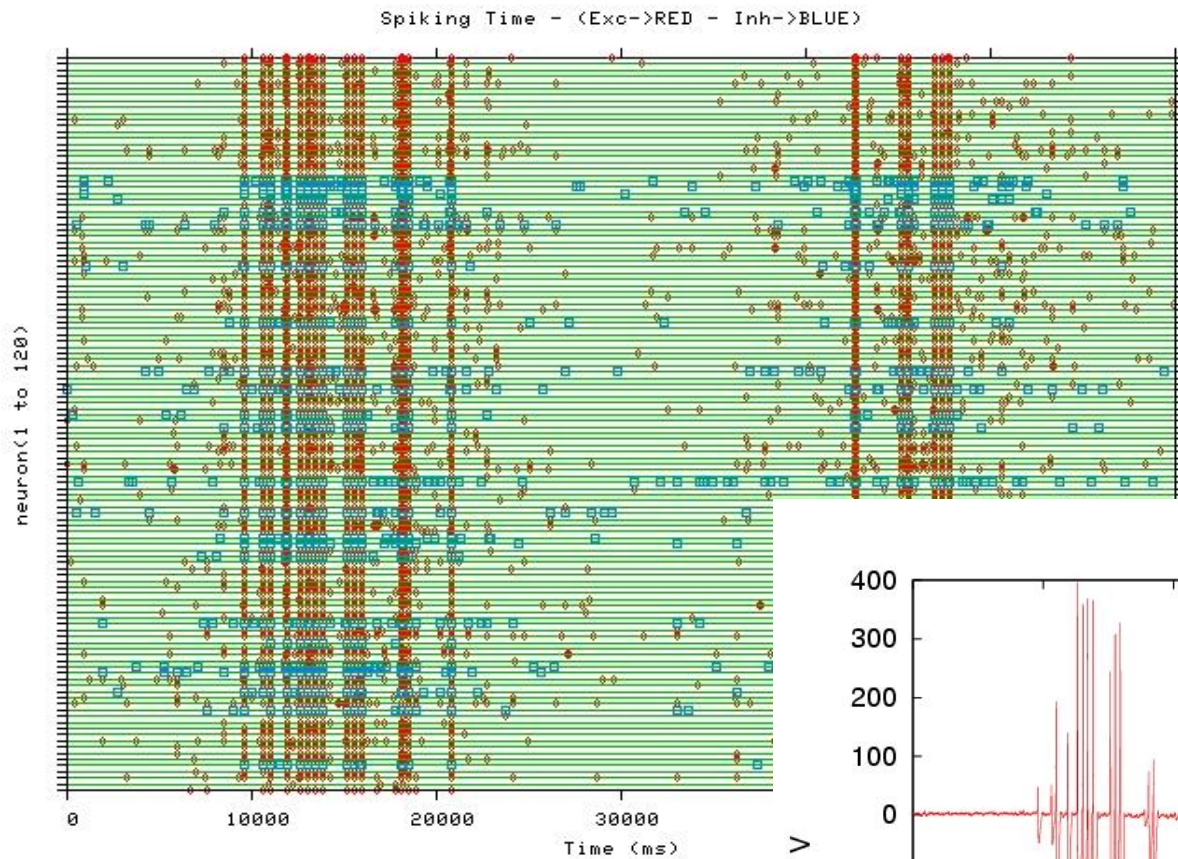
Neuron Parameters



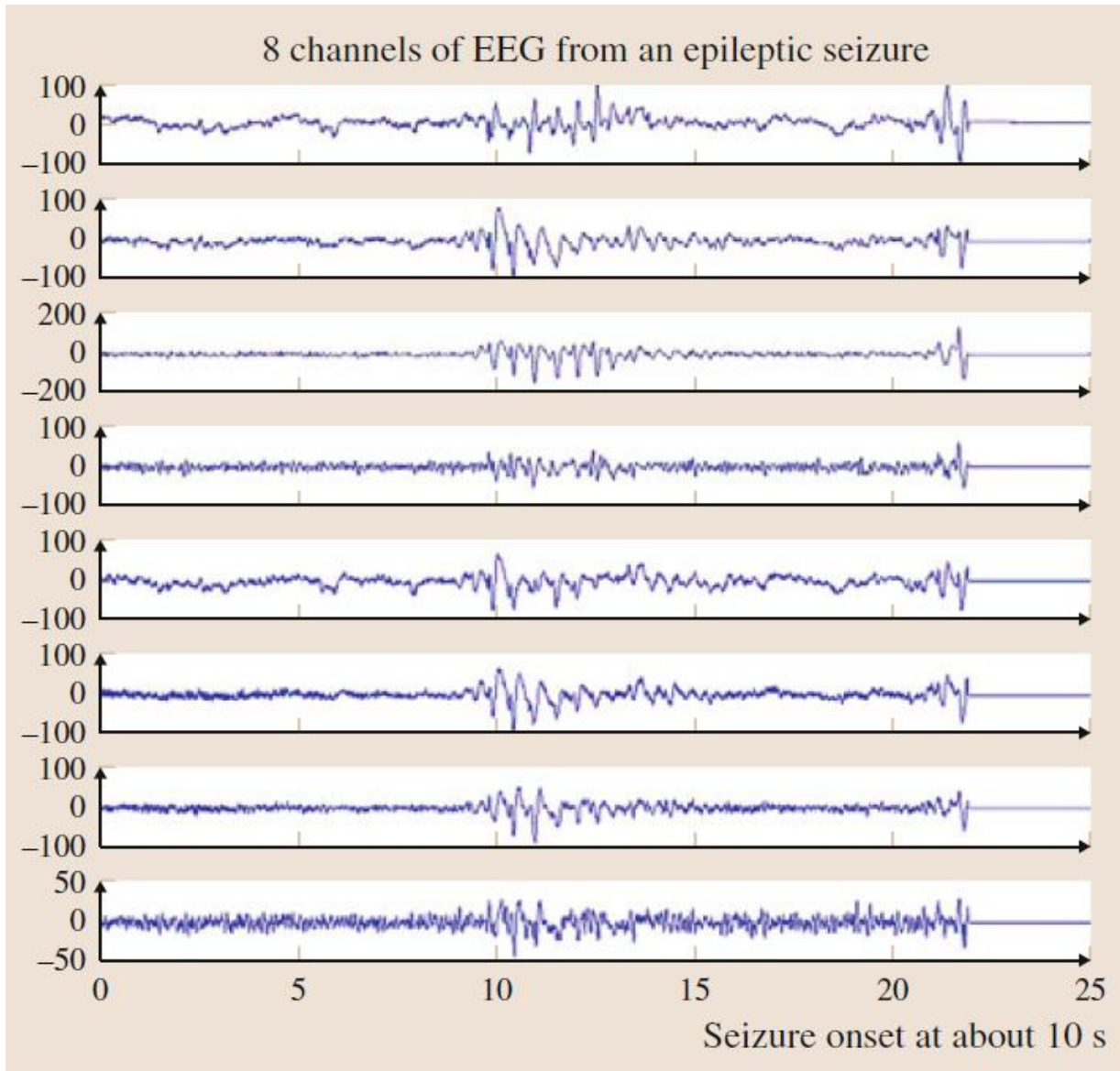
Neuron Parameters



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 all.
- 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.