Electroceuticals in Neurologic and Psychiatric Disorders

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Disclosures

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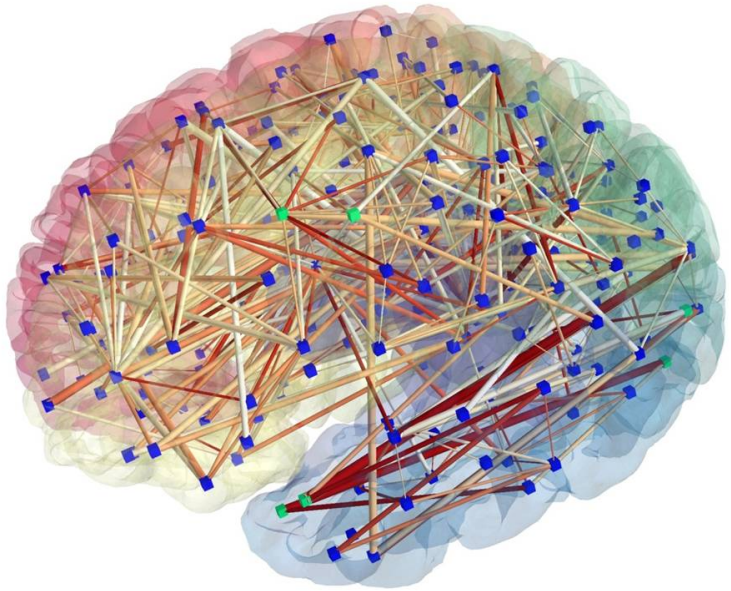
- ***Advisory Board:*** Prapela, Inc.

Learning Objective 1

Identify the role of electroceutical treatment in neurologic and psychiatric disorders.

Central question in neuroscience:

How do neural circuits determine behavior?



How can we normalize dysfunctional circuits using external stimuli?

Zamora-Lopez G, et al. *Front Neuroinform*. 2010;19:4:1.

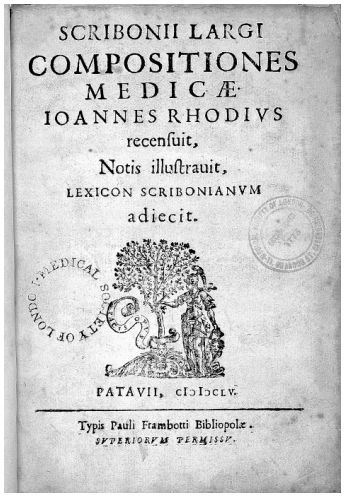
Electricity in Medicine

Medicinal Electric Fish

Ancient Egyptian and Roman physicians treated a range of painful conditions. Scribonius Largus published use of torpedo fish to treat headache.

2500 BC – 45 AD

jstor.org

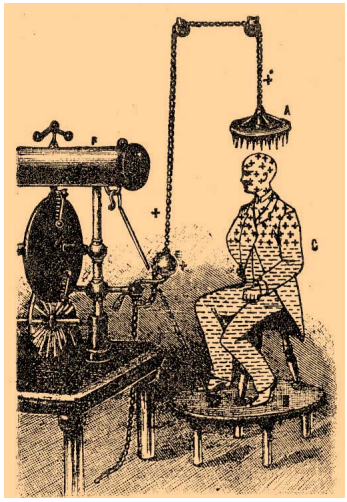


wellcomecollection.org

Electrotherapy

Benjamin Franklin
Luigi Galvani
Giovanni Aldini
G.B.C. Duchenne

1750 - 1850



https://en.wikipedia.org/wiki/Electric_bath_(electrotherapy)

Electroconvulsive Therapy

Ugo Cerletti
Lucio Bini
Friedrich Meggendorfer

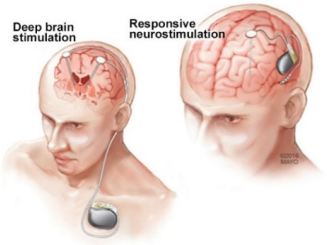
1934 - 1944

https://commons.wikimedia.org/wiki/File:Electroconvulsive_Therapy.png

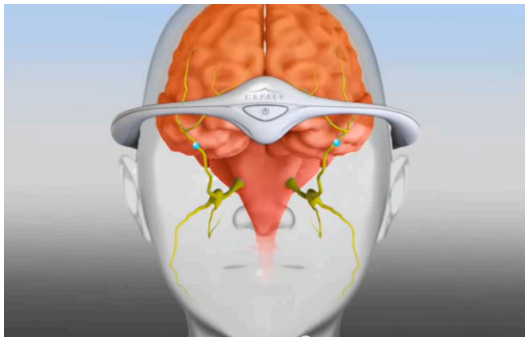
Implanted Stimulators

Spinal cord stimulator
Cochlear implants
Retinal implants
Deep brain stimulators

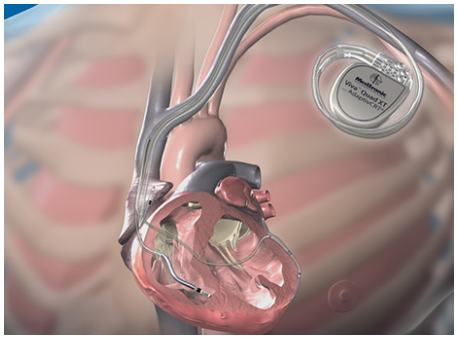
1960 - present



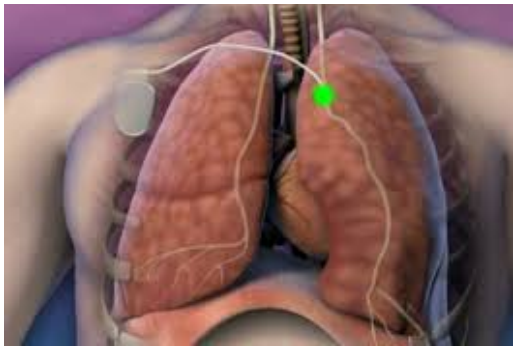
https://www.nidcd.nih.gov/
https://www.ninds.nih.gov/



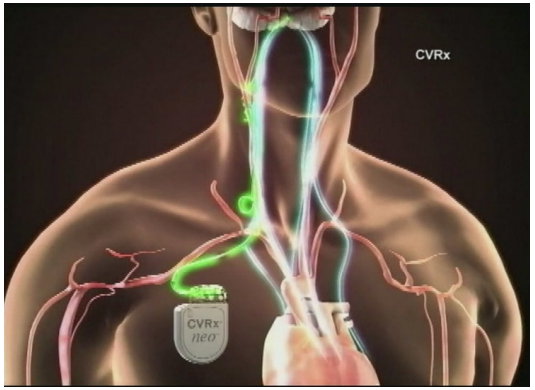
Trigeminal Nerves
Migraine



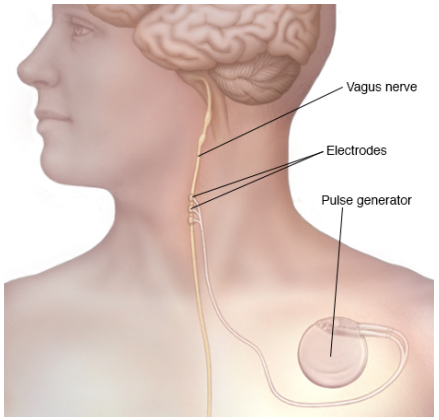
Cardiac Conduction Nerves
Arrhythmias, Heart Failure



