Clique of functional hubs in developmentally regulated neural networks

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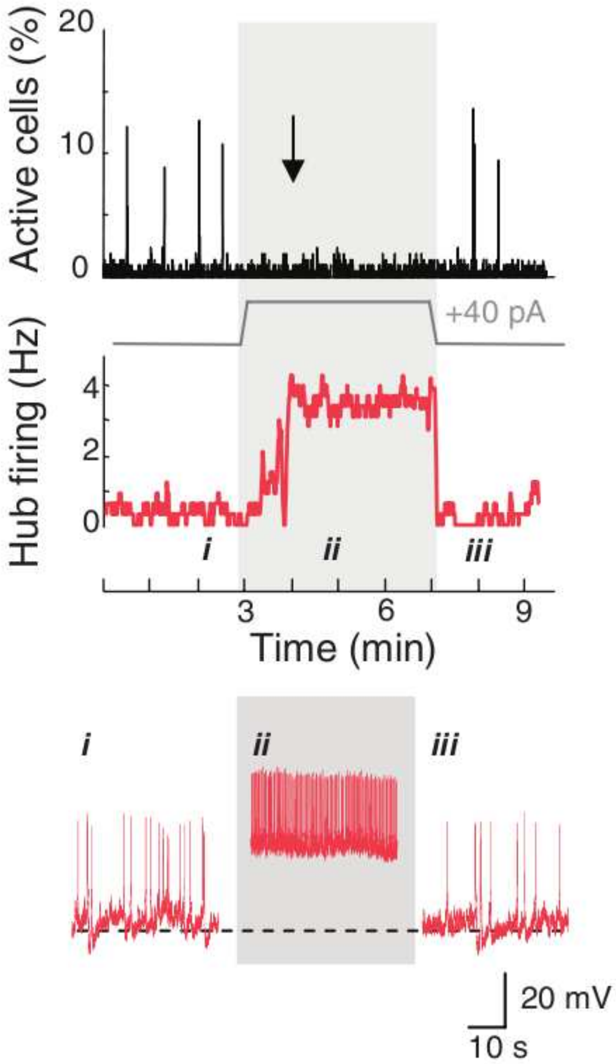
Main Inspiration



Bonifazi *et al*, Science 2009

- Immature hyppocampal circuits exhibit
  - Rhytmic collective oscillations
    giant depolarizing potentials
  - Excitatory action of GABAergic transmission
  - Presence of functional and structural hub neurons
- Single neuron stimulation can silence the network activity - GABAergic hub interneurons

General questions

- To which extent a single neuron can influence brain circuits / network dynamics ?
- Why only few neurons displays such a strong power ?

Summary

Neural Network Model:

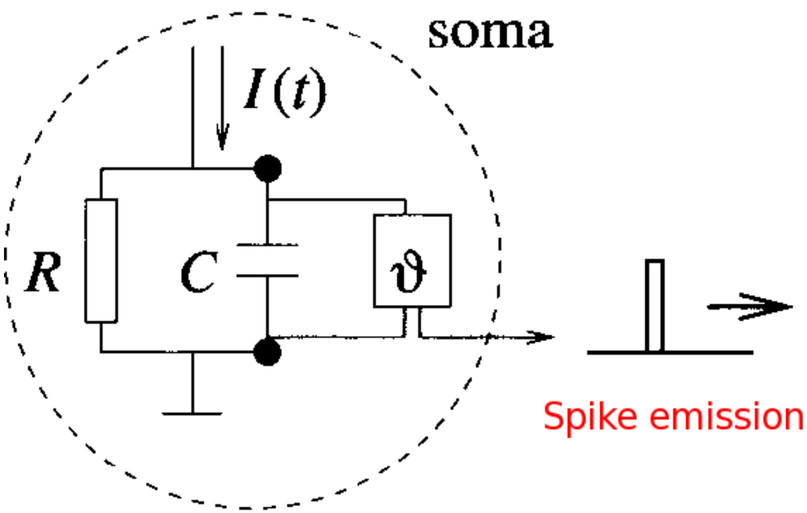
- Network of Leaky Integrate-and-Fire neurons with Short-Term Synaptic Plasticity
- Developing neuronal circuit → Excitatory cells
- Topology → Random (Erdös-Reniy) network (no scale free topology)
- Key Ingredients:
  - Developmentally regulated constraints on single neuron excitability and connectivity (Correlations)
- Dynamics
  - Population Bursts - Collective rhytmic oscillations

Results:

- Few critical neurons control the population activity - Functional Hubs
- Critical neurons are arranged into a clique

The Model

Leaky-integrate-and-fire neuron



$$\tau_m \dot{V}(t) = -V(t) + I(t) \qquad t < t_f \qquad (\tau_m = RC)$$

$$V(t_f^-) = \theta \quad \rightarrow \quad \text{spike emission} \quad \delta(t - t_f)$$

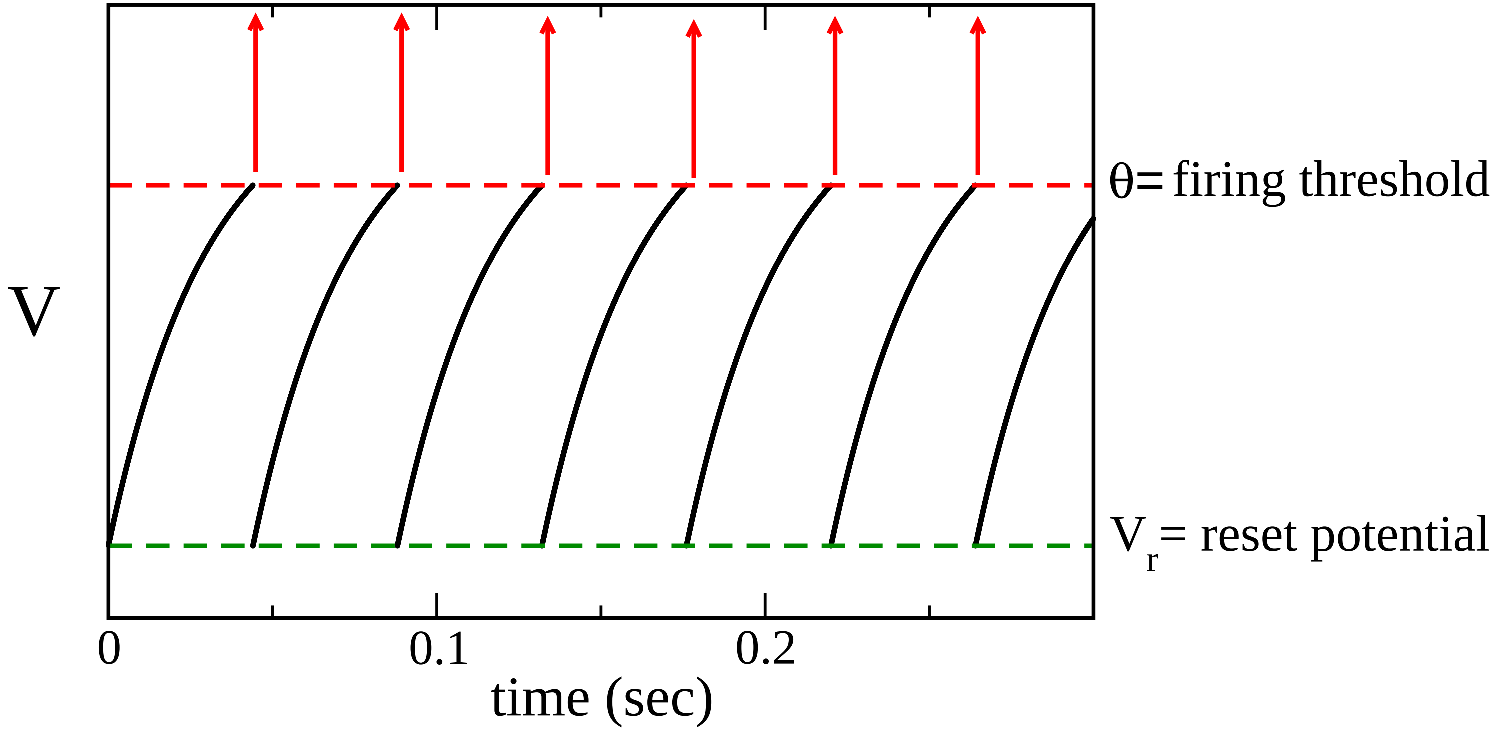
$$V(t_f^+) = V_r \quad \rightarrow \quad \text{resetting mechanism}$$

Parameters: $\tau_{\rm m} = 30$ ms, $V_{\rm r} = 13.5$ mV, $\theta = 15$ mV

Leaky-integrate-and-fire neuron

Response to a constant synaptic current

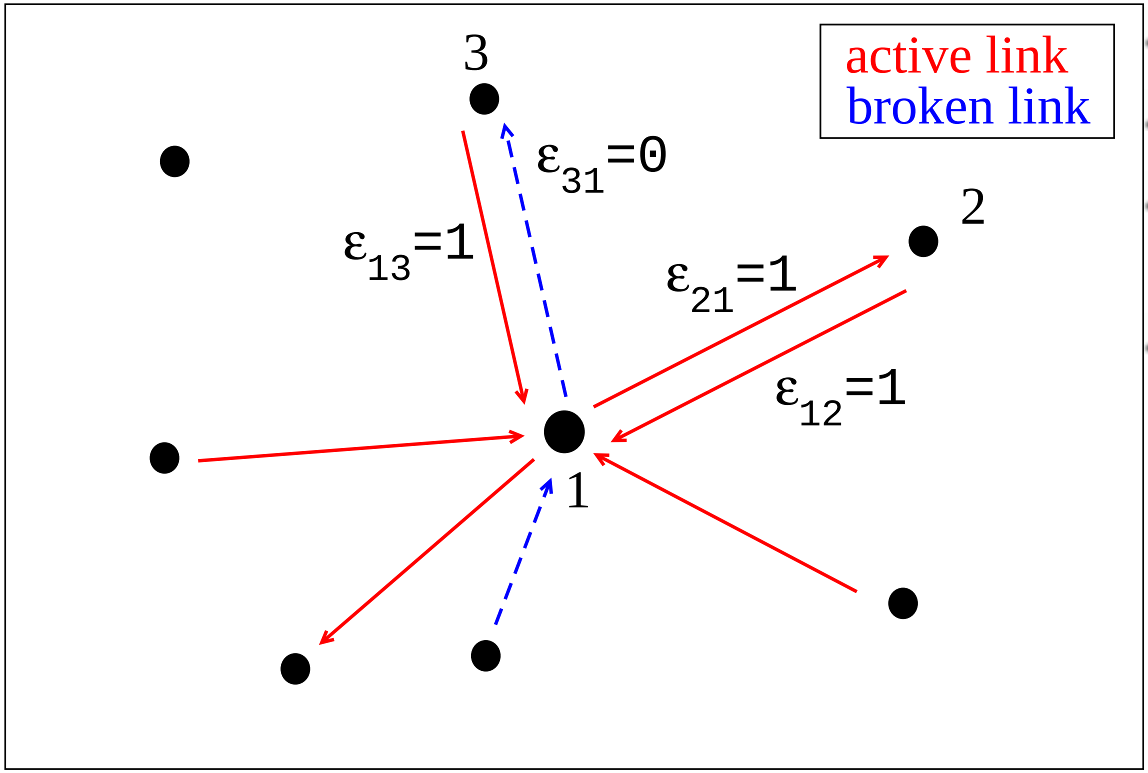
$$I(t)=I^b$$



$I^b > \theta$ ---> periodic firing

$I^b < \theta$ ---> silent neuron (no spikes!)

