# Breakdown of spatial coding and neural synchronization in epilepsy using a computational model

S. Chavlis[1,2], I. Pandi[2,3], T. Shuman[4], D. Aharoni[5], D. Cai[4], P. Golshani[5], P. Poirazi[2]

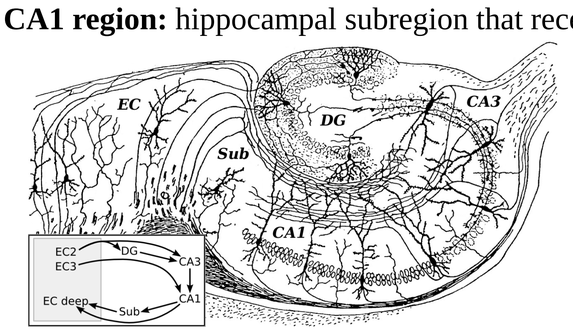
[1]Institute of Computer Science, Foundation for Research and Technology Hellas, Heraklion, Greece
[2]Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology Hellas, Heraklion, Greece
[3]School of Medicine, University of Crete, Heraklion, Greece
[4]Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, USA
[5]Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, USA

## ABSTRACT

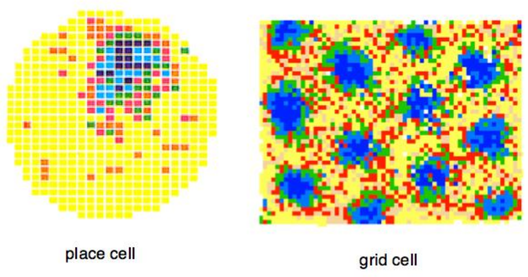
Temporal lobe epilepsy causes significant cognitive deficits in both humans and rodents, yet the specific circuit mechanisms underlying these deficits remain unknown. There is profound and selective interneuron death and axonal reorganization within the hippocampus of both humans and animal models of temporal lobe epilepsy. To assess the specific contribution of these mechanisms on spatial coding, we developed a biophysically constrained network model of the CA1 region that consists of different subtypes of interneurons. The tuning properties of these cells are very similar to the ones observed experimentally in awake, behaving animals. To examine the role of interneuron death and axonal reorganization in the formation and/or tuning properties of place fields we selectively varied the contribution of each interneuron type and desynchronized the two excitatory inputs. We found that desynchronized inputs were critical in reproducing the experimental data.

## INTRODUCTION

- **Place cell /Place field:** A place cell is a pyramidal neuron within the hippocampus that is activated when an animal enters a particular location in its environment which is known as the place field.
- **CA1 region:** hippocampal subregion that receives information from both CA3 and EC layer III.



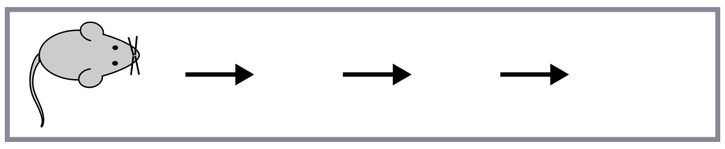

Santiago Ramón y Cajal (1911) [1909] Histologie du Système nerveux de l'Homme et des Vertébrés, Paris: A. Maloine




**AIM: Unravel the underlying mechanisms of memory deficits under epileptic conditions**

## Simulation paradigm

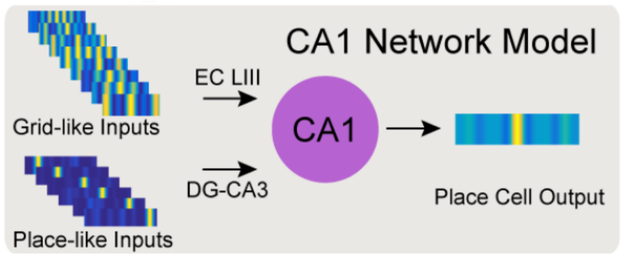
- Ten virtual animals were simulated
- 10 runs per virtual animal
- The animals had a constant speed with [0,10] random stops



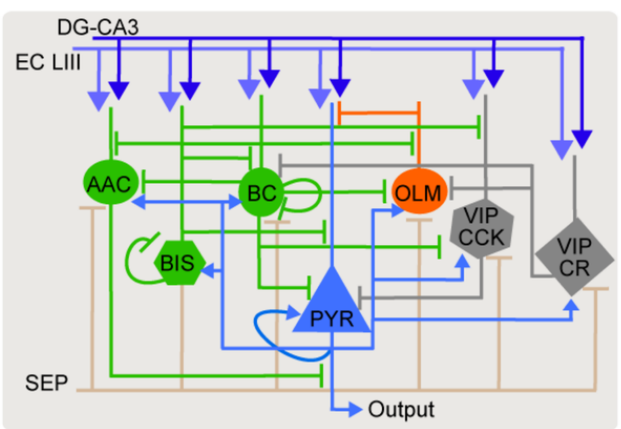
## Quantification metrics

$$I = \sum_{i=1}^{N} p_i \frac{\lambda_i}{\bar{\lambda}} \log_2 \frac{\lambda_i}{\bar{\lambda}}, p_i = \frac{t_i}{\sum_{i=1}^{N} t_i}, \bar{\lambda} = \sum_{i=1}^{N} p_i \lambda_i$$