Phrenic Nerves
Paralysis of the Diaphragm



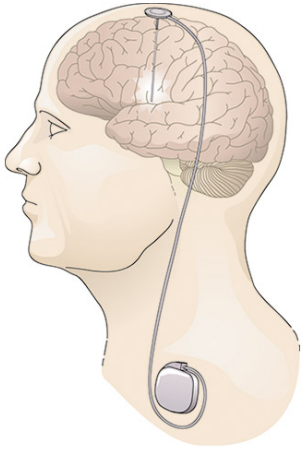
Carotid Sinus Nerve
Hypertension



Vagus Nerve
Epilepsy, Immune Modulation

Dorsal Column of Spinal Cord
Intractable Pain

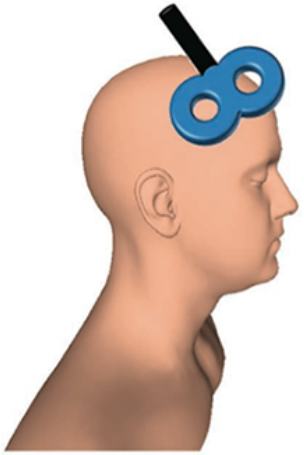
Deep Brain Stimulation (DBS)



ninds.nih.gov

Movement Disorders
Epilepsy
Depression
Coma
Cognitive Impairment

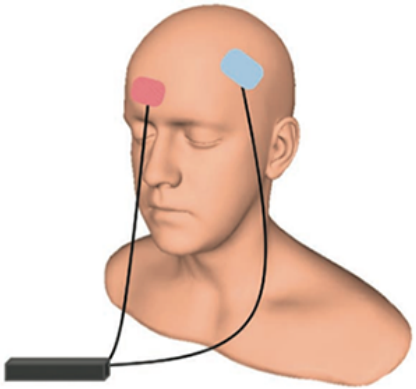
Transcranial Magnetic Stimulation (TMS)



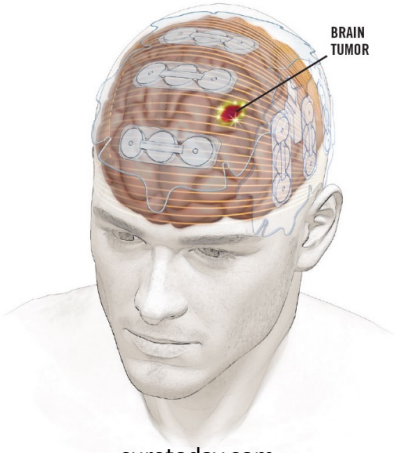
ninds.nih.gov

Obsessive Compulsive Disorder
Depression
Migraine Pain
Addiction
Stroke Rehabilitation

Transcranial Direct Current Stimulation (TDCS)



Tumor Treating Fields (TTF)



curetoday.com

Glioma
Brain Metastasis

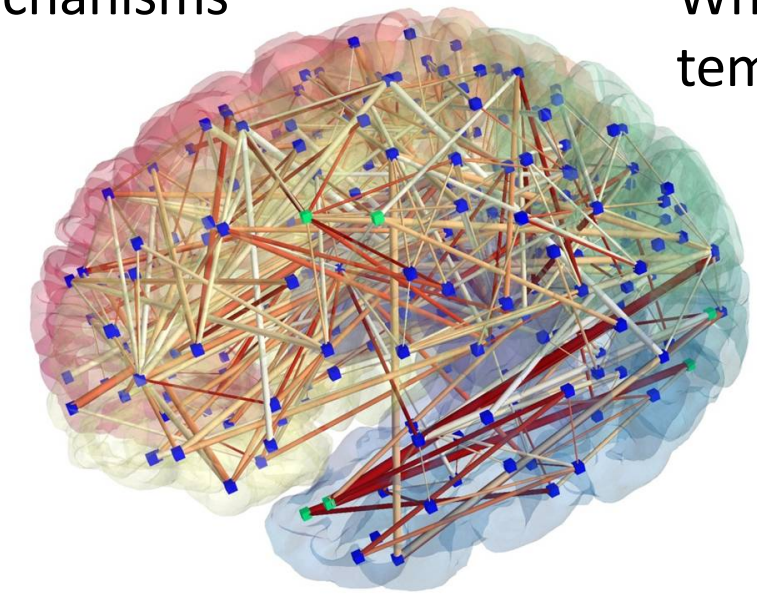
What have we learned in 4,500 years?

2500 BC
Medicinal Electric Fish

2020 AD
Implanted Electric Stimulators

Electroceutical Science

What are the mechanisms of action?