Directed Erdös-Rényi network



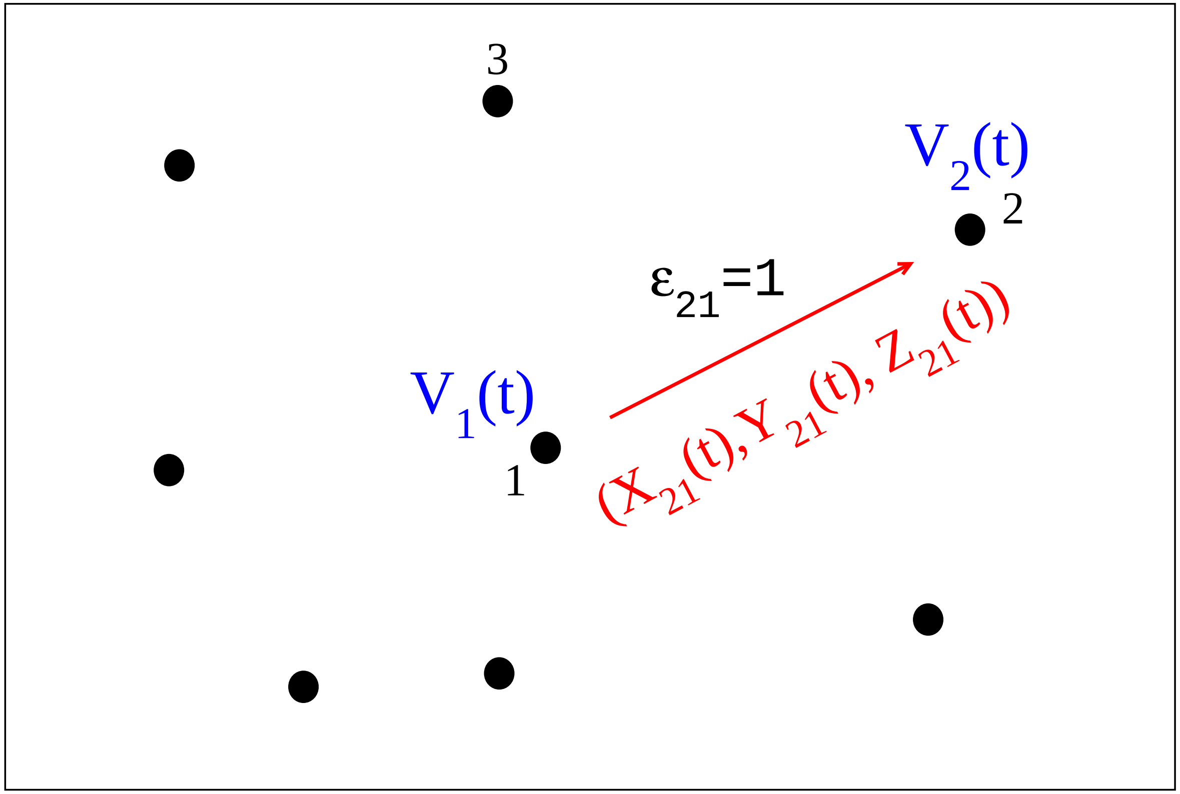
connection probability ---> p = 10 %

connectivity matrix ---> ε_{ij}

- K_i^I Input connectivity
- K_i^O Output connectivity
- $K_i^T = K_i^I + K_i^O$ Total connectivity
- On average $K^I = K^0 = p \times N$

Short-term synaptic plasticity

Tsodyks, Uziel, Markram (J. Neurosc. 2000) → T.U.M. model

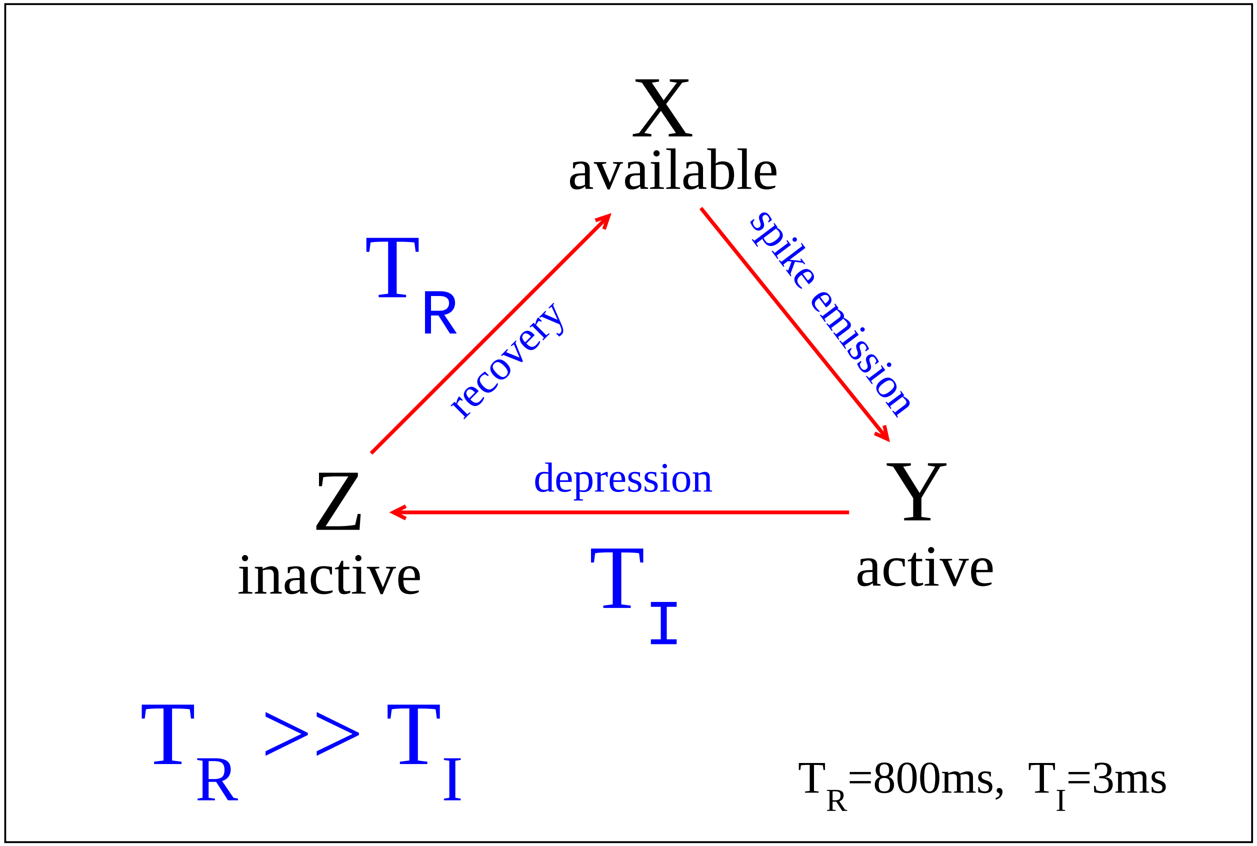


ε_{ij} ---> connectivity matrix

Mongillo, Barak, Tsodyks, Synaptic Theory of working memory, Science (2008)

Short-term synaptic depression

Dynamics of the synaptic resources



$$X + Y + Z = 1$$

The Complete Model

Network of N leaky integrate-and-fire neurons with short-term plasticity

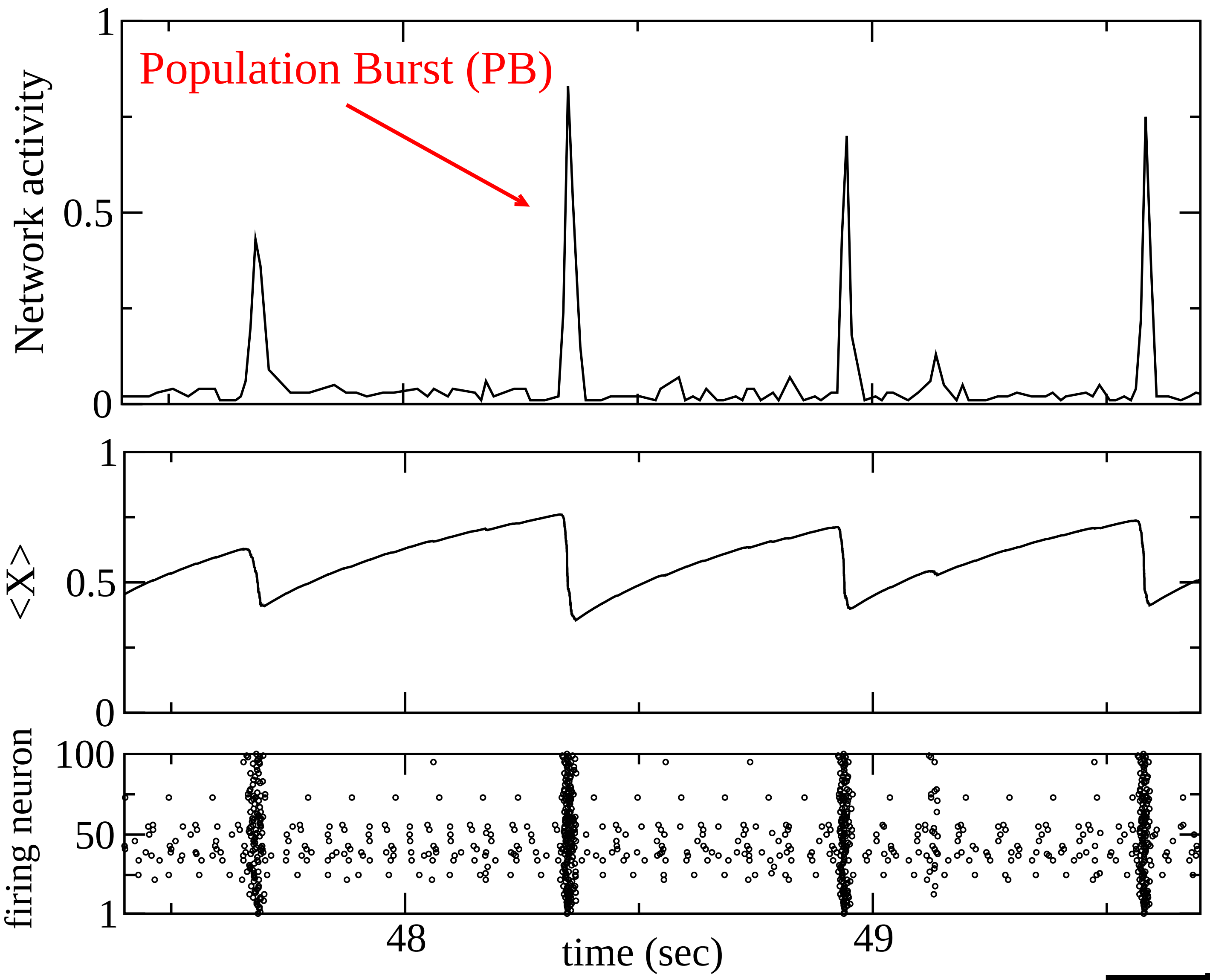
$$\tau_{\rm m}\dot{V}_i = -V_i + I_i^{\rm b} + \frac{G_i}{K_i^I}\sum_{j\neq i}\epsilon_{ij}Y_{ij} \rightarrow \text{ synaptic strengths modulated by } Y_{ij}$$

$$\dot{Y}_{ij} = -\frac{Y_{ij}}{T_{ij}^I} + u_{ij}X_{ij}\sum_m \delta(t - t_j(m)) \quad \rightarrow \text{ spike train}$$

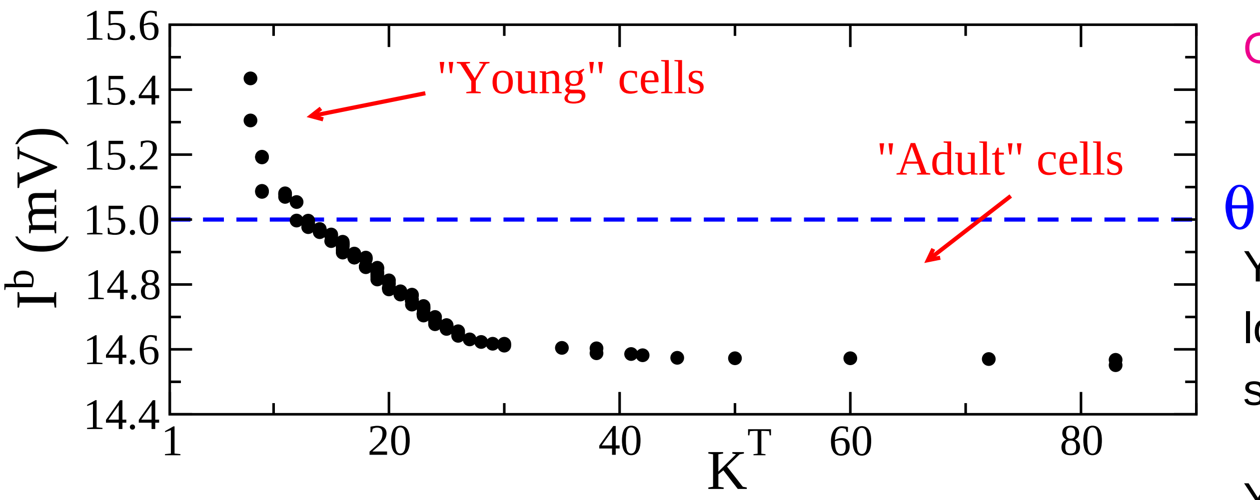
$$\dot{Z}_{ij} = \frac{Y_{ij}}{T_{ij}^{\rm I}} - \frac{Z_{ij}}{T_{ij}^{\rm R}} \qquad\qquad (X_{ij} + Y_{ij} + Z_{ij} = 1)$$

