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Application (CMSLTM) Parallelizing computational models of memory function for the investigation of sustained activity in the prefrontal cortex

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The HP-SEE initiative is co-funded by the European Commission under the FP7 Research Infrastructures contract no. 261499

Computational models of short and long term memory (CMSLTM)

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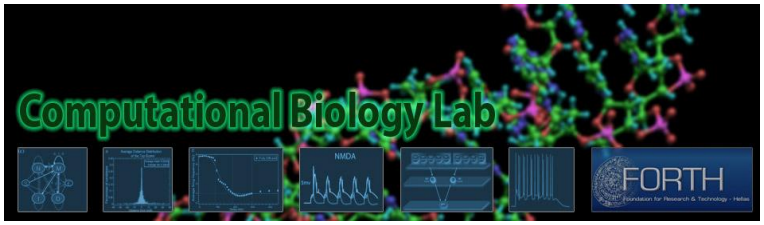
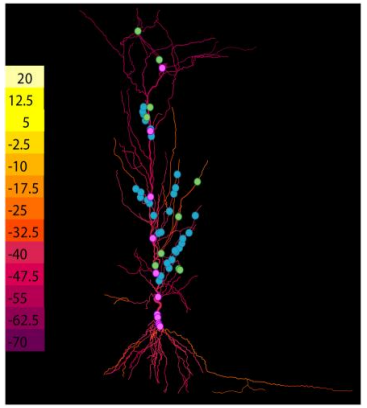
Description of CMSLTM application

- In order to study learning and memory processes, we develop detailed biophysical models of individual neurons as well as small neural circuits in key brain regions such as the amygdala, the hippocampus and the prefrontal cortex (PFC)



- We use these models to study dendritic computations, the role of biophysical and anatomical mechanisms in persistent activity as well as dissect the contribution of different types of interneurons in this activity.
- Aims:
  - To provide some of the most realistic biophysical models of neurons in the brain which are publicly available and used by numerous labs worldwide
  - To generate interesting predictions which steer the interest of the neuroscience community and open up new avenues for experimental verifications.



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- **Structure**
  - The application is composed of 2 projects:
    - Prefrontal Cortex Microcircuit simulations (related to working memory)
    - Theta oscillations in the CA1 region (related to long term memory formation)
- **Problems solved**
  - Identification of mechanisms involved in memory functions i.e. sustained activity
  - Assessment of memory capacity of different brain circuits/regions (size of network)
  - Identification of processes related to the firing delay of hippocampal cells during theta oscillations (what causes delay)
- **Impact**
  - Some of the most realistic biophysical models of neurons in the brain which are publicly available and used by numerous labs worldwide.
  - Interesting predictions which steer the interest of the neuroscience community and open up new avenues for experimental verifications.
  - Significant contribution to our understanding of memory formation and mechanisms that may be associated with memory loss. May lead to health care advances or novel pharmaceutical research.
  - Attempt to identify the biophysical causes of observed spike statistics in the hippocampus

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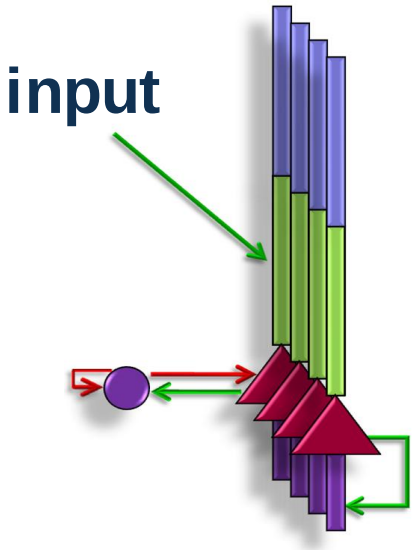
Prefrontal Cortex Microcircuit Simulations

Description

The aim of this work is to simulate sustained neuronal activity in Prefrontal Cortex Microcircuits. Sustained activity is believed to be related to working memory functions in the brain. We initialize the network with synaptic stimulus and observe the emergence of sustained firing activity in the neuronal network.

We scaled a pre-existing network of 4 neurons to progressively larger populations. We performed neuronal modeling of a network of 25 and 50 compartmental PFC neurons using NEURON.