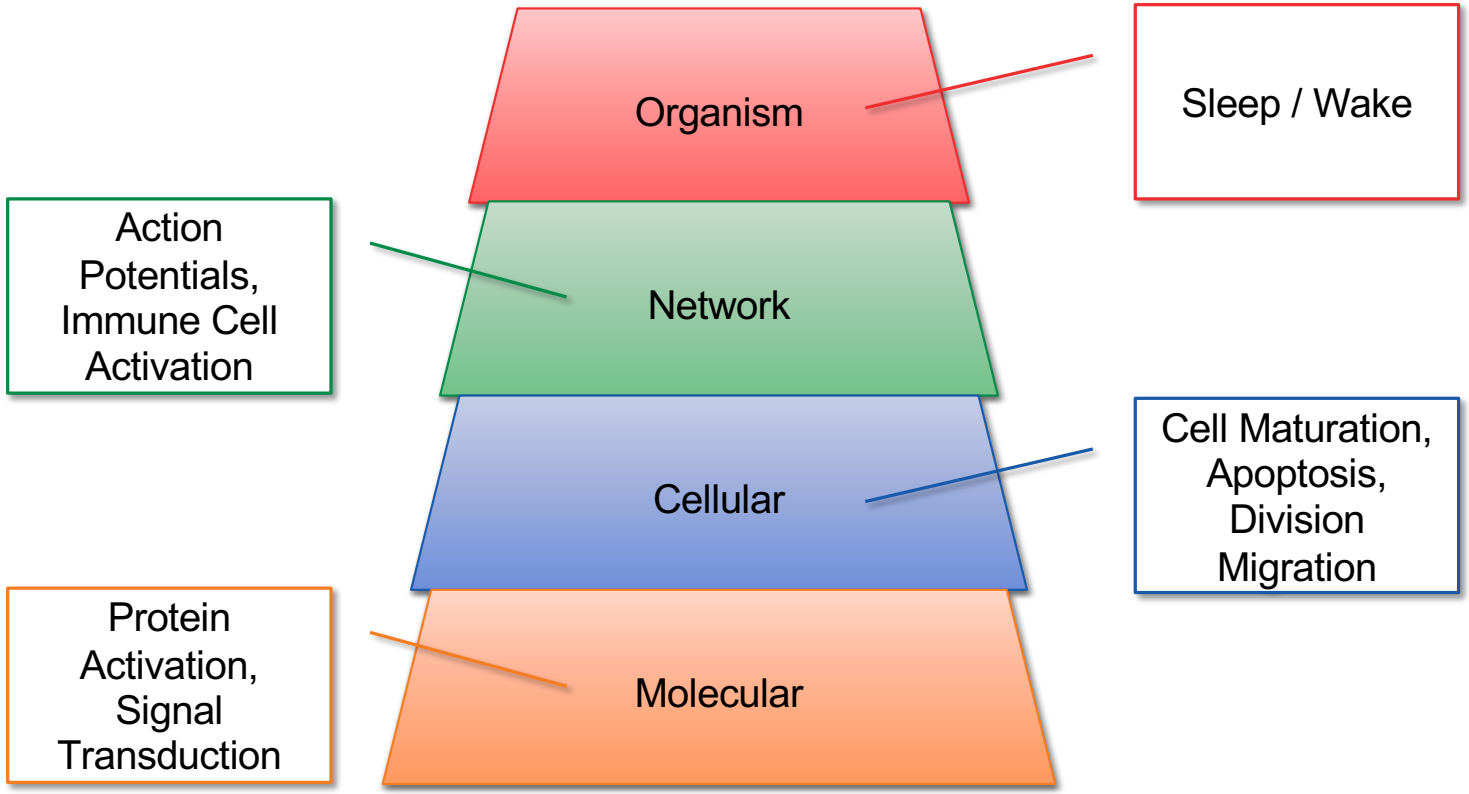


What are the spatial and temporal scales of effect?

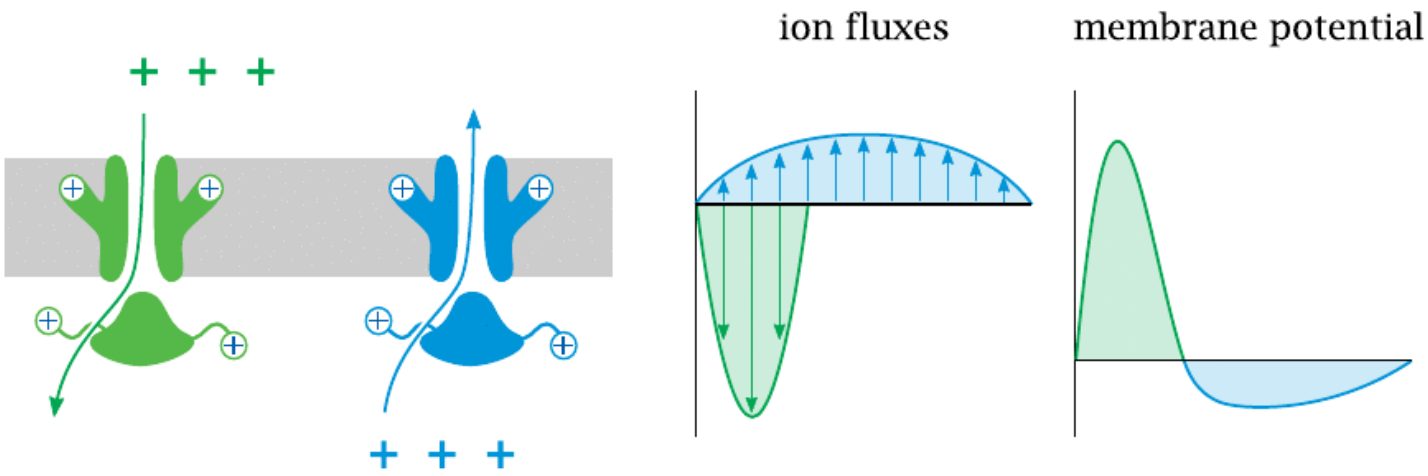
How is optimal dose profile determined?

Zamora-Lopez G, et al. *Front Neuroinform*. 2010;19:4:1.

