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COMPUTATIONAL MODELING OF EPILEPSY: FROM SINGLE NEURONS TO PATHOLOGY

ANATOLY BUCHIN, REBECCA DE FRATES, STEPHEN MCCONOUGHHEY, STACI SORENSEN, RYDER GWINN, JONATHAN TING & COSTAS A. ANASTASSIOU
The human brain is the most complex piece of organized matter in the known universe. We use our singular approach to uncover its mysteries and share valuable resources with the global community of neuroscientists.
The Institute model

Research Papers
Computational Models

Data
Software Tools
http://www.brain-map.org/

SCIENCE VIGNETTES

DEVELOPING MOUSE
NON-HUMAN PRIMATE
MOUSE SPINAL CORD
GLIOBLASTOMA
AGING, DEMENTIA AND TBI
REFERENCE ATLASES
APPLICATION PROGRAMMING INTERFACE (API)
SOFTWARE DEVELOPMENT KIT (SDK)

DATA & TOOLS

CELL TYPES
BRAIN OBSERVATORY
MOUSE BRAIN
HUMAN BRAIN

THE GENETIC GEOGRAPHY OF THE BRAIN
HUMAN EPILEPSY
What are seizures?

- **Epilepsy** is a group of neurological diseases characterized by epileptic seizures.

- **Epileptic seizure** is a brief episode of symptoms due to abnormal synchronous neuronal activity in the brain.

- Approximately 1% of the world population: ~50,000,000 people.

- ~50% of adult epileptic patients have the **temporal lobe epilepsy**.

- ~40% of patients do not respond to the pharmacological treatment.

Fisher et al 2005
Many anti-epileptic drugs fail to deliver

Löscher and Schmidt 2011
Many anti-epileptic drugs fail to deliver

~40% of patients do not respond to the pharmacological treatment

Mouse epilepsy is the main model of human epilepsy

Löscher and Schmidt 2011

healthcare.utah.edu
HUMAN EPILEPSY AT THE ALLEN INSTITUTE
Data generation from brain slices of human epilepsy patients undergoing hippocampal resection

Wyler grade 1

Wyler grade 4

Mild sclerosis (WG1)

Severe sclerosis (WG4)
Data generation from brain slices of human epilepsy patients undergoing hippocampal resection

Wyler grade 1

Wyler grade 4

Granule cell from hippocampus

Mild sclerosis (WG1)

Severe sclerosis (WG4)

single-neuron ephys and morphology reconstructions
What happens with human neurons in the epileptic region when it becomes more sclerotic?
Electrophysiology feature-based analysis of human DG granule cells

Wyler grade 1

Wyler grade 4

Features

AP frequency

Adaptation index

AP amplitude

AP threshold

AP width

https://github.com/AllenInstitute/AllenSDK
## Electrophysiological features

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*F=30 (Features)*

N=50
*(Neurons)*

-Data has been scaled
Ephys features robustly cluster with Wyler Grade

A

Wyler grade 1

20 mV
2 ms

Wyler grade 4

20 mV
2 ms

B

WG4 (N=23)
WG1 (N=27)

C

WG4 (2 patients)
WG1 (3 patients)

D

88% accuracy
Random forest

88% accuracy
Random forest

E

Pairwise comparison

F

Random forest

Buchin et al, in preparation
Morphological features do not cluster with Wyler Grade

68% accuracy
Random forest

Pairwise comparison

Buchin et al, in preparation
WG4 cells have more spines than WG1 cells

synapse <-> spine

Rebecca de Frates
Conclusions I

- There are specific ephys features characterising WG1 (less sclerotic) and WG4 (more sclerotic) pathology in granule cells of human hippocampus.

- Morphological features are not significantly different between WG1 and WG4 cells.

- WG4 cells have about twice as many spines as WG1 cells (larger synaptic input).
SINGLE NEURON MODEL GENERATION
Computational model of a biological neuron

A. Characterized Neuron

B. Cable Model

C. Compartmental Model

http://ecee.colorado.edu/
Parameter optimization using genetic algorithms

https://github.com/BlueBrain/BluePyOpt

Ani Nandi
What are computational models of neurons for?
Compare predicted channel conductances and RNA-seq data to find the genes specific for epilepsy (WG1 vs WG4)
WG-dependent activation scenarios of granule cells

“WG1” activation scenario: $N_{syn} = 114$

“WG4” activation scenario: $N_{syn} = 399$
WG-dependent activation scenarios of granule cells

“WG1” activation scenario: $N_{syn} = 114$

“WG4” activation scenario: $N_{syn} = 399$
Neural network model of human dentate gyrus
Software developed at Allen Institute: Brain Modeling Toolkit

Simulator hierarchy

Network structure

https://github.com/AllenInstitute/bmtk
Neural network model of human Dentate Gyrus (DG)
Neural network model of human Dentate Gyrus (DG)

Ullah et al 2009

6 Basket cells (inhibitory)

500 Granule cells (excitatory)

External input (cortex)
Spiking activity in the WG1 network

- Initial response
- External input (cortex)
WG1 network with 48% WG4 cells

External input (cortex)

Spontaneous activity!
WG1 network with 64% WG4 cells

External input (cortex)  Spontaneous activity!
Conclusions II

• We have developed realistic single neuron models of human granule cells from hippocampus

• We found that WG4 cells are more excitable than WG1 cells when received the same synaptic input

• Addition of WG4 cells to WG1 network of dentate gyrus leads to the development of spontaneous activity
Neural network model of human Dentate Gyrus (DG)

Ullah et al 2009

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500 Granule cells (excitatory)
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THANK YOU

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alleninstitute.org
brain-map.org