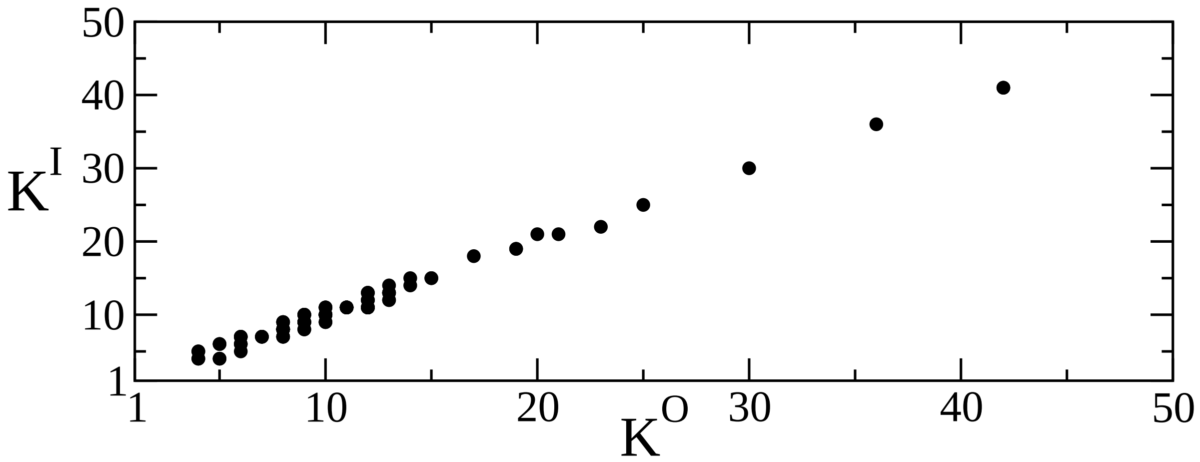
- Excitatory Neurons – $G_i > 0$
- I_i^b = intrinsic excitability $\rightarrow$ if $I_i^b > \theta$ neurons can fire even if isolated !
- The currents are measured in mV, since they incorporate the membrane input resistance

Typical dynamics



Developmentally regulated network





Our hypothesis:

Young (adult) cells have low (large) number of synapses K^T

Young cells are more excitable than adult ones

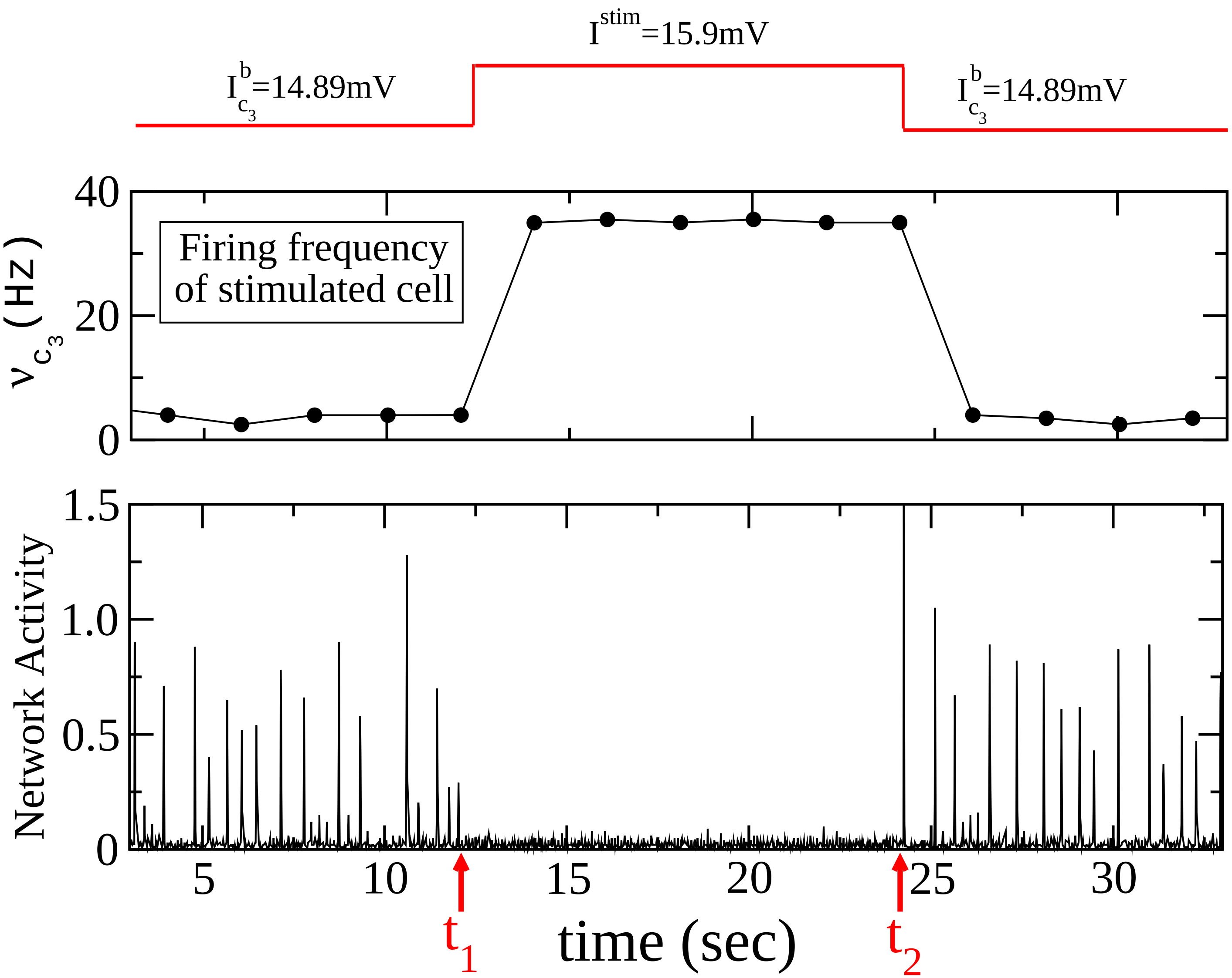
Number of afferent K^I and efferent K^O synapses are proportional

Ge et al, Nature (2005); Doetsch and Hen, Curr Op Neurob. (2005)
Karayannis at al, Frontiers neural circuits (2012)

Numerical Results

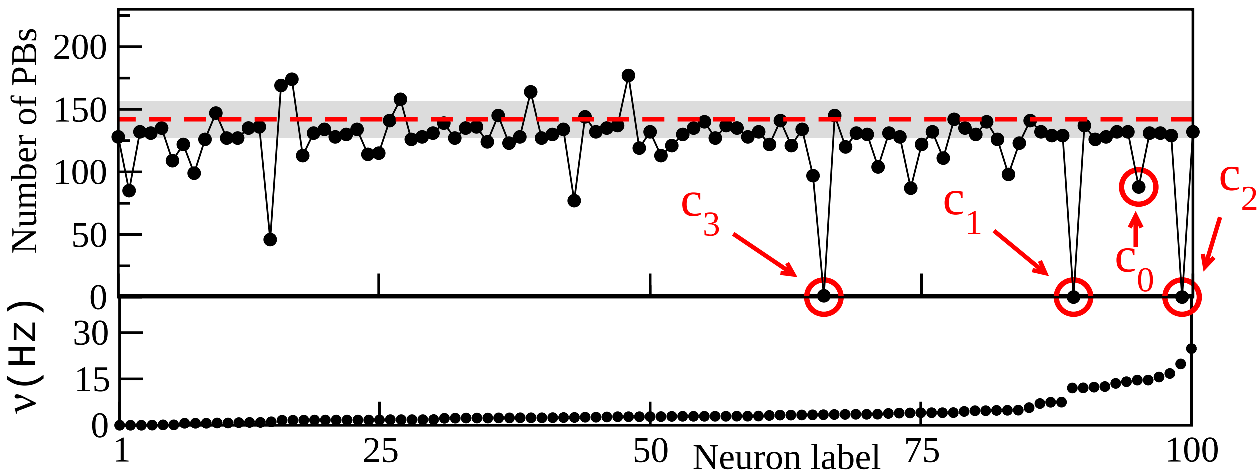
- Single Neuron Stimulation (SNS)
- Single Neuron Deletion (SND)

Single neuron stimulation

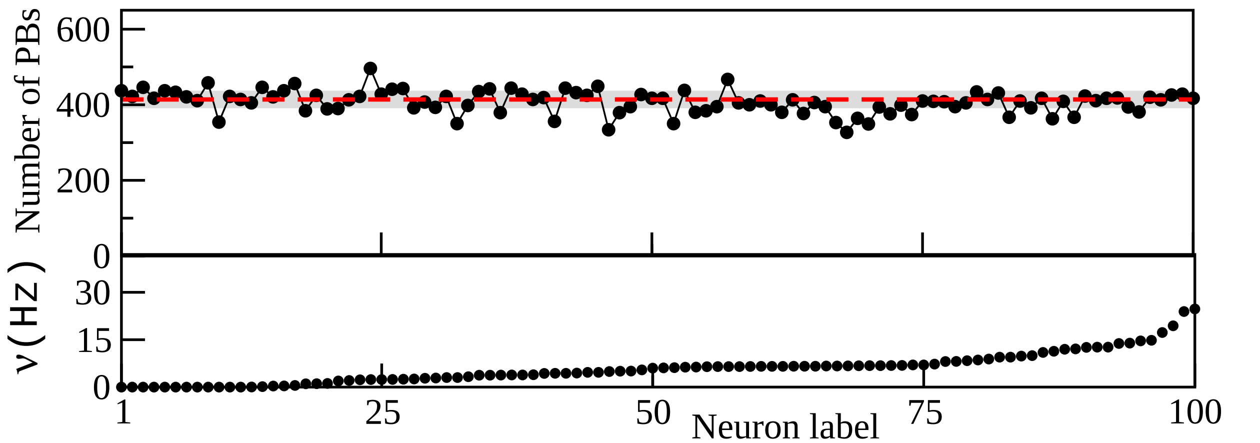


Single neuron stimulation

Network with correlations

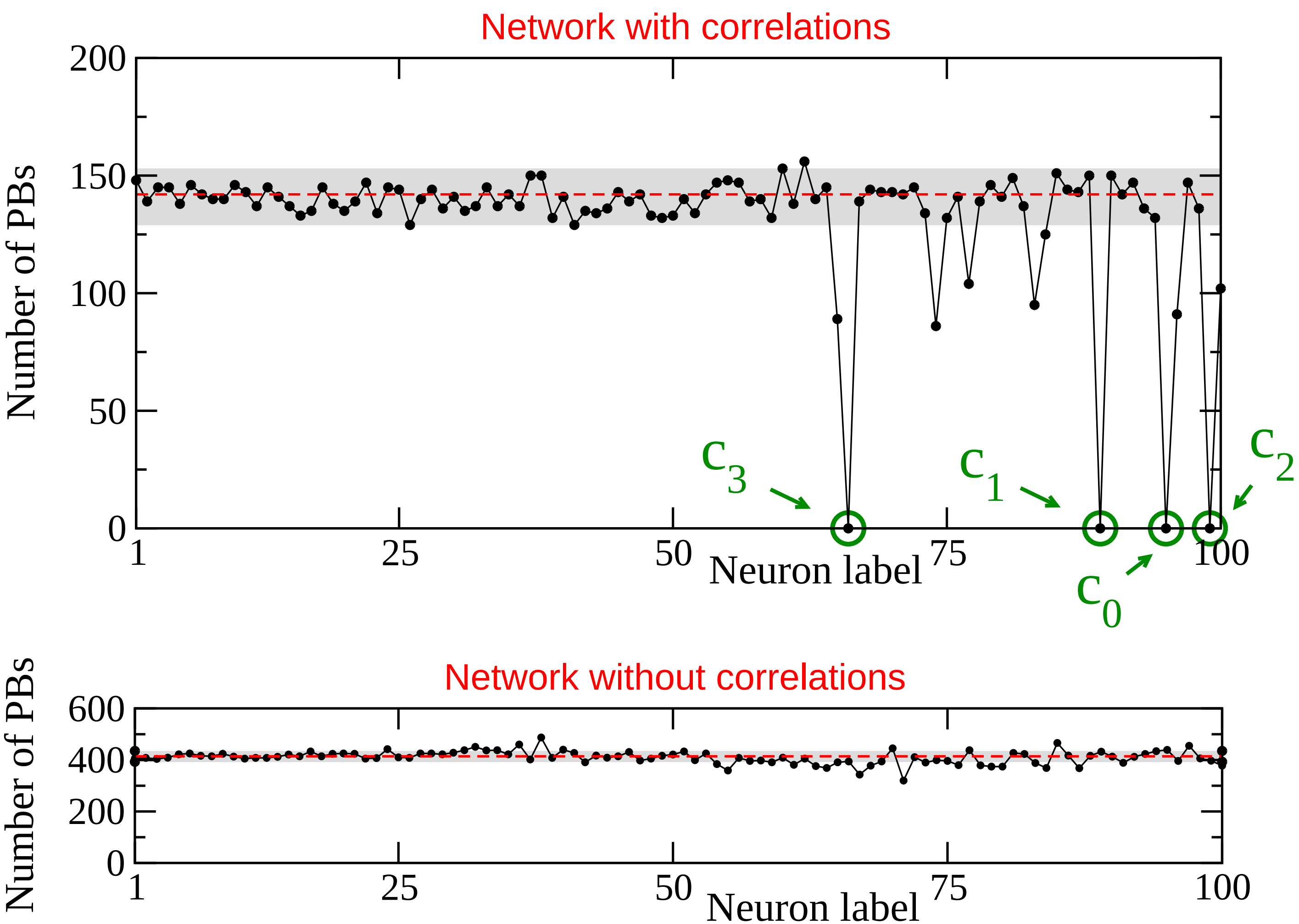


Network without correlations



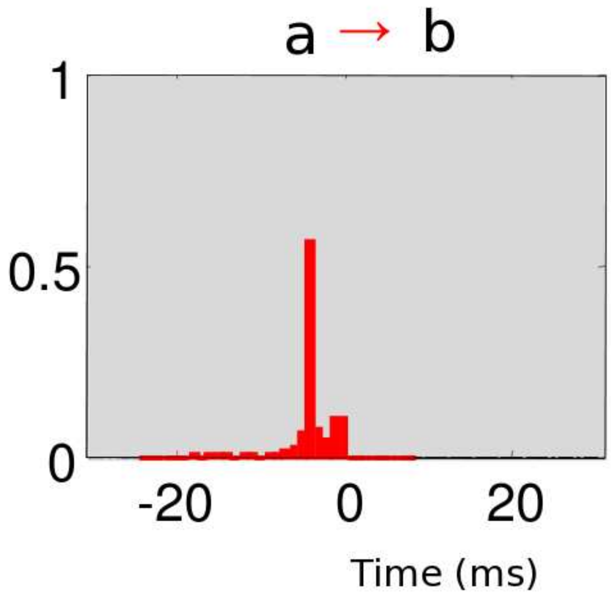
Neurons are ordered according to their firing rate ν under control conditions