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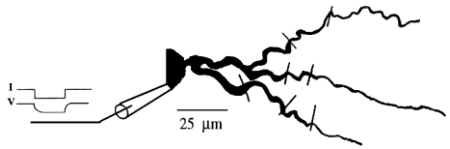
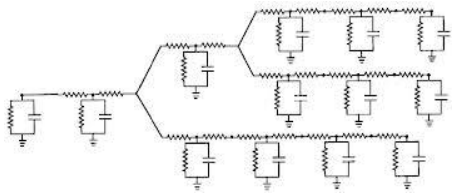
- NEURON (www.neuron.yale.edu) is a simulator used to build and use biophysically realistic compartmental models of neurons(Hines 1997)
- In models, neuronal cells are represented by a large number of cylindrical electric compartments.
- Existing models have to be parallelized using the built-in ParallelContext manager. In our case, cell simulations were scattered through available nodes so that each whole cell is simulated on a single node.
- The way ParallelContext works is that each processor integrates the model equations for an interval equal to the minimum neural connection delay (Migliore 2006)
- The simulations were run on the HPCG cluster in Sofia





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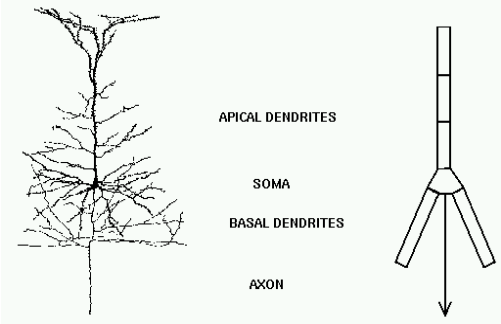
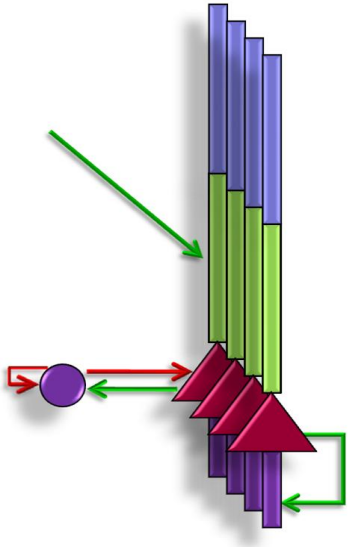
- Cells are composed of 4 compartments representing the soma, apical (distal and proximal) and basal dendrites. Each compartment contains a different mix of 13 different ionic mechanisms
- 20% inhibitory / 80% excitatory cells.
- Connectivity: all cells receive synaptic input, this is propagated to all other cells and the interneuron
- Aim: to study and detect the properties of the emergence of self-sustained firing activity in the network





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Results

•Self-sustained firing activity emerges in the network with appropriate initial synaptic stimulus (C up)

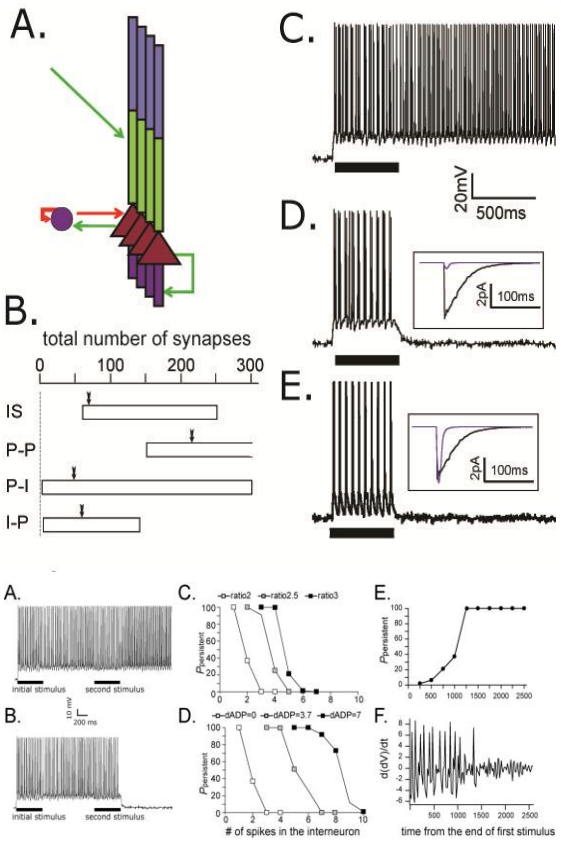
•Sustained activity is not elicited when NMDA receptors activation is blocked (D up)

•Similarly, no sustained activity when using fast NMDA dynamics (E up)