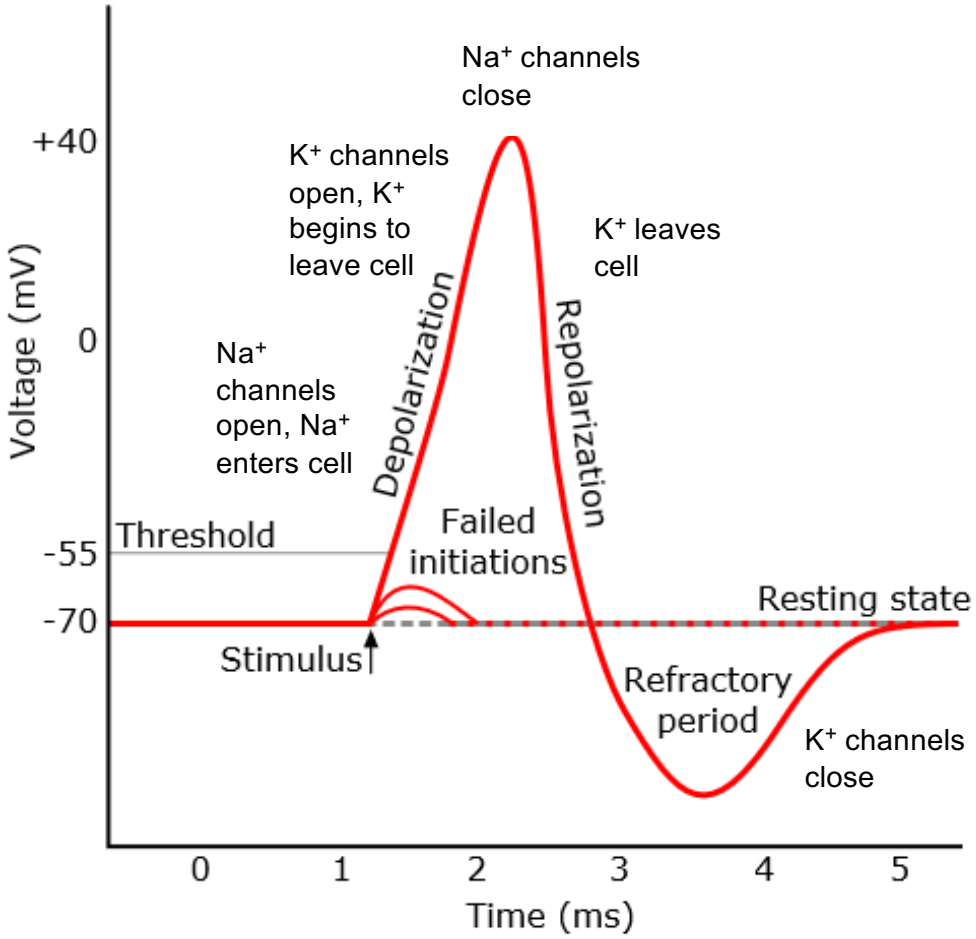
Charge-Sensitive Biological Switches



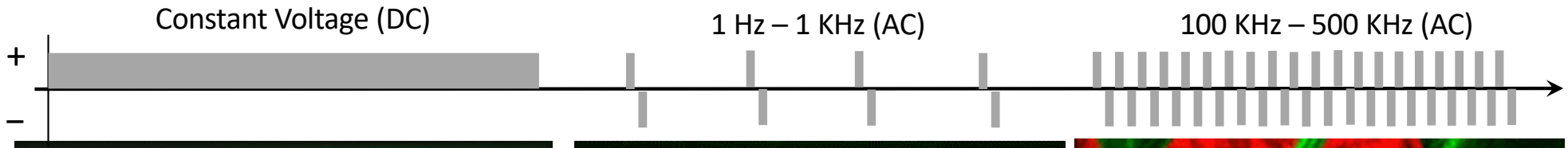
Voltage-sensitive membrane proteins regulate ion fluxes and generate the action potential