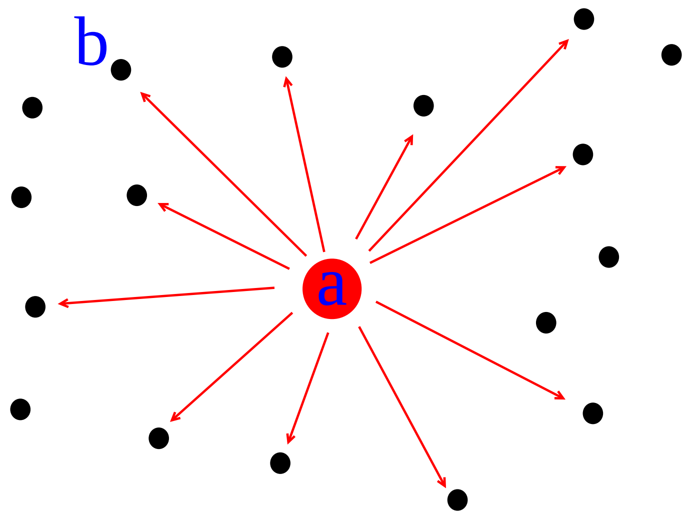
Single neuron deletion



Functional Connectivity analysis

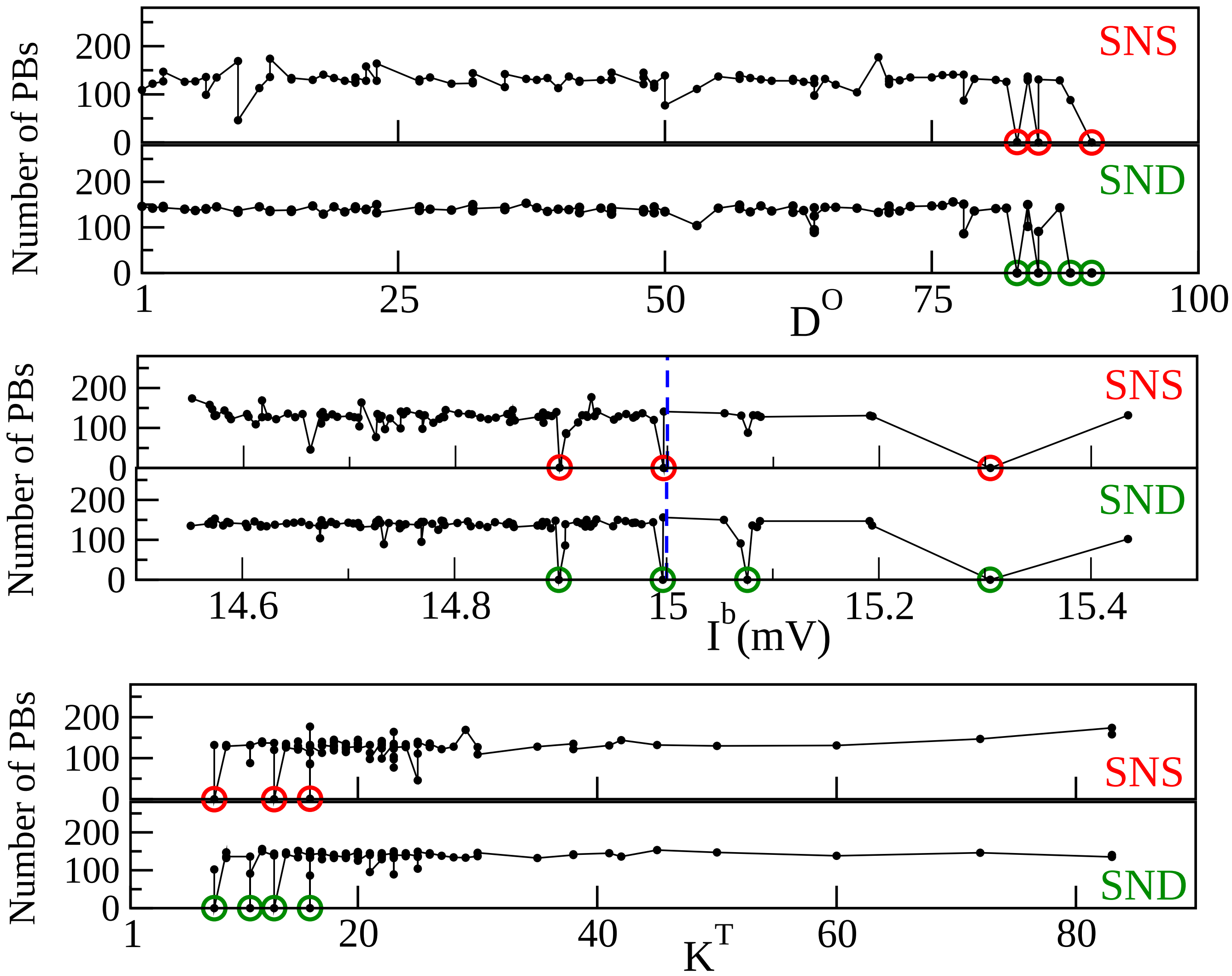
Assignment of a functional degree to each cell of the network





D_a^o=functional out-degree of cell $a \longrightarrow$ number of cells activated after its firing

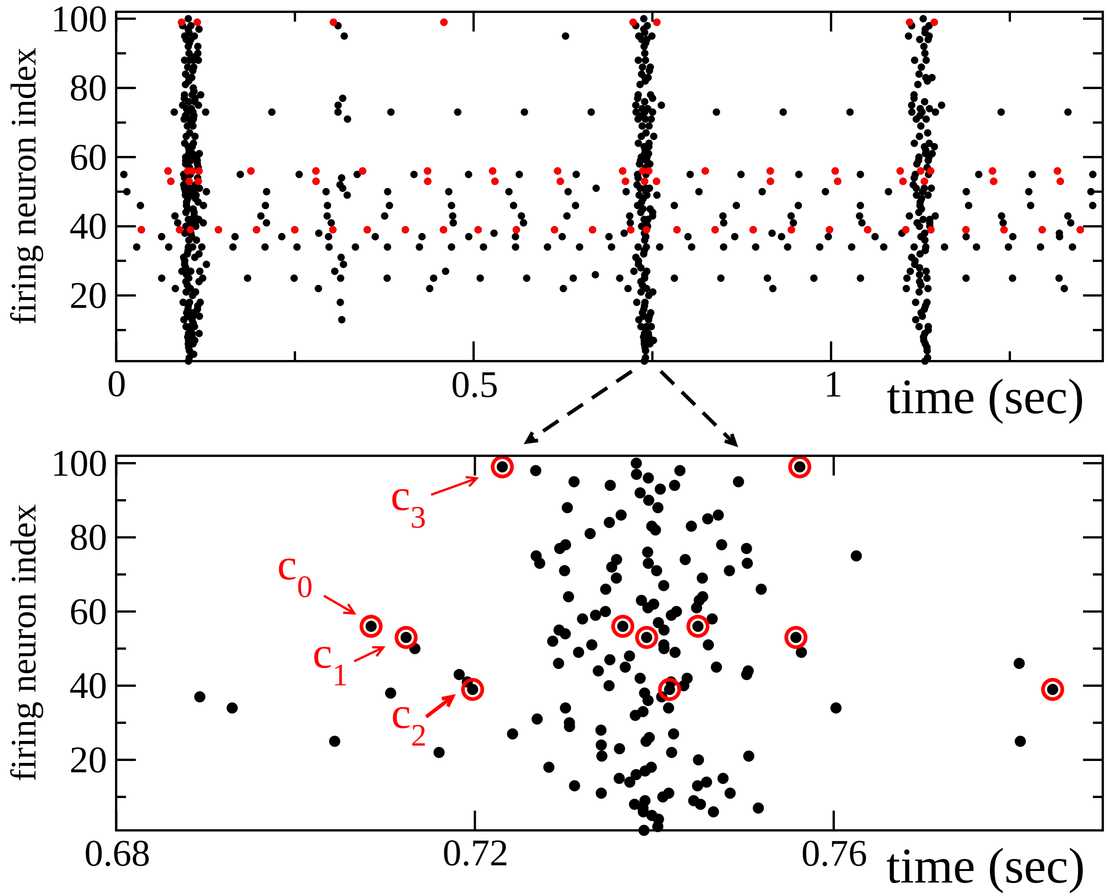
Properties of critical neurons



The functional clique

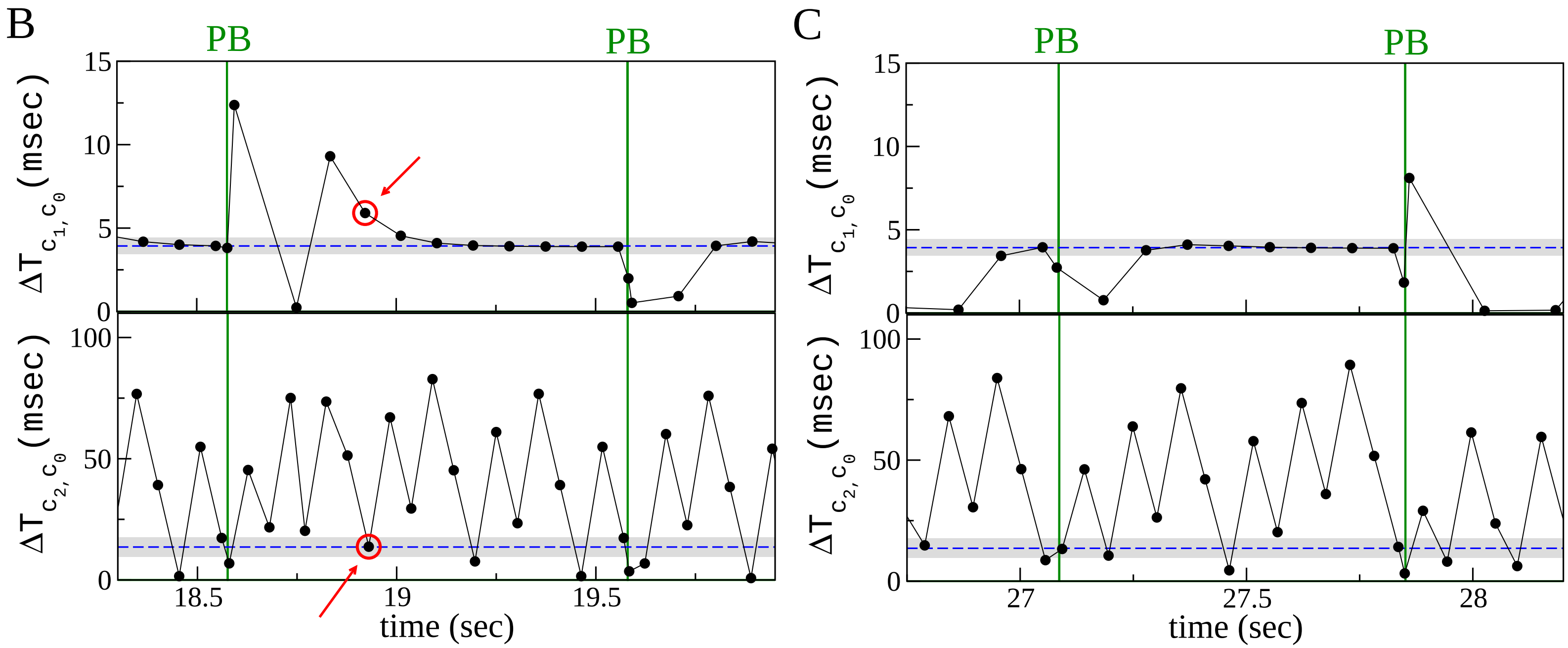
Population Burst build up

Population bursts are anticipated by the sequence $c_0 \to c_1 \to c_2 \to c_3$



$$\Delta T_{c_1,c_0} = 3.94 \pm 0.5\text{ms} \quad \Delta T_{c_2,c_1} = 9.6 \pm 3.3\text{ms} \quad \Delta T_{c_3,c_2} = 3.3 \pm 1.0\text{ms}$$