- Spatial information
- Stability
- Peak firing rate
- Size of the place field




- A model of CA1[1,2] is implemented containing seven major neuronal types; pyramidal cells, basket cells, bistratified cells, axoaxonic cells, OLM cells, VIP/CCK cells and VIP/CR cells.
- 130 PCs, 8 BCs, 2 BSCs, 2 OLMs, 2 AACs, 1 VIP/CCKs, 4 VIP/CRs.
- 328 EC Layer III cells and 246 CA3 (input) simulated as grid-like and place-like spike trains, respectively.
- Synaptic mechanisms: AMPA, NMDA, $GABA_A$, $GABA_B$
- Neurons are simulated as biophysical compartmental models with various compartments.

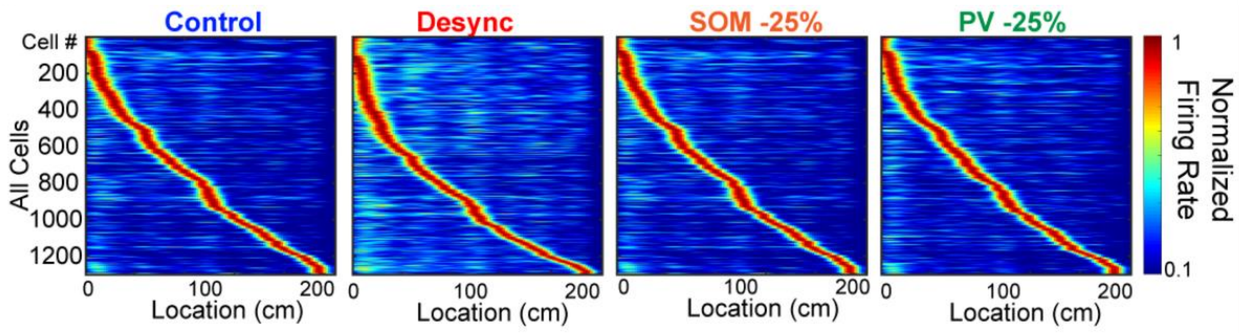



## Place-like inputs

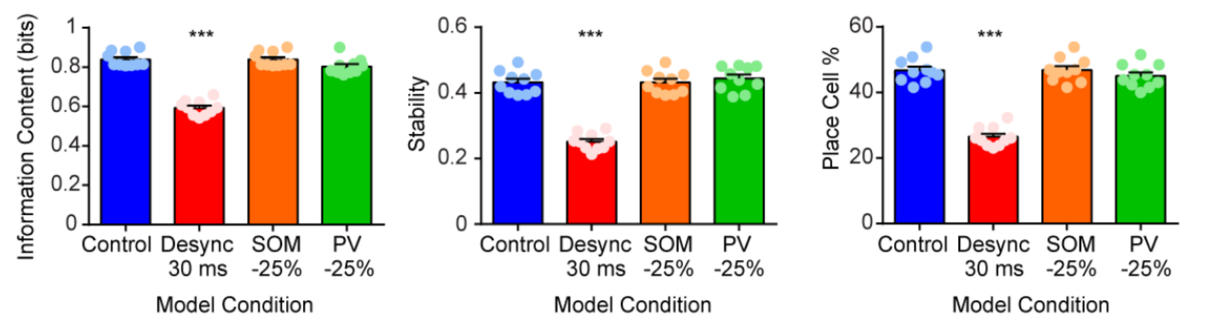
$$\sum_{j=1}^{8} N_{EC}^{[j]} = N_{EC,pooled} = \begin{cases} N_{in}, if\ x_{center} - x_{left} \leq \text{spiketime} \leq x_{center} + x_{right} \\ N_{out}, \text{otherwise} \end{cases}$$

$$N_{CA3}^{[j]} = N_{in} * \mathcal{N}(\mu = 0.16, \sigma = 0.002) + N_{out} * \mathcal{N}(\mu = 0.016, \sigma = 0.002), j = 1, \dots, 6$$