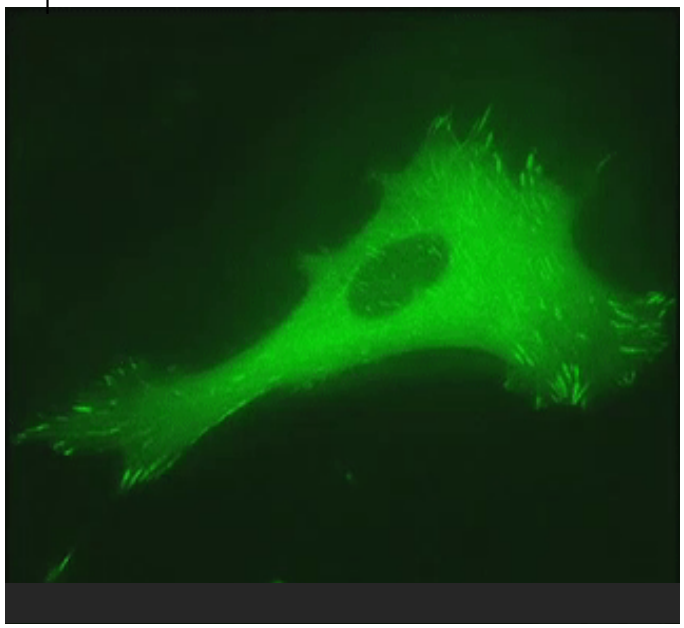


The Action Potential

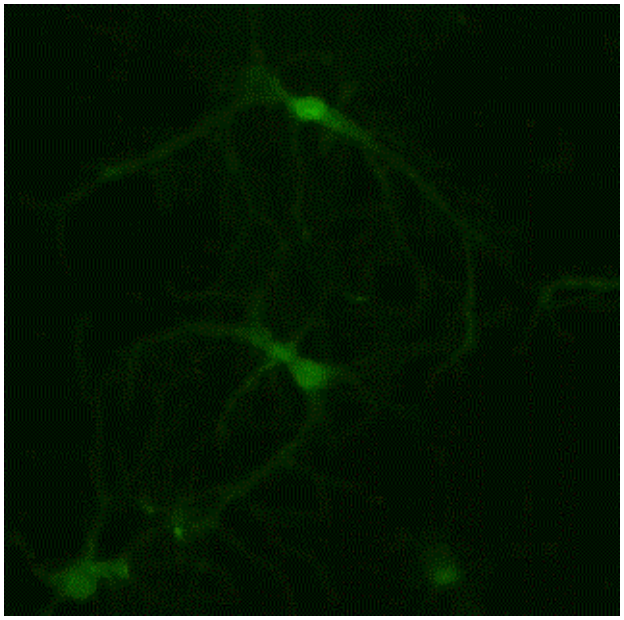


Electric field effect on cells is highly dependent on stimulus frequency

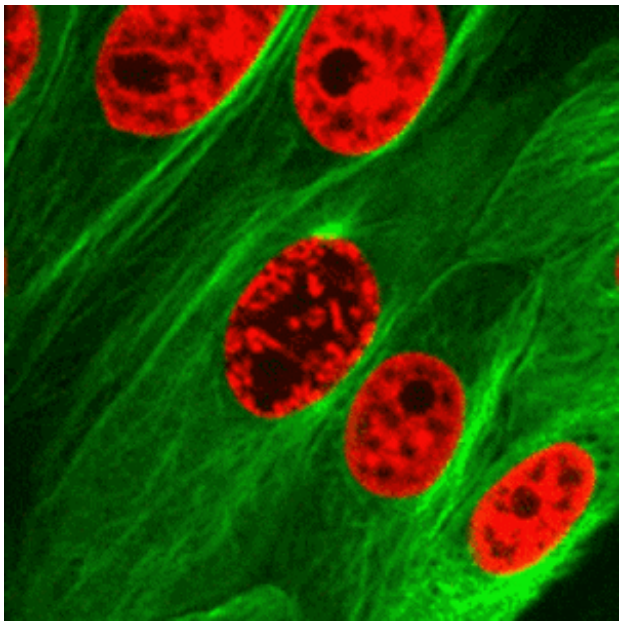




Alignment & Migration
Actin Filaments/Adhesion

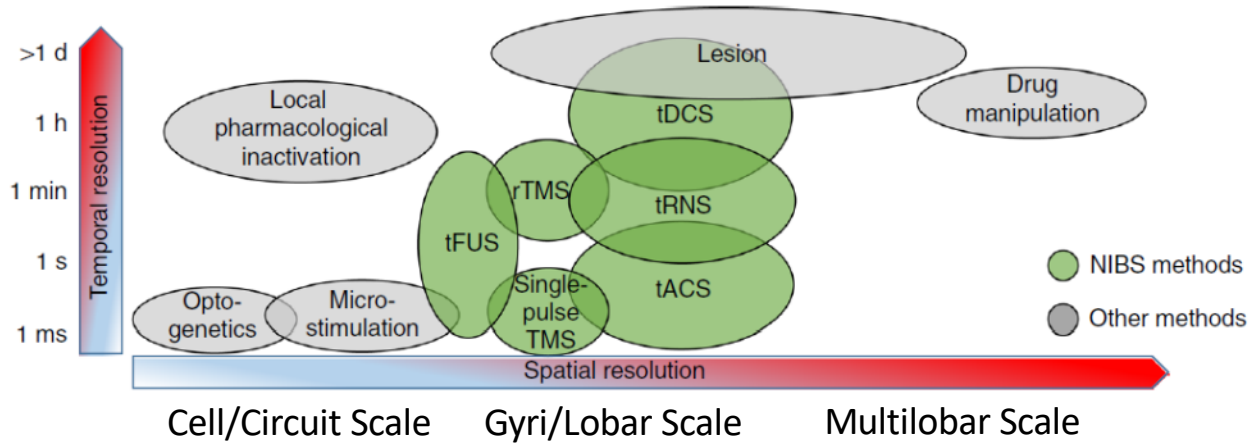


Depolarization & Hyperpolarization
Voltage-Sensitive Ionic Channels



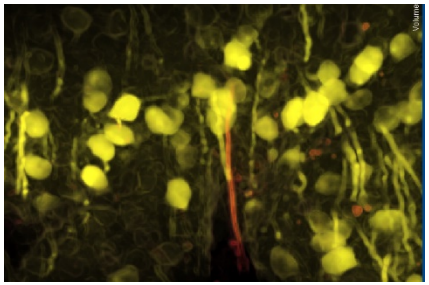
Mitotic Inhibition & Apoptosis
Microtubule Assembly

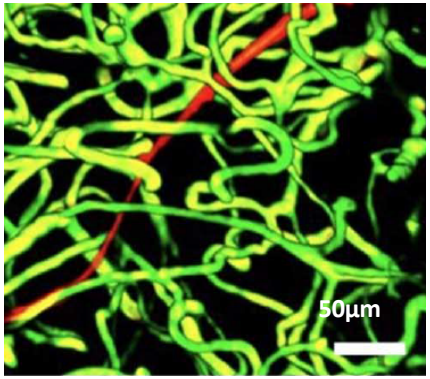
Temporal and spatial scales of neural stimulation techniques



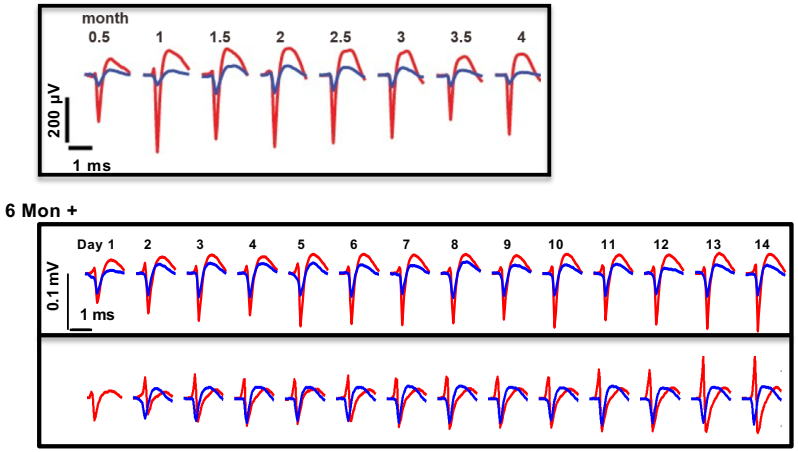
Polanía R, et al. *Nat Neurosci.* 2018;21(2):174-187.

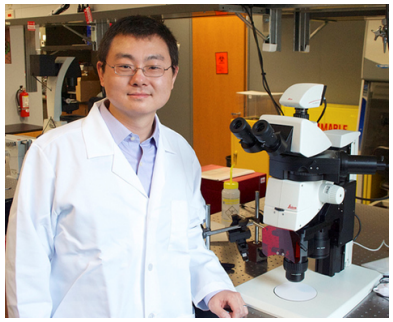
A new class of micro-electrodes – ultra-flexible & biocompatible





Flexible electrode (red)
Neurons (yellow)
Vascular network (green)





Chong Xie, PhD
Rice University

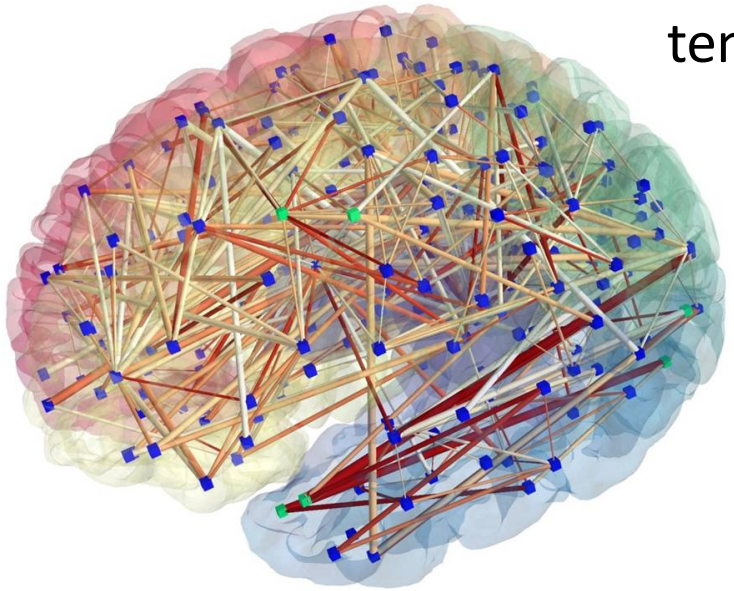
Stable *in vivo* recording from individual neurons long-term (> 1 year)

Luan L, et al. *Sci Adv* 2017;3(2):e1601966.

Electroceutical Science - Main Questions

What are the mechanisms of action?

What are the spatial and temporal scales of effect?



