Full-scale biophysical modeling of hippocampal networks during spatial navigation

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Introduction

I use Blue Waters to construct, simulate and analyze full-scale biophysical computational models of the rodent hippocampus and understand the role of the neural circuitry in processing spatial information.

- **Full-scale**: 1:1 correspondence between model neurons and biological system (completed model will have approximately $2 \times 10^6$ neurons and $4 \times 10^{10}$ connections)

- **Biophysical**: detailed neuronal morphology, synaptic connections, equations of ion channel and synapse currents (each model neuron can have thousands of state variables)

- **Hippocampus**: part of the brain responsible for learning, memory, and spatial navigation
Introduction

Yi et al., 2016
The brain’s navigational system

Sequential Activity in the Hippocampus

Position of mouse

Path of mouse

One place cell’s firing pattern

Firing patterns of multiple place cells

One grid cell’s firing pattern

Firing patterns of multiple grid cells
Cellular diversity and recurrent connectivity enable rhythm generation in a full scale model of CA1


<table>
<thead>
<tr>
<th>Biological realism:</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
</table>

| Model: | Bezaire, Raikov & Soltesz, 2016 |
| Network configuration: | CA1 |
| # of principal cells | >300,000 |
| # of synapses / principal cell | ~20,000 |
| Cell excitability model | Biophysical |
| # of cell types | 9 |
| Cell-type-specific connectivity | Distance-dependent |
| Input pattern | Constant |
| Input strengths | Equal |
| Long-term plasticity | None |

| Network output: | Rhythmicity: Theta, gamma, ripple |
| Rhythmicity | Theta, gamma, ripple |
| Output selectivity | None |
| Output fraction active (%) | ~100% |

Key insight: Cellular and circuit mechanisms of rhythm generation
Diversity of information representation in the hippocampus and cortex

- Neuronal sequences are organized internally and do not require sensory inputs or motor outputs.
- The internally organized sequences can represent spatial and temporal information and planned behaviors corresponding to the near future.
- The aim of this project is to decipher the cellular and network mechanisms of the formation of population activity sequences that represent spatiotemporal information.

Fujisawa et al., 2017
Topographical connectivity in the hippocampus

Harland, Contreras and Fellous, 2017
Large-scale biophysical model of spatial coding in the hippocampal dentate gyrus

**Biological realism:**
- High
- Intermediate
- Low

*In progress*

**Previous work**
- Model: Raikov, Milstein & Soltesz
- Network configuration:
  - # of principal cells: 1,000,000
  - # of synapses / principal cell: ~10,000
  - Cell excitability model: Biophysical
  - # of cell types: 9
  - Cell-type-specific connectivity: Distance-dependent
  - Input pattern: Selective (grid + place)
  - Input strengths: *History-dependent*
  - Long-term plasticity: None

**Network output:**
- Rhythmicity: Theta, gamma
- Output selectivity: *Realistic anatomical gradient of field widths*  
- Output fraction active (%): *<2% GC, >15% MC*

**Key insight:** Role of feedback excitation from mossy cells in regulating sparsity and selectivity in the dentate gyrus.

Realistic geometry in a full scale model of the dentate gyrus

Schneider et al., PloS Comp Biol, 2014
Topographical connectivity and input patterns in a large-scale biophysical model of the hippocampal dentate gyrus

Topography of spatial inputs to the hippocampus from entorhinal grid cells

From Stensola et al., *Nature*, 2012.

Spatial selectivity and sparsity of dentate gyrus model

Spatial selectivity and sparsity of dentate gyrus model

Spatial selectivity and sparsity of dentate gyrus model
Spatial selectivity and sparsity of dentate gyrus model

Testing a theory for hippocampal interactions in sequence generation

Conclusions

- We have made significant progress developing a full-scale, biophysical model of the rodent hippocampus

- Model comprised of realistically diverse cell types, cell-type-specific connectivity, realistic anatomical distribution of cells, and non-uniform distributions of synaptic input strengths

- The dentate gyrus (DG) model generates sparse, selective, and sequential population activity that matches in vivo experimental data

- Prototype to develop general software infrastructure to specify, simulate, optimize, and analyze large-scale biophysically-detailed neuronal network models

- Scalable across tens of thousands of processors on Blue Waters

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### Simulation run time on Blue Waters

<table>
<thead>
<tr>
<th>Model</th>
<th>Number of Nodes</th>
<th>Simulated time</th>
<th>Run time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dentate gyrus</td>
<td>2048</td>
<td>10 s</td>
<td>7.5 hours</td>
</tr>
<tr>
<td>Dentate gyrus</td>
<td>4096</td>
<td>10 s</td>
<td>6.1 hours</td>
</tr>
<tr>
<td>CA1</td>
<td>1024</td>
<td>10 s</td>
<td>12.8 hours</td>
</tr>
<tr>
<td>CA1</td>
<td>2048</td>
<td>10 s</td>
<td>6.2 hours</td>
</tr>
</tbody>
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