•A second stimulus delivered on the interneurons, when appropriately timed can terminate the sustained spiking activity (B down)

•With increased NMDA activity, stronger stimulus is required for the termination of sustained firing (C down)

•Similarly, when the dADP current is increased, stronger terminating stimulus is required (D down)



Papoutsi et al, CNS poster , 2009

Papoutsi et al, to be submitted

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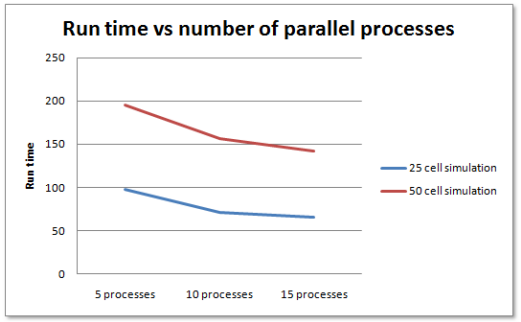
Benchmarking

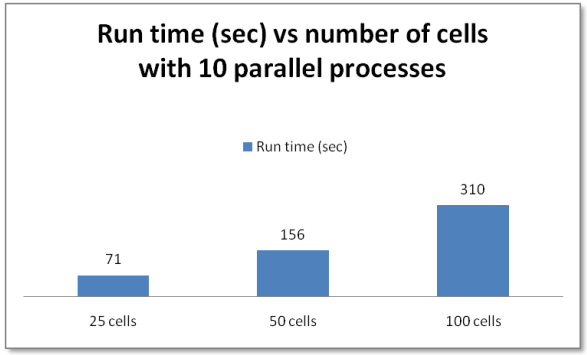
- We generally observe sub-linear speedup in the parallel simulations
- We attribute this to the high spiking activity which leads to delays due to spike delivery and syncing

No of Neurons simulated	Number of parallel processes	Run time (sec)
25	5	98
25	10	71
25	15	66
50	5	195
50	10	156
50	15	142



Network simulation time scales linearly with time, despite increased connectivity complexity

No of Neurons simulated	Number of parallel processes	Run time (sec)
25	10	71
50	10	156
100	10	310



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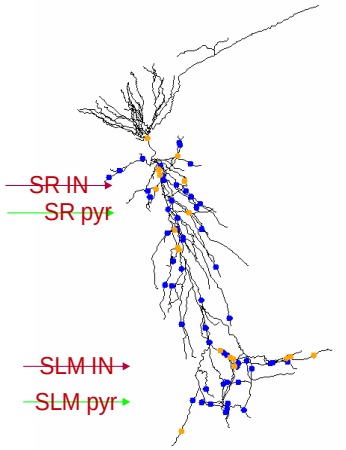
CA1 Theta Simulations:

The spiking phase of CA1 neurons in the hippocampus shows a characteristic delay during chronic hippocampal recordings of theta rhythms (Mizuseki 2009). Our aim is to attempt to identify possible causes that would cause long delays in the firing of CA1 cells during theta activity.



We used our preexisting validated detailed CA1 pyramidal neuron model (Poirazi, 2003), stimulating it in batch with theta-like artificial patterns, compatible with recorded data that was made available to us by the Buszaki lab.

Serial application split in parametric processes using pbs (job manager)

Simulating Theta Rhythms

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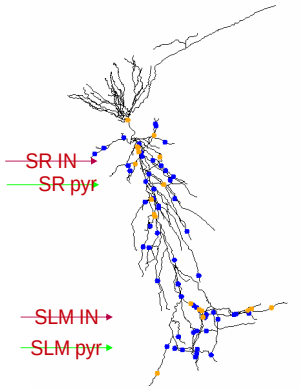
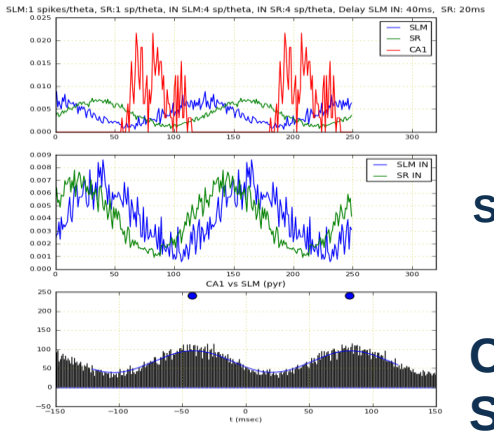
- Our CA1 compartmental model has been previously validated and used in a number of studies (Poirazi 2003, Pissadaki 2010, Gomez 2010).
- For our simulations we used artificial inputs targeting the SR and SLM layers of the apical dendrite of the cell. In our model, we assume that the SLM input comes from layer 3 of the Entorhinal Cortex, while SR input originates from CA3 region.
- We simulated the Theta using trains of spikes distributed normally around the peaks of the theta rhythm. In our simulations, theta frequency=8Hz (theta period=125 msec)
- We simulated both excitatory and inhibitory inputs to both layers.
- The number of inputs in each layer was variable, but the ratio of excitatory / inhibitory inputs was kept constant.
- We performed batch exploratory simulations on the HPCG cluster. **Parallelization of the model is not required**.