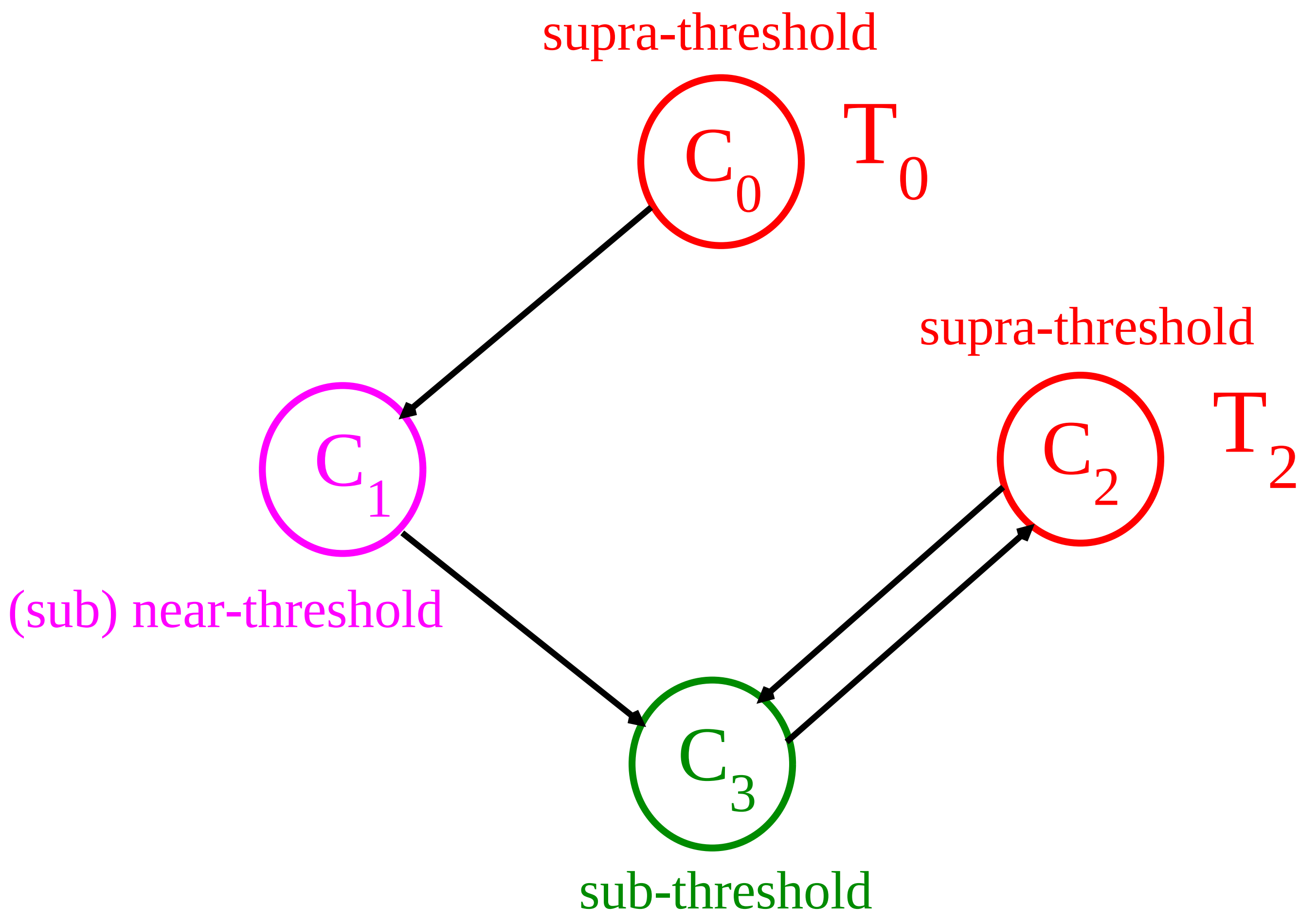
Failures and successes in PB build-up



- c_1 fires almost always with a fixed time delay after c_0, apart just after PB emission
- c_2 fires quite independently with respect to c_1 (c_2 has his own evolution)

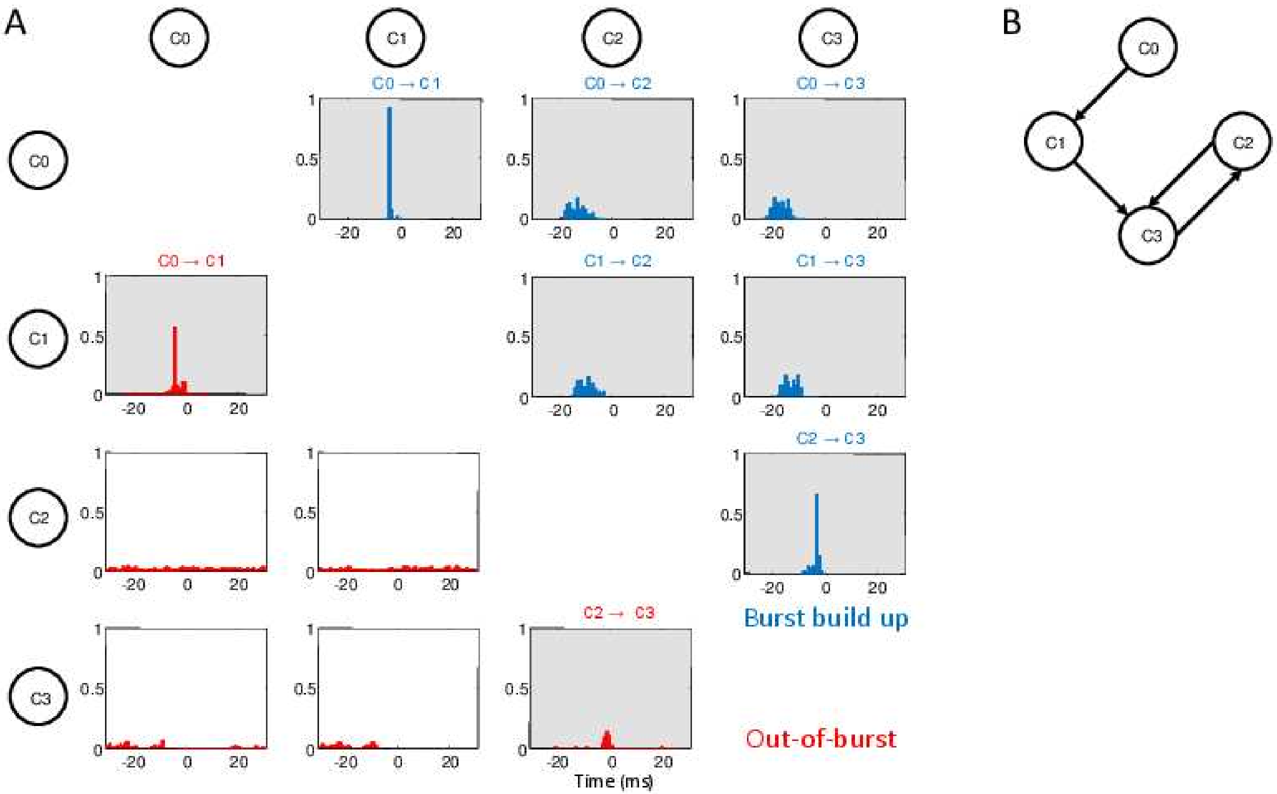
The functional clique

“Clocks“ and ”Followers“

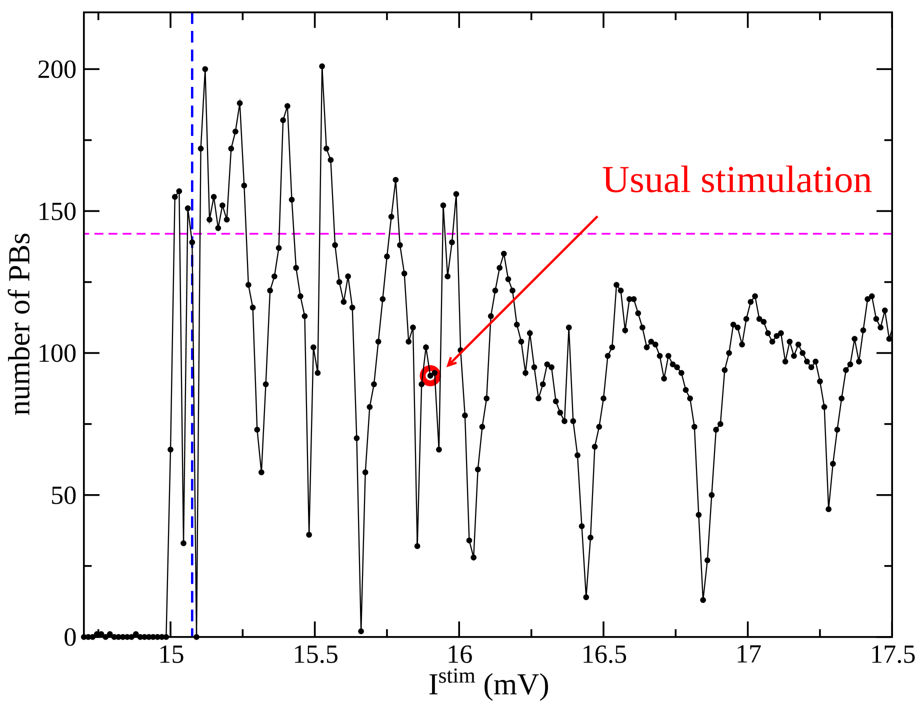


The mechanism

- c_1 follows the firing of c_0 (also out of burst)
- c_3 follows the firing of c_2 (also out of burst)
- No structural connections among the two “clocks” c_0 and c_2
- Only when the two “clocks” fire unsupervised in the correct order and in a precise time sequence the PB can occur ($\Delta T_{c_2 c_0} \simeq 15 ms$)

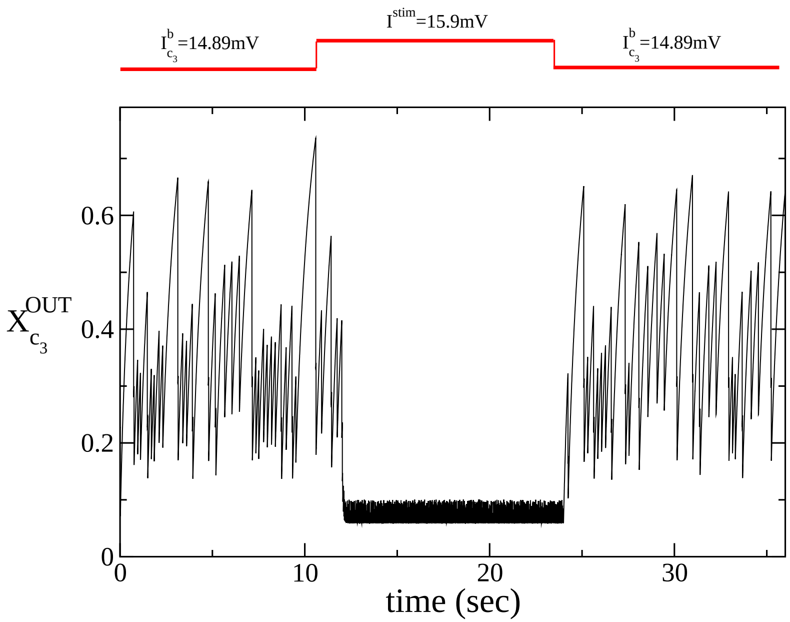


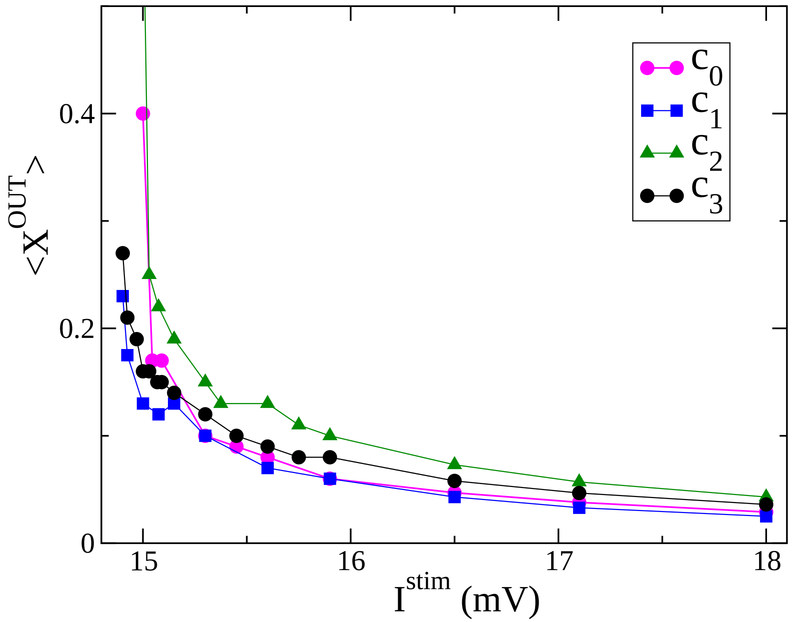
Stimulating the clique leader c_0



- Minima in the PB activity (antiresonances) correspond to mode locking
  - The periods of the two "clocks" c_0, c_2 are related $\boxed{mT_0 = nT_2}$
  - The possibility that they fire with the required delay by chance goes almost to zero
- The number of PBs decreases with I^{stim}