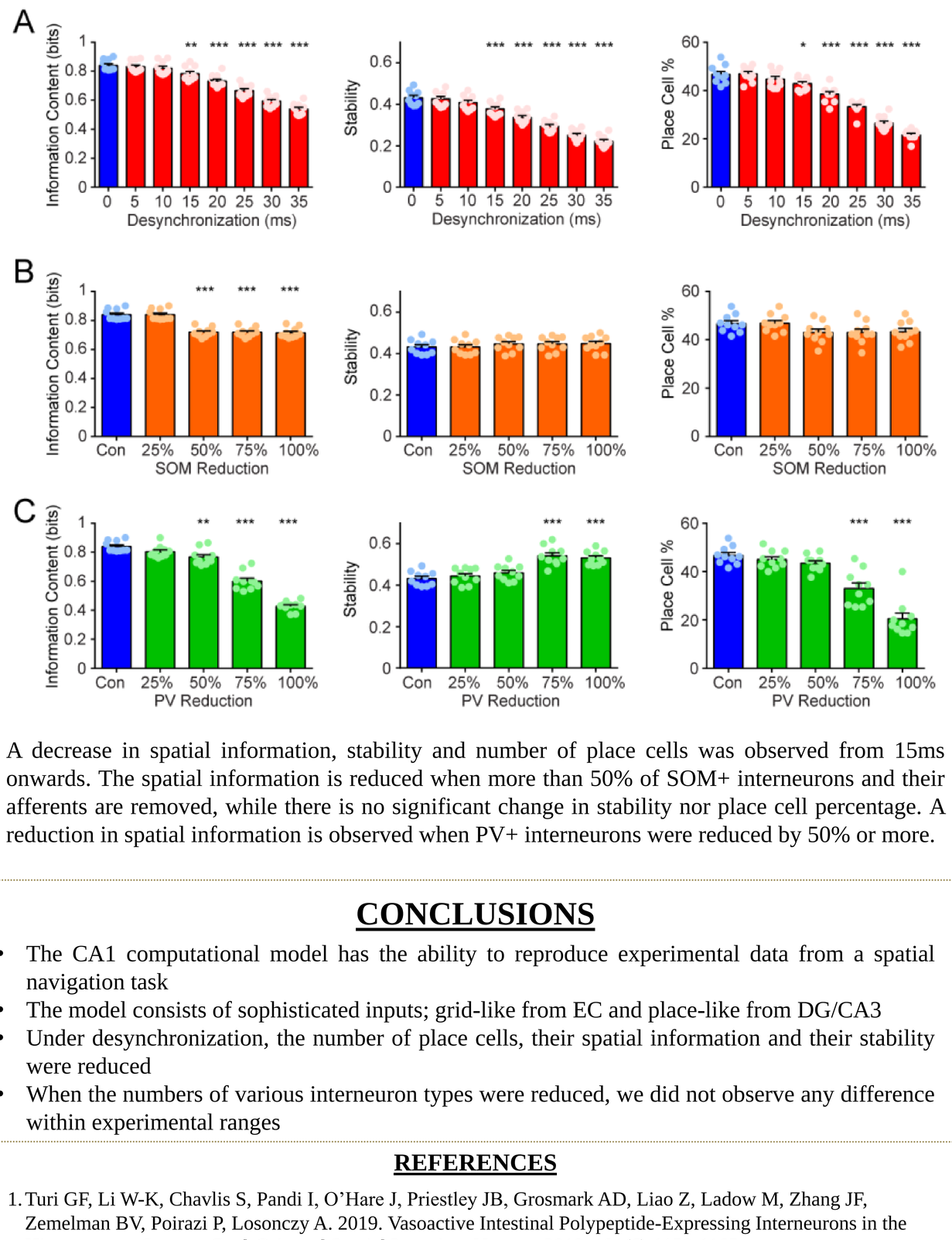
## RESULTS




Normalized spatial firing rates for each condition tested. Noise was increased with desynchronization, but remained almost intact in PV+ or SOM+ reduction conditions. This suggests that desynchronization of inputs is the key mediator of spatial memory dysfunction under epileptic conditions.




For all cells, information content was reduced only in the desynchronization conditions. For all cells, stability was reduced only in the desynchronization conditions. The percentage of place cells was reduced only in the desynchronization conditions.




A decrease in spatial information, stability and number of place cells was observed from 15ms onwards. The spatial information is reduced when more than 50% of SOM+ interneurons and their afferents are removed, while there is no significant change in stability nor place cell percentage. A reduction in spatial information is observed when PV+ interneurons were reduced by 50% or more.

## CONCLUSIONS

- The CA1 computational model has the ability to reproduce experimental data from a spatial navigation task
- The model consists of sophisticated inputs; grid-like from EC and place-like from DG/CA3
- Under desynchronization, the number of place cells, their spatial information and their stability were reduced
- When the numbers of various interneuron types were reduced, we did not observe any difference within experimental ranges

## REFERENCES

1. Turi GF, Li W-K, Chavlis S, Pandi I, O'Hare J, Priestley JB, Grosmark AD, Liao Z, Ladow M, Zhang JF, Zemelman BV, Poirazi P, Losonczy A. 2019. Vasoactive Intestinal Polypeptide-Expressing Interneurons in the Hippocampus Support Goal-Oriented Spatial Learning. Neuron. 2019. 101(6):1150-1165.

2. Shuman T, Aharoni D, Cai DJ, Lee CR, Chavlis S, Taxidis J, Flores SE, Cheng K, Javaherian M, Kaba CC, Shtrahman M, Kakhurin KI, Masmanidis S, Khakh BS, Poirazi P, Silva AJ, Golshani P. 2018. Breakdown of spatial coding and neural synchronization in epilepsy. bioRxiv.

## ACKNOWLEDGEMENTS

We thank Stavros Niarchos Foundation – FORTH Fellowships for supporting Spyridon Chavlis with ARCHERS project: Advancing Young Researchers' Human Capital in Cutting Edge Technologies in the Preservation of Cultural Heritage and the Tackling of Societal Challenges.