excitatory

Synaptic Input rates inhibitory

CA1 output rate
Shows delay in CA
With respect to excitatory input

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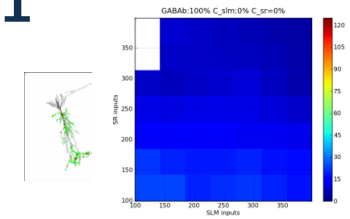
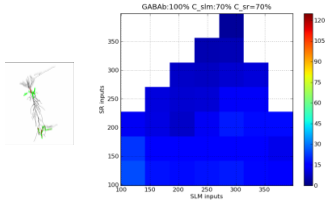
Results

- 1. Clustering of synaptic inputs does not affect CA1 firing delays
- 2. Increased GABAb receptors levels cause only moderate delays in CA1 firing
- 3. Delay is not dependent on CA1 firing frequency (no-correlation)
- 4. Delay of CA1 is dependent on the frequency of inhibitory input, however still smaller than the observed delays.

1



Non Clustered



Clustered

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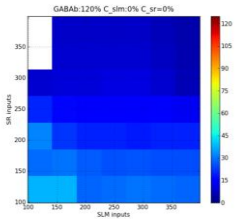
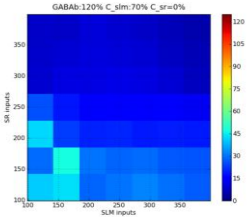
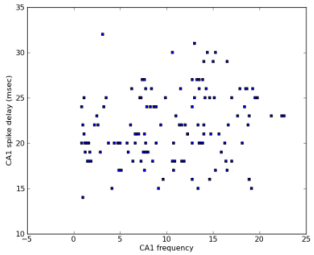


Increased GABAb



Increased GABAb +Clustering

3



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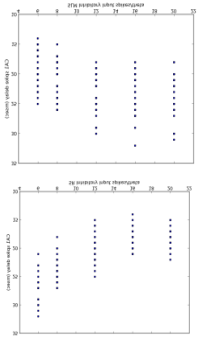

Conclusions

- PFC simulations
  - We have obtained results for (prefrontal cortex) PFC experiment (100 neurons).
  - We have successfully been able to scale up our previous prefrontal cortex microcircuits.
  - Further work should concentrate on refining the all-to-all connectivity patterns that we used.
- Theta simulations
  - The interplay of the timing of inhibitory inputs to CA1 SR and SLM layers determines the phase of CA1 spiking.
  - GABAb, input clustering, and the firing frequency of inhibitory inputs can affect the CA1 spiking phase profile.
  - Future work entails the investigation of other sources of CA1 delay.

- **Publications & Presentations**
  - Kryoneriti D, Papoutsi A, Poirazi P., "Mechanisms underlying the emergence of Up and Down states in a model PFC microcircuit", Oral Presentation, CNS 2011, Stockholm, Sweden, July 22-28 **and** Poster, EMBO Series Meeting on the Functional Organization of Neural Assemblies, Ascona, Switzerland, September 23-29
  - Papoutsi A, Sidiropoulou K and Poirazi P., "Temporal Dynamics underlie bi-stability in a model PFC microcircuit" (submitted)
  - Papoutsi et al, "Mechanisms underlying persistent activity in a model PFC microcircuit", CNS poster , 2009
  - Poirazi P. "Dendrites and Information processing" invited seminar, Bernstein Center Freiburg, 27/3/2012.

Acknowledgements

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Thank you for your attention

People

- **Yiota Poirazi** (Supervision)
- George Kastellakis (Development)

- Acknowledgements:
  - Athanasia Papoutsi
  - Ioannis Liabotis

- Collaborations:
  - György Buzsáki
  - Kenji Mizuseki

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