The role of plasticity

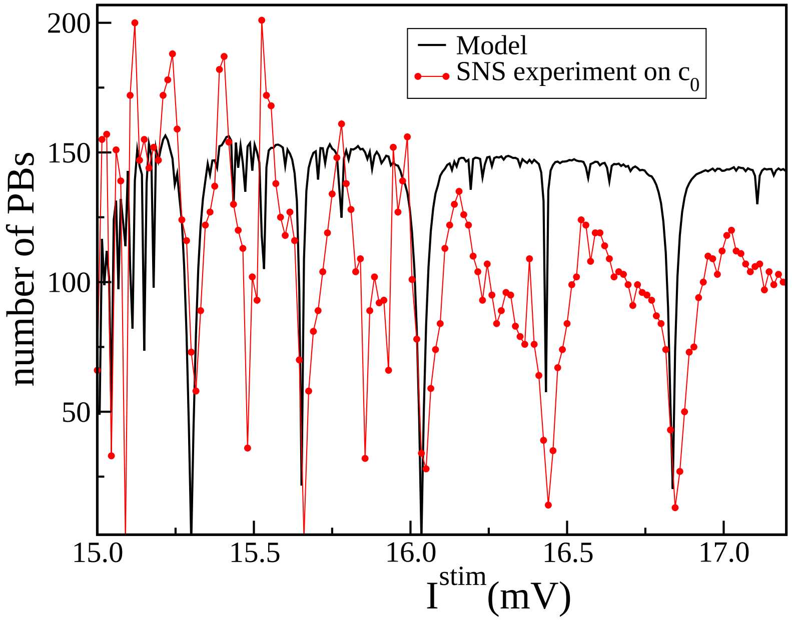




$$X_i^{OUT} = \frac{1}{K_i^O} \sum_{k \neq i} \epsilon_{ki} X_{ki}$$

The afferent synapses are depressed by increasing the stimulation and this explains the decrease in the number of PBs with I^{stim}, but this does not explain antiresonances

A simple model



We have developed a simple model to reproduce the stimulation experiment on c_0

- c_0 and c_2 are two independent LIF neurons suprathreshold
- The emission of a PB is probabilistic process controlled by the synaptic depression, $\mathcal{P}(I^{stim}) \propto \langle X_{c_0}^{OUT} \rangle$

A PB is emitted whenever the following 2 conditions are fulfilled

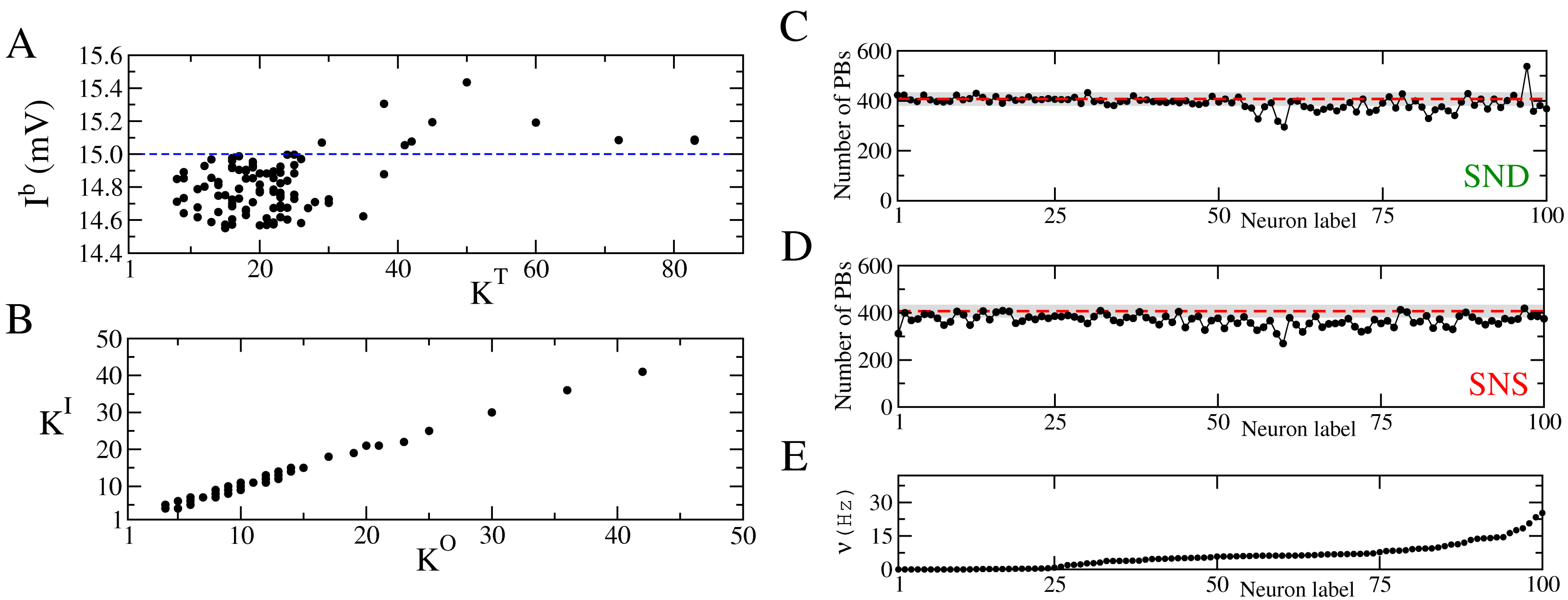
- c_2 fires after c_0 with a time delay $\Delta T_{c2,c0}$
- an extracted random number $r < \mathcal{P}(I^{stim})$

This extremely simplified model reproduces more than 70% of the antiresonances

Other correlation setups

- setup T1: positive correlation between the in-degree and out-degree of each neuron;
- setup T2: negative correlation between the intrinsic neuronal excitability and the total connectivity (in-degree plus out-degree);
- setup T3: positive correlation between the intrinsic neuronal excitability and the total connectivity (in-degree plus out-degree).

Correlated networks with all possible combinations of the setups T1-T3 have been examined, only the networks with correlations T1 + T2 show sensitivity to SNS and SND



Conclusions

- We considered a developmentally regulated neural network
- We have found that :
  - single neuron stimulation/deletion of a few critical neurons is able to strongly impact the bursting activity
  - critical neurons are functional hubs
  - critical neurons are arranged in a clique controlling the neuronal activity
    - the clique is composed by “clocks” and “followers”
    - their ordered activations is required for the generation of a burst
    - the activation of the “clocks” is not mediated by structural connections
  - the synaptic resources regulate the interburst period, but they are not the key element for PB occurrence

We have verified the validity of our findings for other 6 realizations of the neural network

S.Luccioli, E. Ben-Jacob, A. Barzilai, P. Bonifazi, AT,
PLOS Computational Biology (2014)

Open problem & Future developments

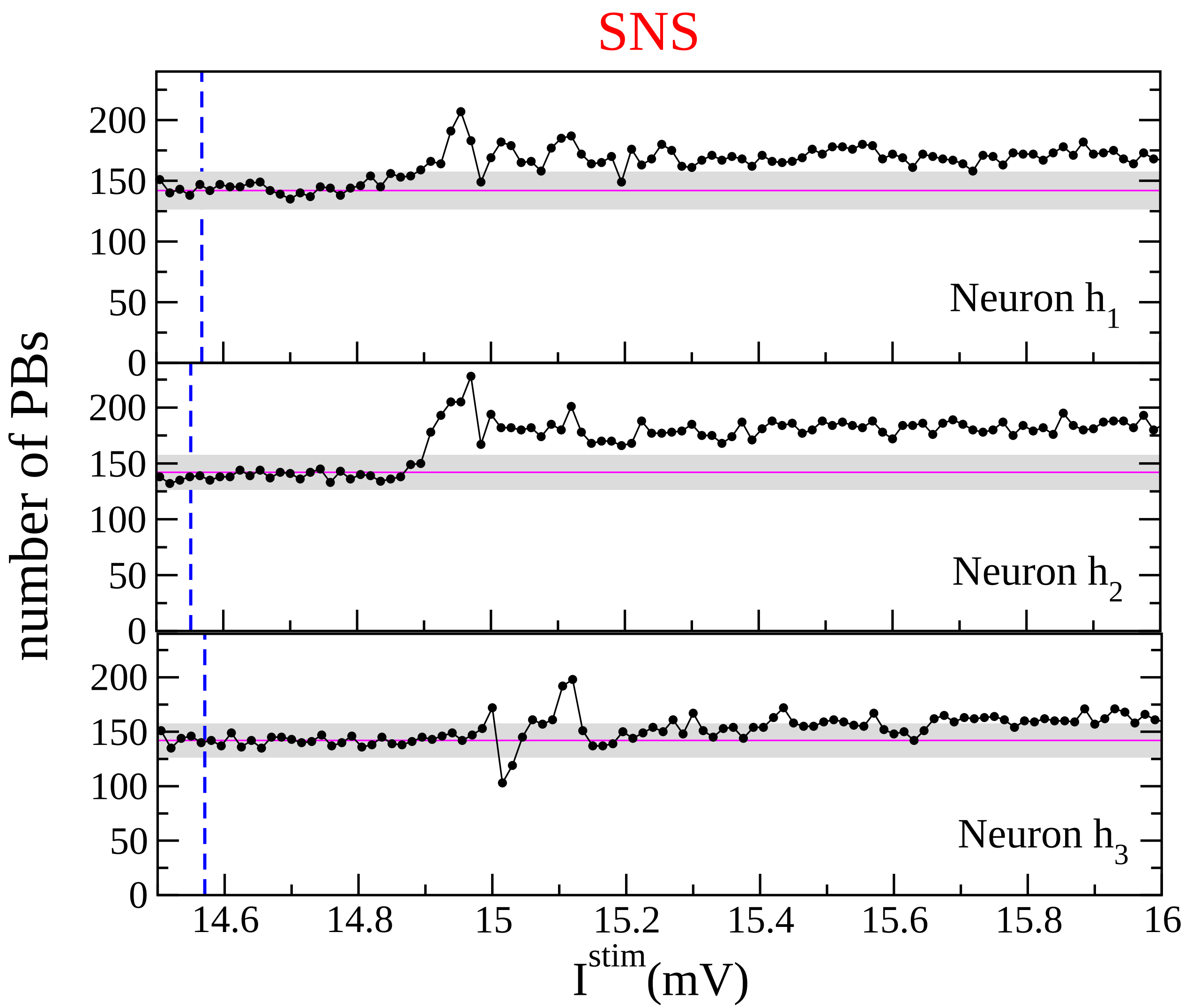
- The grandient of the excitability can be explained by assuming a less depolarizing action of GABAergic transmission on mature cells with respect to younger ones ?
- Some of our findings can be experimentally tested ?
  Antiresonances — Sequential Activation of Neurons
- What will change with scale-free topologies ?
- These results can be of interest for network controllability
  Liu, Slotine, Barabasi, Nature (2011); Menichetti, Dall'Asta Bianconi, PRL (2014)