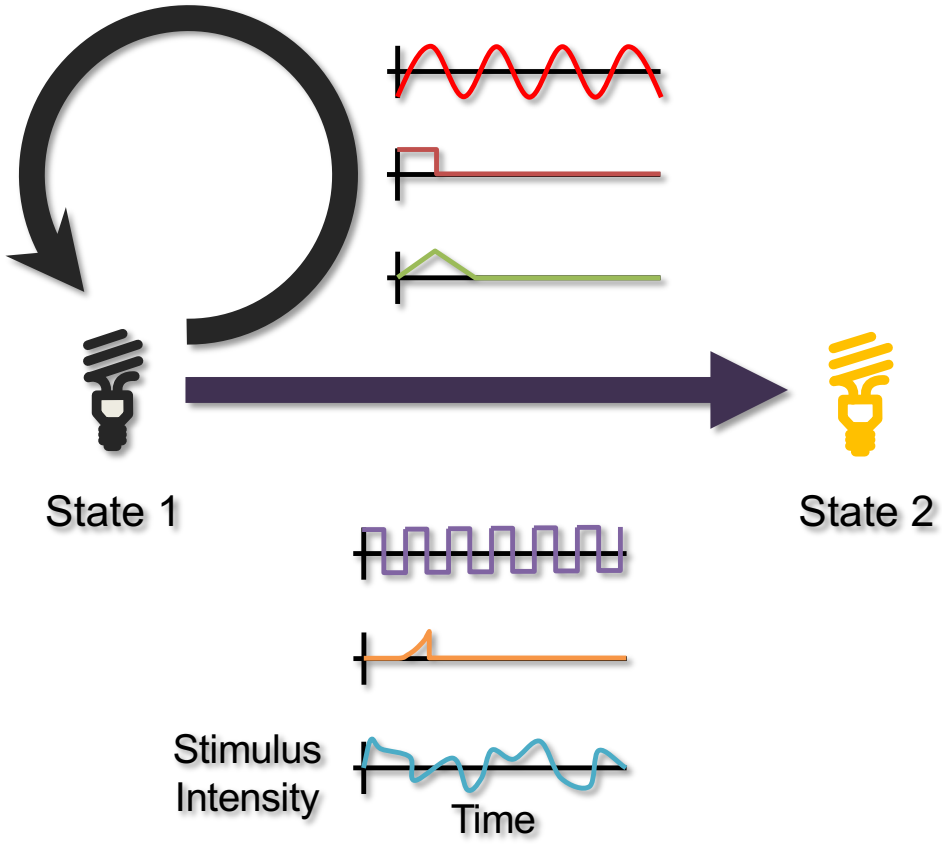
How is optimal dose profile determined?

Zamora-Lopez G, et al. *Front Neuroinform*. 2010;19:4:1.

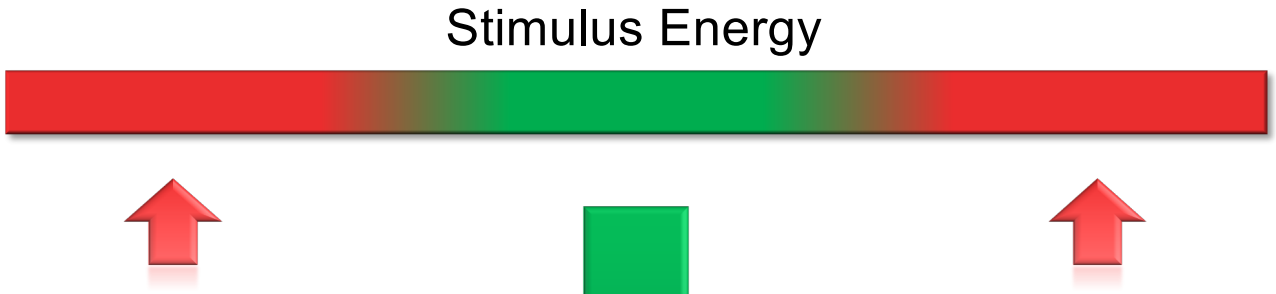
Electrical stimulation can induce switching between pathological and healthy states

State 1	Stimulation	State 2
Cardiac arrhythmias	Cardiac Conduction System	Normal sinus rhythm
Parkinsonian tremors	Subthalamic Nucleus	No tremors
Epileptic seizures	Thalamocortical Circuits	Normal brain activity
Migraine	Trigeminal Nerves	No headache

State switching



Goldilocks Principle



Too Little Energy

- Failed outcome
- Wasted energy

Just Right

Too Much Energy

- Decreased battery life
- Off target effects
- Damaged tissue

Epilepsy

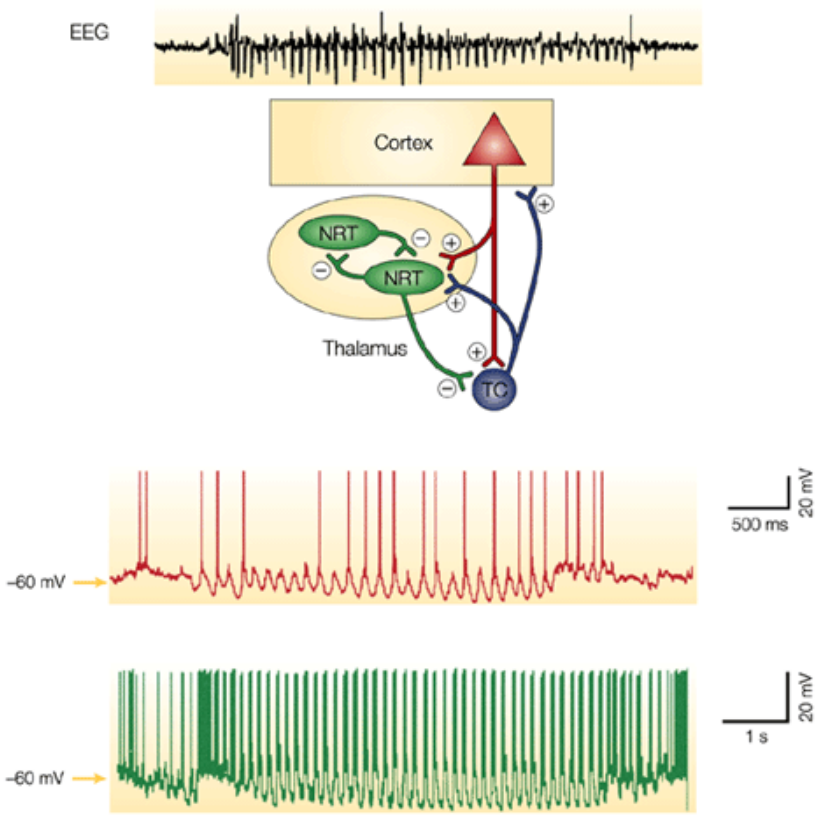
Prevalence (US):

- 2.3 million adults and over 450,000 children
- Diagnose roughly 150,000 new cases each year
- Financial burden - $9.6 billion in 2009

