Epilepsy and Neural Engineering

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- Epilepsy is defined as repeated occurrence of unprovoked seizures
- 1 – 3% of general population suffers from epilepsy (5-6 million people in US)
- In 70% of cases, epilepsy is controlled by antiepileptic medication (anticonvulsants).
- Medications are not curative; patients have to continuously take meds to control seizures
- Anticonvulsants have side-effects
- In 30% of cases, epilepsy is not controlled by medication, or becomes drug-resistant. These patients may have to undergo surgery
Risk factors for developing epilepsy

- Military head injury (HI)
- Civilian HI (severe)
- Civilian HI (moderate)
- Civilian HI (mild)*
- Stroke
- Encephalitis
- Bacterial meningitis
- Aseptic meningitis*
- Alzheimer disease
- Multiple sclerosis
- Parkinsonism
- Embolic risk factors
- Hypertension and LVH
- LVH with RX**
- Hypertension*
- Migraine with aura
- Alcohol
- Heroin
- Marijuana**
- Cocaine
- Depression
- Suicidality
- Neuroleptic drug
- Tricyclic antidepressive
- Electroconvulsive therapy*
- ADD
- HD*
- No risk

Rate ratio
Age-specific incidence of epilepsy

Causes of epilepsy

- Tumor: 2.7%
- Trauma: 8.8%
- Neurodegenerative diseases: 1.3%
- Other: 4.0%
- Alcohol: 5.8%
- MR/CP: 3.5%
- Stroke: 9.3%
- Infection: 2.2%
- Unknown: 62.4%
• Incidence after military head injury in up to **53%** of patients (Vietnam veterans)
• Incidence after civilian head injury - **17%**

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Raymont V et al. Neurology 2010;75:224-229

Neuron potentials can be detected with electrodes outside the cell
Electroencephalography (EEG) from the scalp, non-invasive

Electrocorticography (ECoG) from the surface of the cortex, invasive

Intracortical Local Field Potentials (LFP) within cortical tissue, invasive
Standard placement of electrodes

EEG in awake human

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100 µV
1 second
EEG activity in a patient with epilepsy

“sharp waves” or interictal spikes
Variety of neurons in cerebral cortex

**Excitatory neurons** (A and B) – release excitatory neurotransmitter, cause other cells to activate

**Inhibitory neurons** (C-H) – release inhibitory neurotransmitter, cause other cells to de-activate
Interplay between excitation and inhibition in seizure focus
A. Partial seizure
1. Spread
2. Secondary generalization
B. Primary generalized seizure

Seizure focus
Thalamus
A  Spike and wave activity in typical absence seizure
Temporal lobe epilepsy

(A), before seizure

(B) aura: feeling of fear

(C) Alteration of consciousness, screaming
Surgical treatment of epilepsy
Development of epilepsy: normal hippocampal circuit
Development of epilepsy

A Normal circuitry

1. Normal circuitry diagram showing the interaction between Dentate gyrus, BC, Mossy cell, and G.

B Temporal lobe epilepsy

1. Temporal lobe epilepsy diagram showing the progression from normal circuitry to increased activity and spread of excitation.

2. Diagram showing the spread of excitation from the Dentate gyrus to the BC and Mossy cell.

3. Diagram showing the focal spread of excitation leading to temporal lobe epilepsy.
Circuit reorganization in epilepsy

Dentate region

CA3

CA1

Schaffer collateral pathway (associative LTP)

Mossy fiber pathway (nonassociative LTP)

Perforant fiber pathway (associative LTP)
Developing treatments for epilepsy:

• stopping seizures with electrical and optical stimulation
• better diagnostics through electrode arrays
• faster drug development with brain-on-a-chip
Vagus Nerve Stimulation

- Vagus nerve: ennervates heart, larynx, lungs and intestines. Carries sensory information back to the brain.
- Stimulation is FDA-approved
- Built by Cyberonics, Inc.
- > 60,000 patients treated
- 20 – 40% reduction in seizure frequency
- Mechanism of action: not understood, but may involve activation of the thalamus and/or release of neurotransmitter norepinephrine.
**Left** vagus nerve is used for stimulation because the right vagus nerve affects the heart rate.
Deep Brain Stimulation

Responsive Neurostimulation System (RNS, NeuroPace, Inc.)

- Detect Seizure
- Record Activity
- Deliver Stimulation to Seizure Focus
- Stop Seizure

Figure 1: Spontaneous Seizure, Electrical Stimulation, Seizure Stops

Legend:

- LOT1-AVG
- LOT2-AVG
- LOT3-AVG
- LOT4-AVG
- LOT5-AVG
- LOT6-AVG
- LOT7-AVG
- LOT8-AVG
- AST1-AVG
- AST2-AVG
ECoG lead

Intracortical lead
Optically controlled channels allow ion flow in and out of a cell.

Inflow of Na⁺ excites neurons.
Inflow of Cl⁻ inhibits neurons.

These channels are proteins from algae and bacteria that can be expressed in mammalian neurons.

O. Yizhar et al, Neuron, 71, 2011
Channelrhodopsin (sensitive to blue light) depolarizes a neuron and triggers a spike
Halorhodopsin (NpHR) (sensitive to yellow light) hyperpolarizes a neuron and inhibits spikes

E. Pastrana, Nature Methods, 8, 2011
Optical stimulation stops seizures

Mapping Seizures– Flexible ECoG array

360 electrodes

J. Viventi et al., *Nature Neuroscience* 2011
Surface of the brain is not even, and activity in sulci is inaccessible to surface electrodes.
Seizures appear as spiral waves of activity on the cortex
Brain-on-a-chip

Tissue chips:
• 3-D chips (with microelectronic or micromechanical components) with living cells and tissues that accurately model the structure and function of human organs: lung, liver, hear and brain. (National Institutes of Health)
• Main application: acceleration of drug development to treat diseases. Predict drug toxicity and effectiveness before clinical trials.
• Also, enable studies into development and function of basic organ units.

Microbrain Bioreactor reproduces blood-brain barrier (Dominic Doyle and Frank Block, Vanderbilt University)
Dissect hippocampus into slices, maintain slices in an incubator for ~ 4 weeks.
All neurons are stained green, and inhibitory (GABAergic neurons) are stained red.
Epilepsy-on-a-chip

4 cultures per chip, 2 electrodes per culture, 8 electrodes total
Known anticonvulsant (phenytoin) is effective in this model

Phenytoin – known anticonvulsant drug, suppresses seizures
Effective in slice culture model of epilepsy, confirms that this model has relevance for human epilepsy
Rapid experiment rate with epilepsy-on-a-chip allowed us to evaluate > 150 drugs for antiepileptic effects, with some unexpected candidates emerging
Constructing neural circuits in a dish
Questions?