Correlations are fundamental

Menichetti, Dell'Asta, Bianconi, Phys. Rev. Lett 113 (2014) 078701

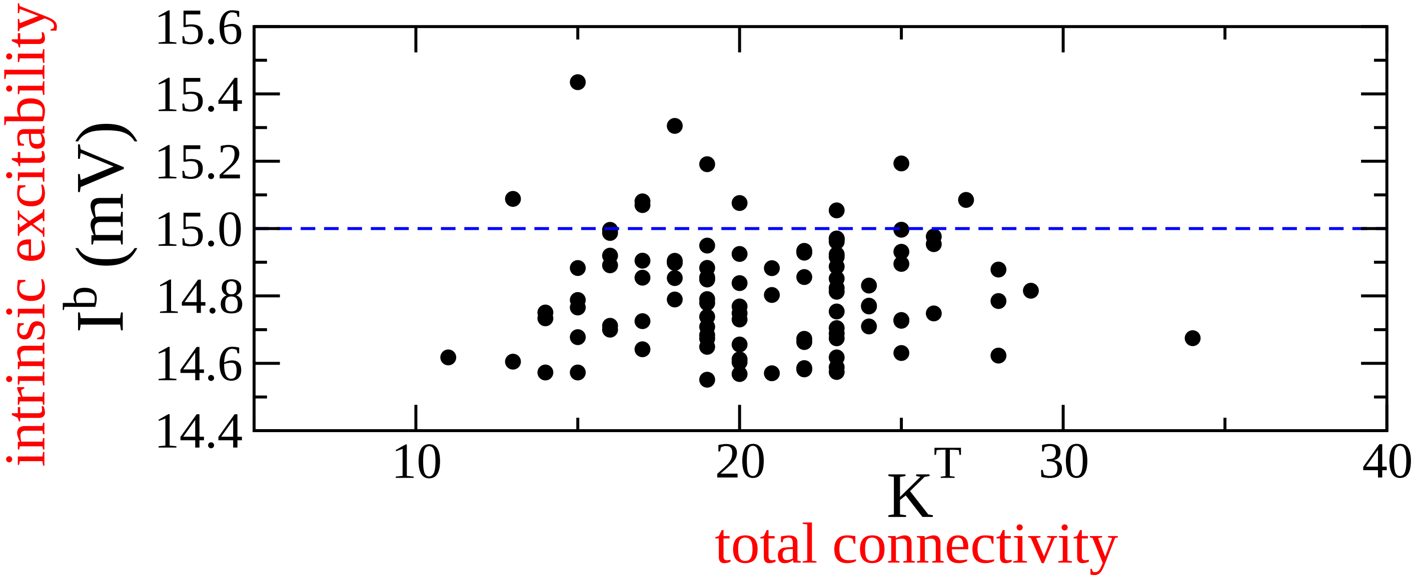
- Driver nodes N_D can bring the network to any desidered dynamical state if a external signal is applied to them;
- In an uncorrelated directed random network $N_D \equiv 0$ if $K^{IN}, K^{OUT} > 2$
- Structural and Dynamical Correlations can change all the story
- The studied model is linear $\dot{\mathbf{x}} = A\mathbf{x} + B\mathbf{u}$

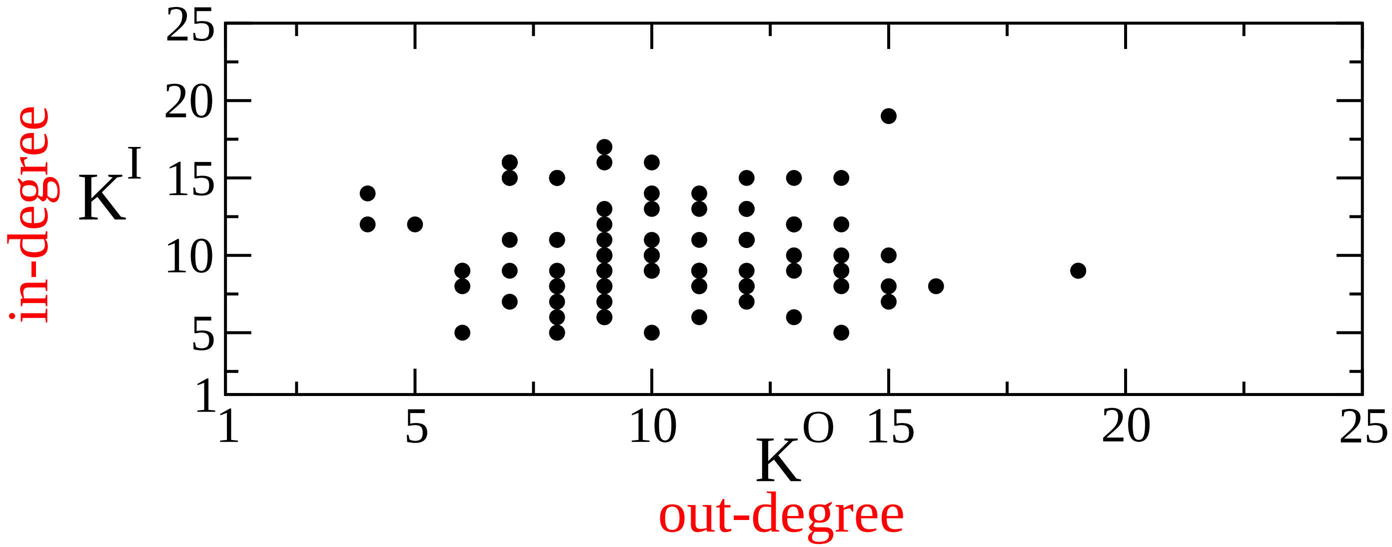
Role of structural hubs



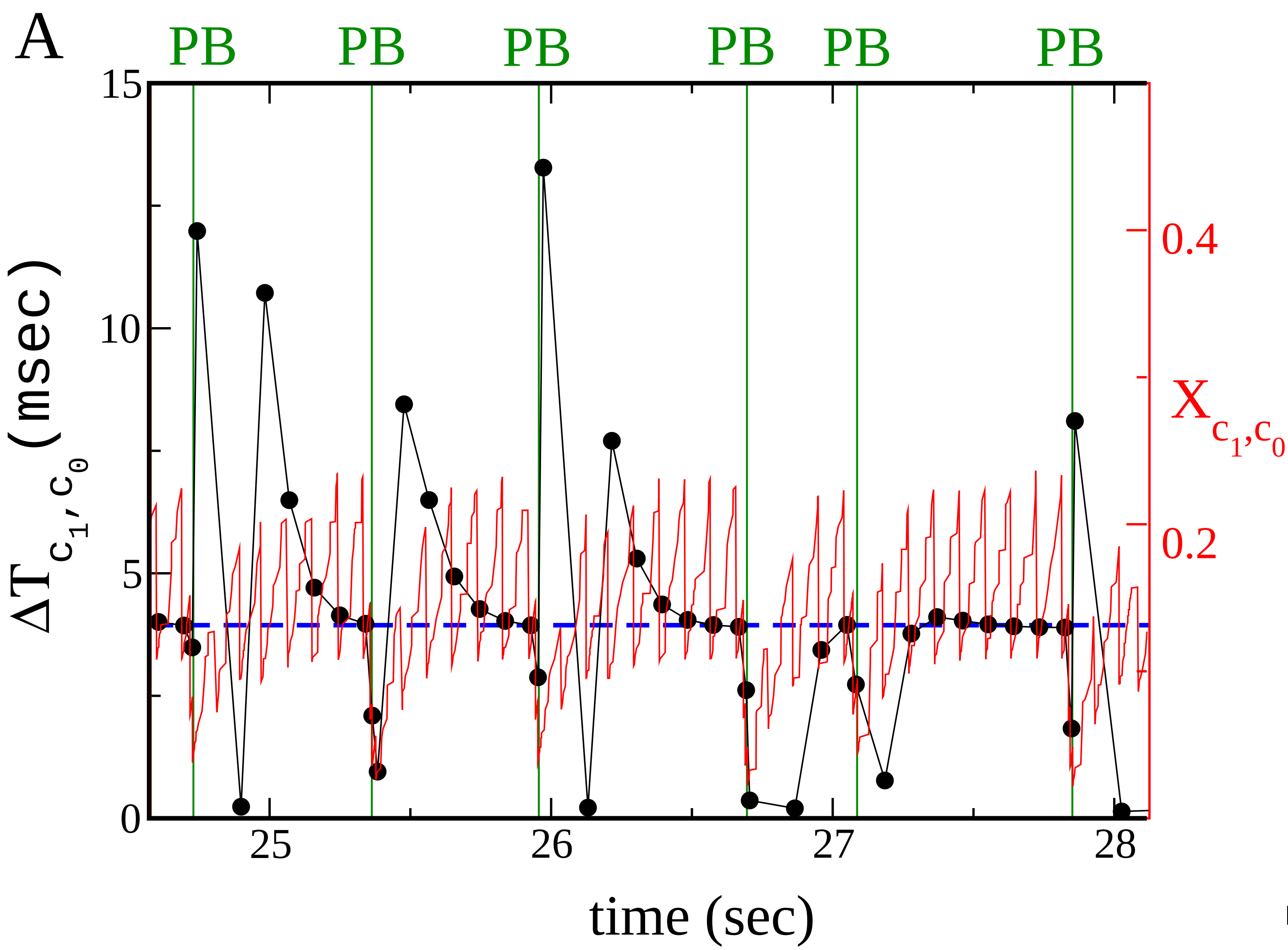
Three neurons have $K^T > 60$ in the network