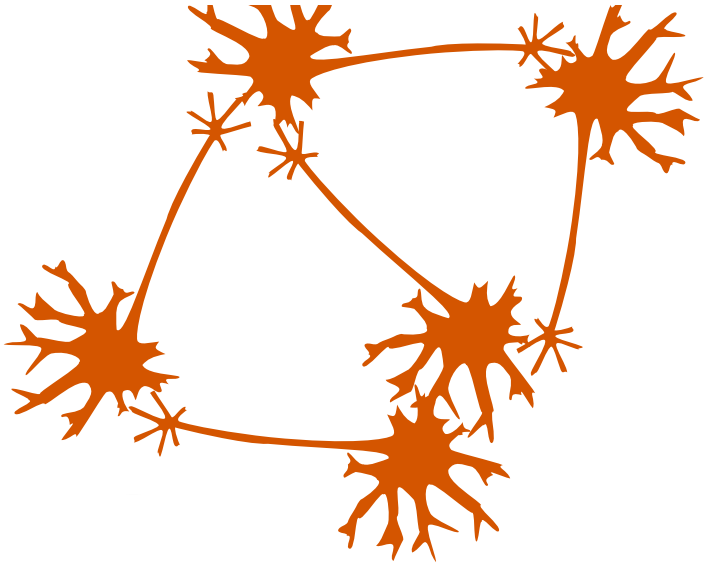
Treatments for Epilepsy

- Drug therapies
- Surgery
- Electrical Stimulation

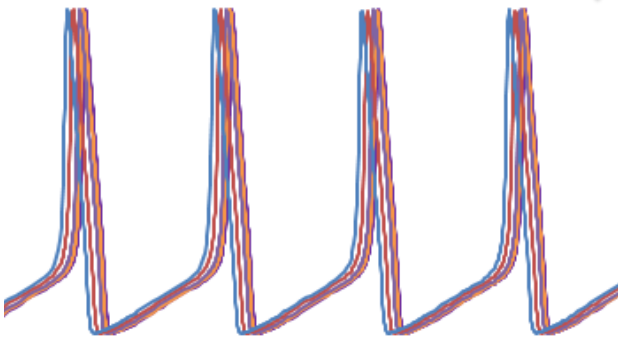
Neuronal synchronization underlying epilepsy



Crunelli V, Leresche N. *Nat Rev Neurosci*. 2002;3(5):371-382.