Network without correlations

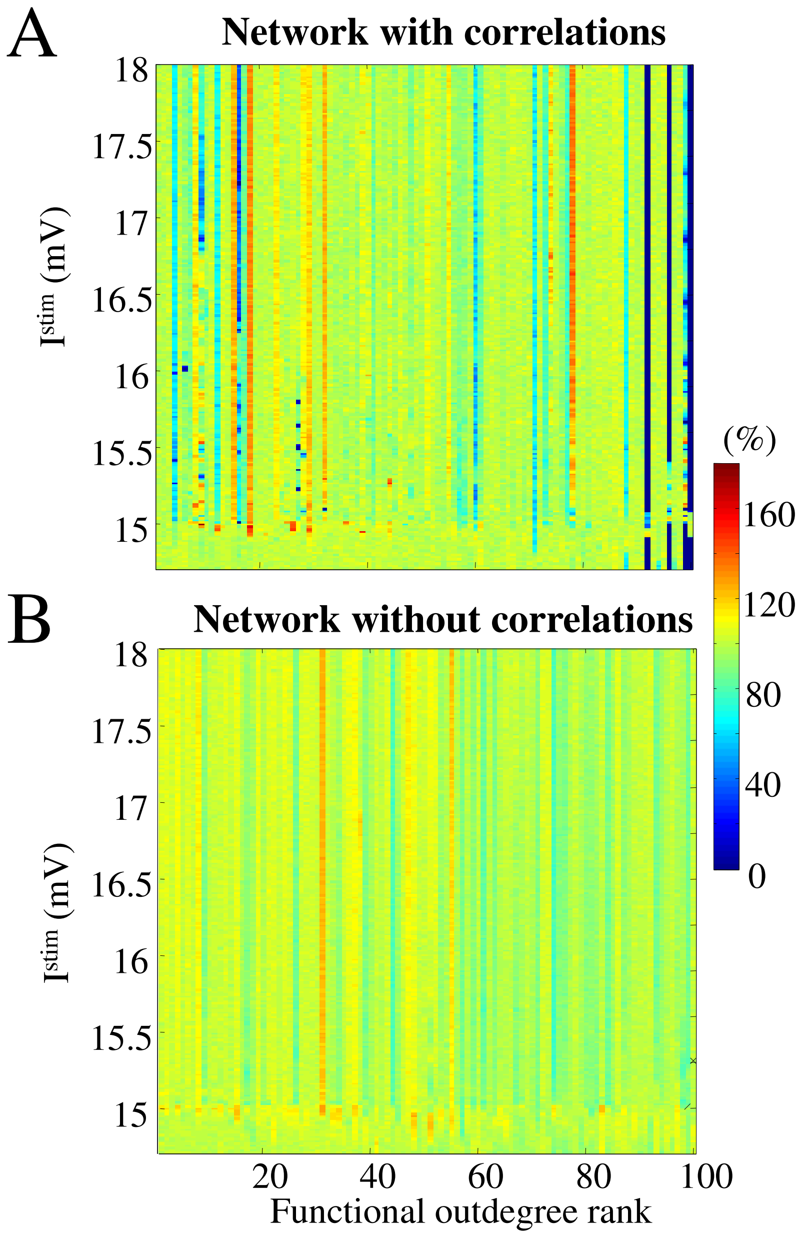




Synaptic strength and firing time delay

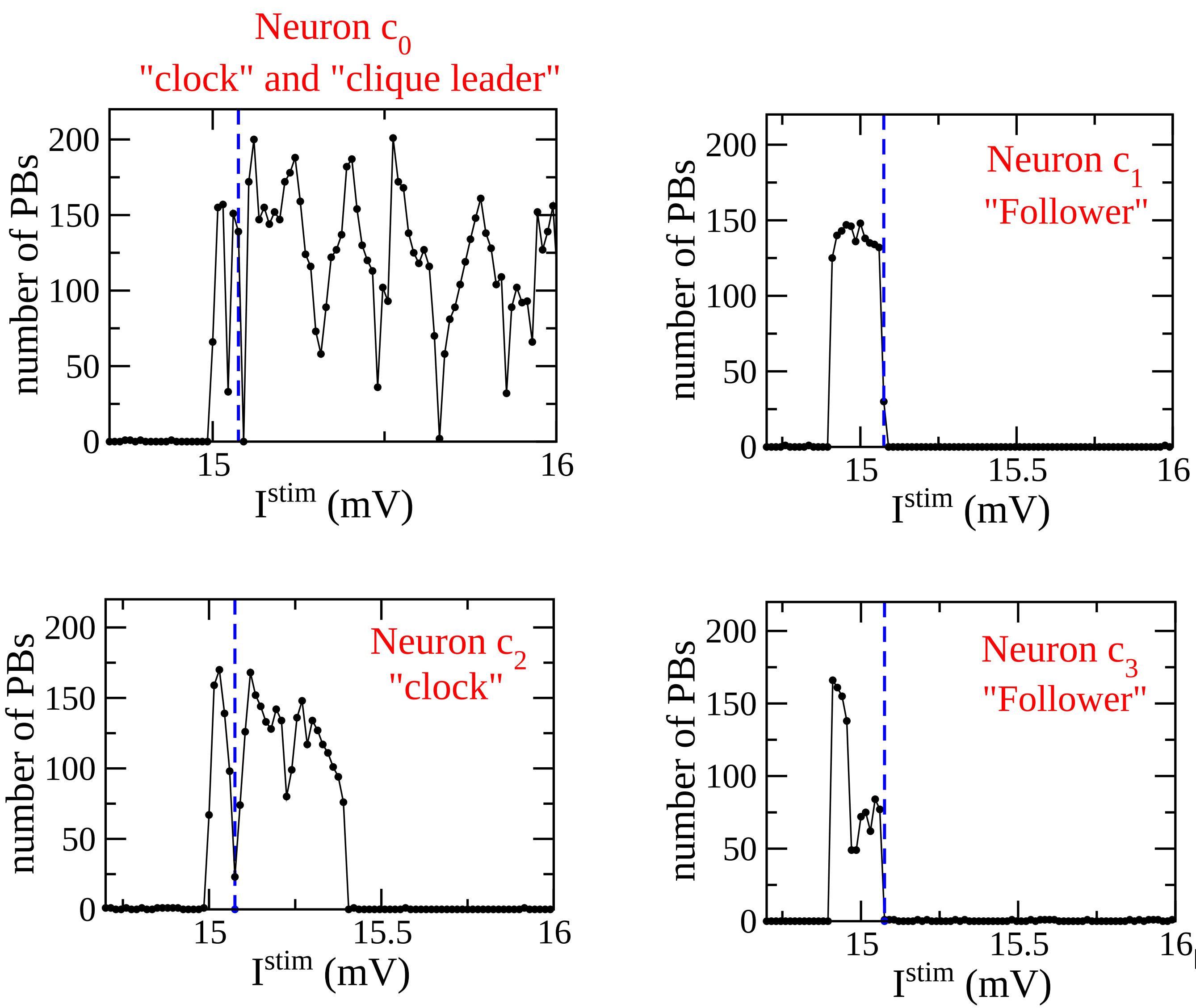


Extensive single neuron stimulation



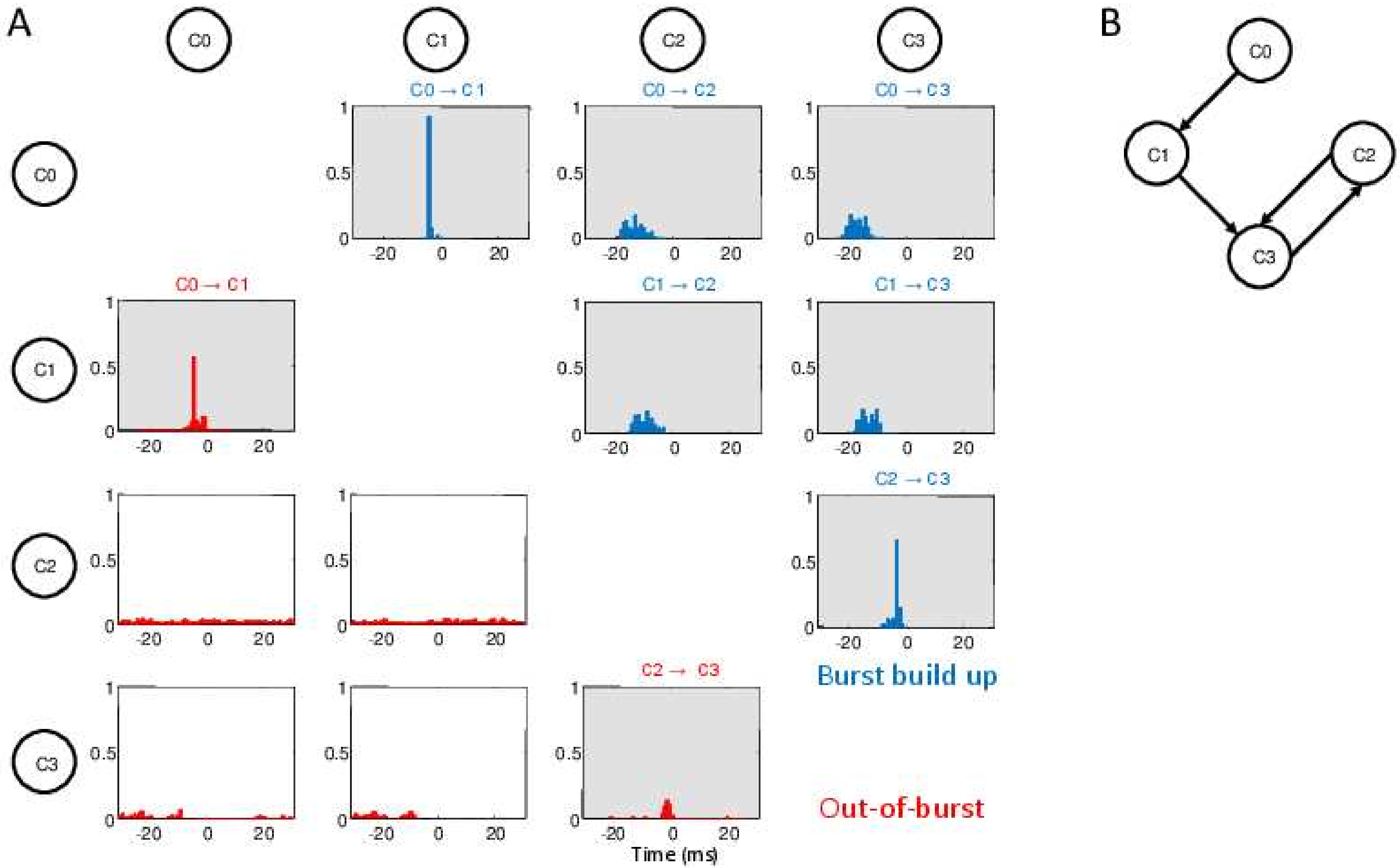
SNS of the critical neurons

Windows of bursting activity

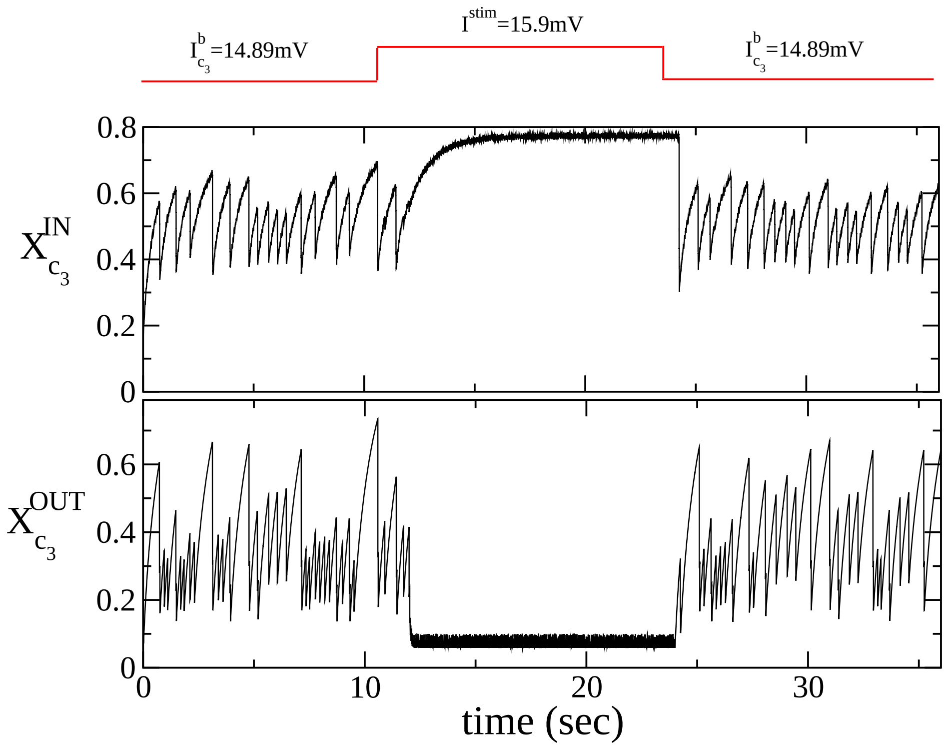


The functional clique - 3

Cross-correlation analysis of the out-of-burst and of the PB build up firing times



The role of plasticity



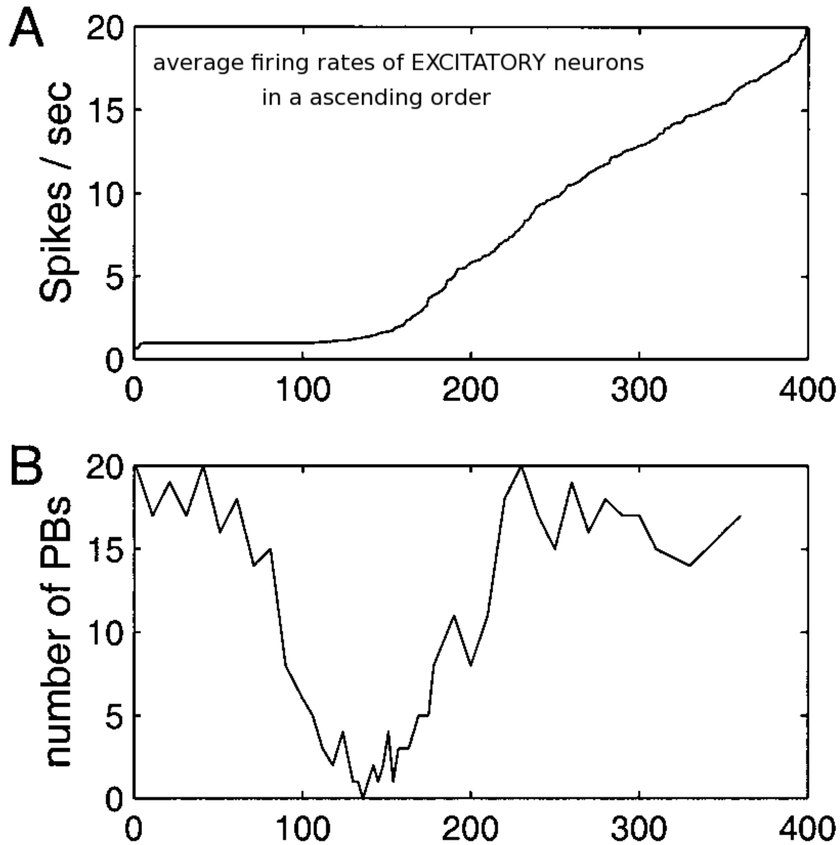
$$X_i^{OUT} = \frac{1}{K_i^O} \sum_{k \neq i} \epsilon_{ki} X_{ki} \quad ,$$

$$X_i^{IN} = \frac{1}{K_i^I} \sum_{j \neq i} \epsilon_{ij} X_{ij}$$

Comparison with TUM experiment

N_{exc}=400, N_{inh}=100

Groups of 30 neurons taken out of the network (TUM, J. Neurosc. 2000)



Collective Effect

Functional Connectivity

- Introduction of binary time series with one millisecond time resolution, where ones (zeros) marked the occurrence (absence) of the action potentials.
- Given the binary time series of two neurons $\{a_t\}$,$\{b_t\}$, the cross correlation was:

$$C_{ab}(\tau) = \frac{\sum_{t=\tau}^{T-\tau} a_{t+\tau} b_t}{min(\sum_{i=1}^{T} a_i, \sum_{k=1}^{T} b_k)}$$

where T was their total duration.

- Whenever $C_{ab}(\tau)$ presented a maximum at some finite time value τ_{max} a functional connection was assigned between the two neurons: for $\tau_{max} < 0$ ($\tau_{max} > 0$) directed from a to b (from b to a).
- A directed functional connection cannot be defined for an uniform cross-correlation corresponding to uncorrelated neurons or for synchronous firing of the two neurons associated to a Gaussian $C_{ab}(\tau)$ centered at zero.
- To exclude the possibility that the cross correlation could be described by a Gaussian with zero mean or by a uniform distribution we employed both the Student´s t-test and the Kolmogorov-Smirnov test with a level of confidence of 5%.
- The functional out-degree D_i^O (in-degree D_i^I) of a neuron i corresponds to the number of neurons which were reliably activated after (before) its firing.