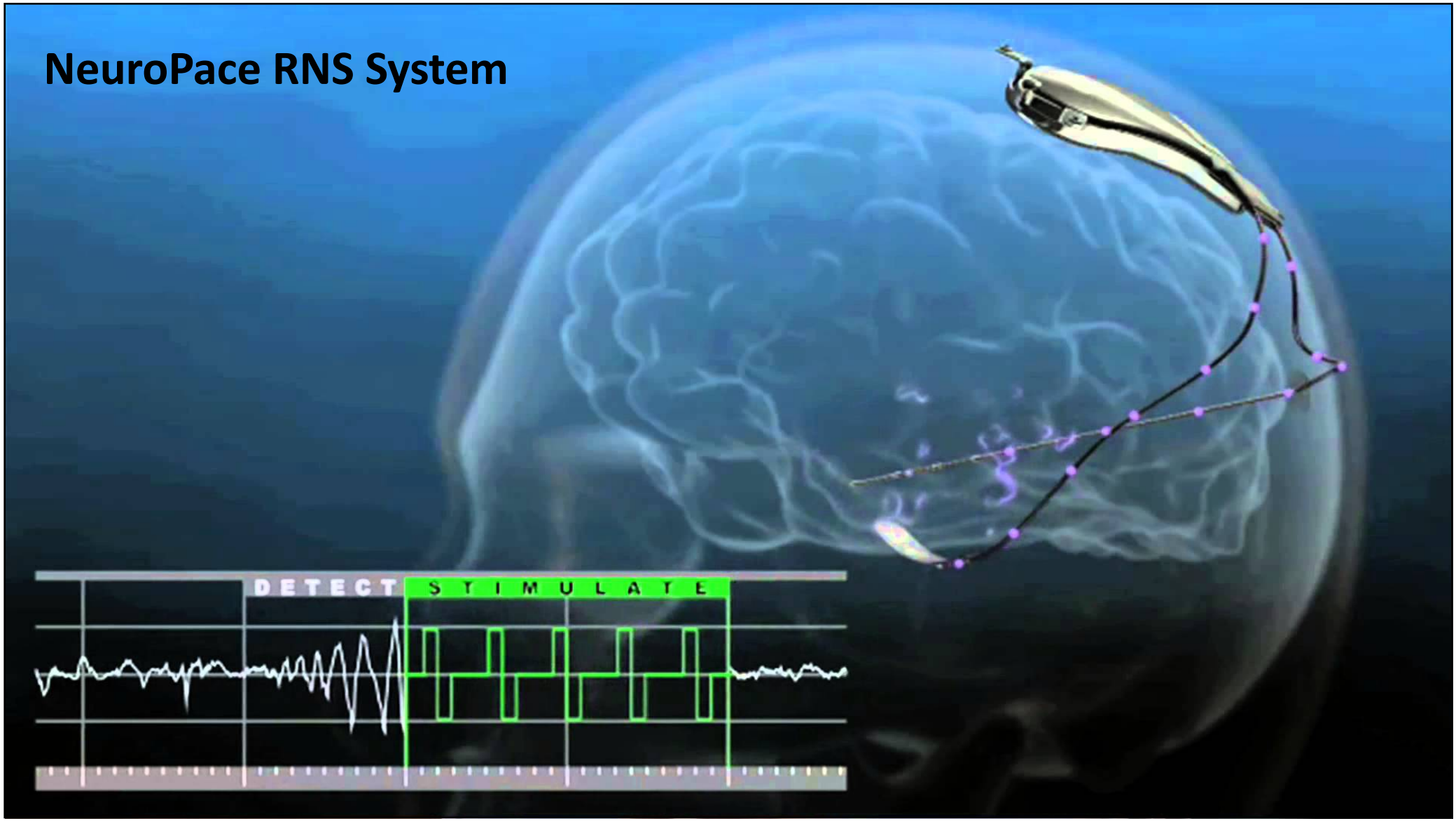


Synchronized Activity

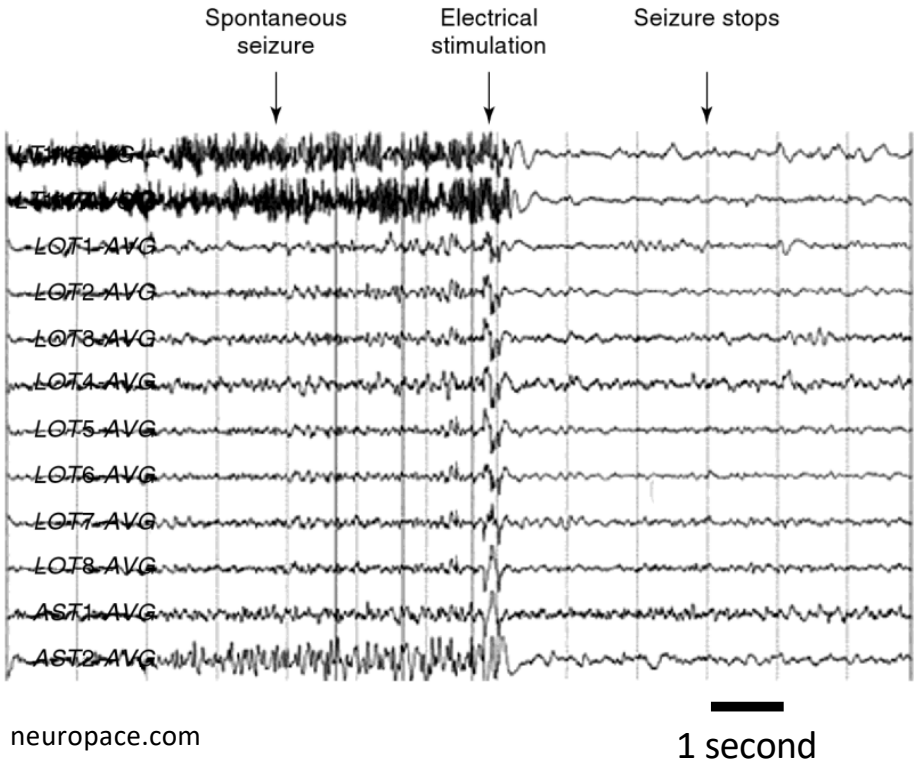


Responsive Neural Stimulation (RNS)

NeuroPace RNS System



RNS suppression of seizure

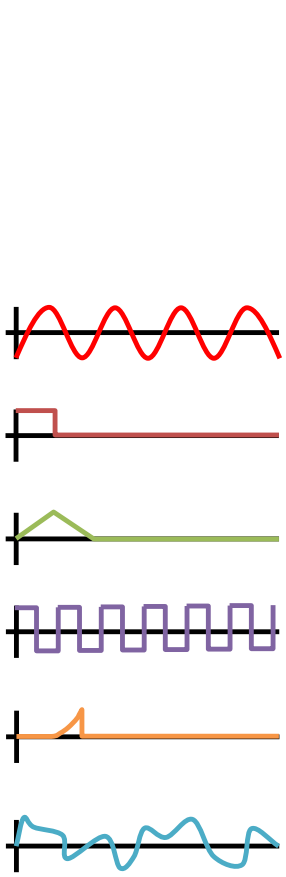


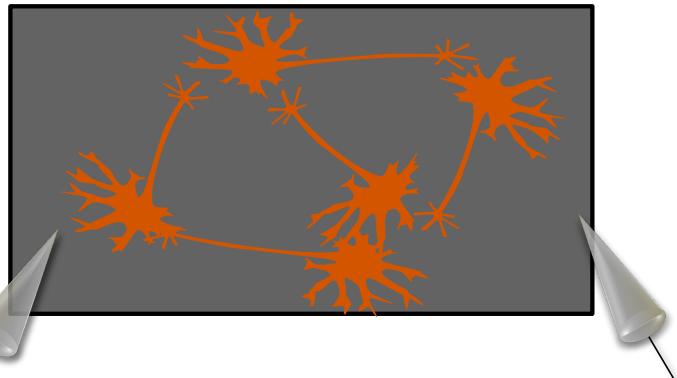
neuropace.com

- Efficacy ~50%
- Off target effects
- Battery life

How can we optimize the stimulus waveforms?

Search Algorithms

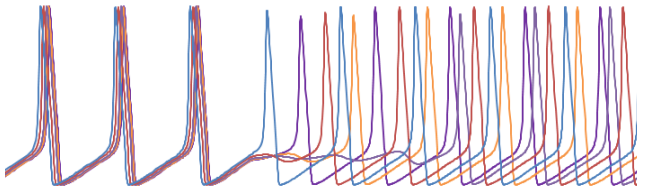




Black Box System

Input

Output



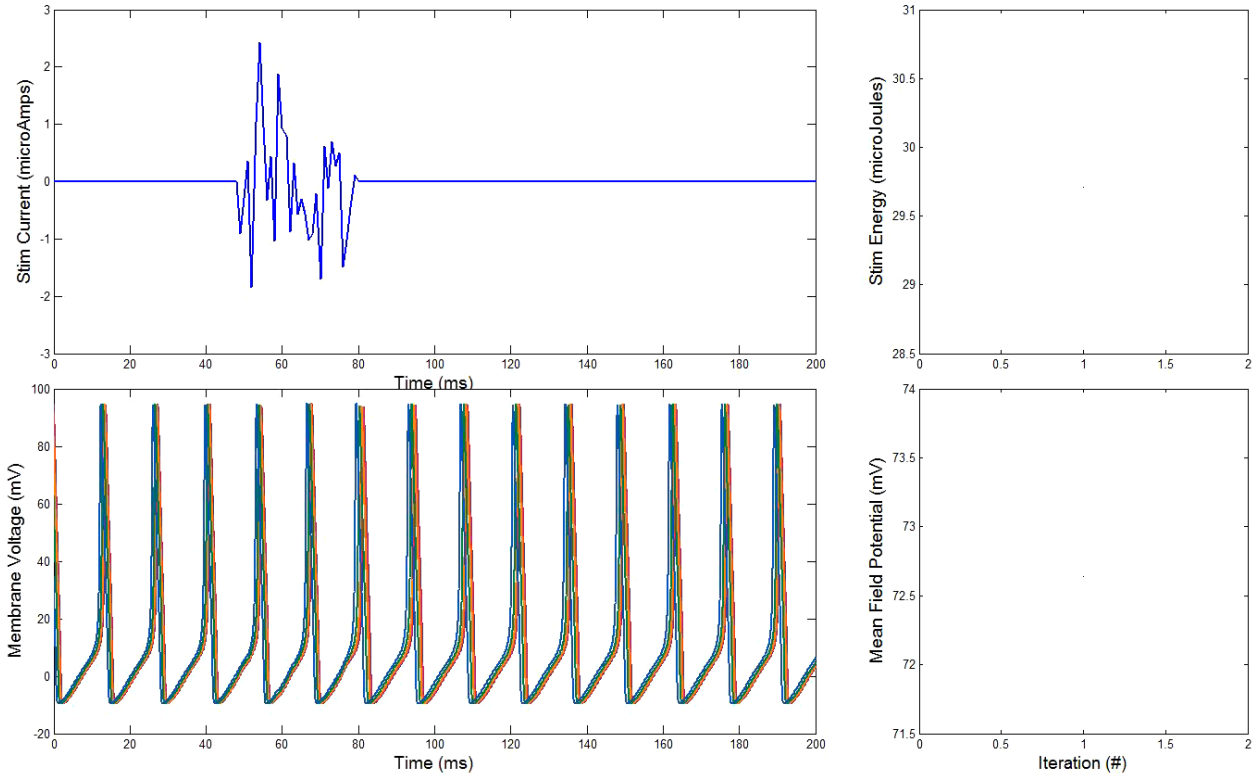
Stochastic Search Algorithm

- Stochastic Hill-Climbing
- Simulated Annealing
- Genetic Algorithms
- Particle Swarm Optimization

Optimal stimulus to desynchronize five coupled neurons

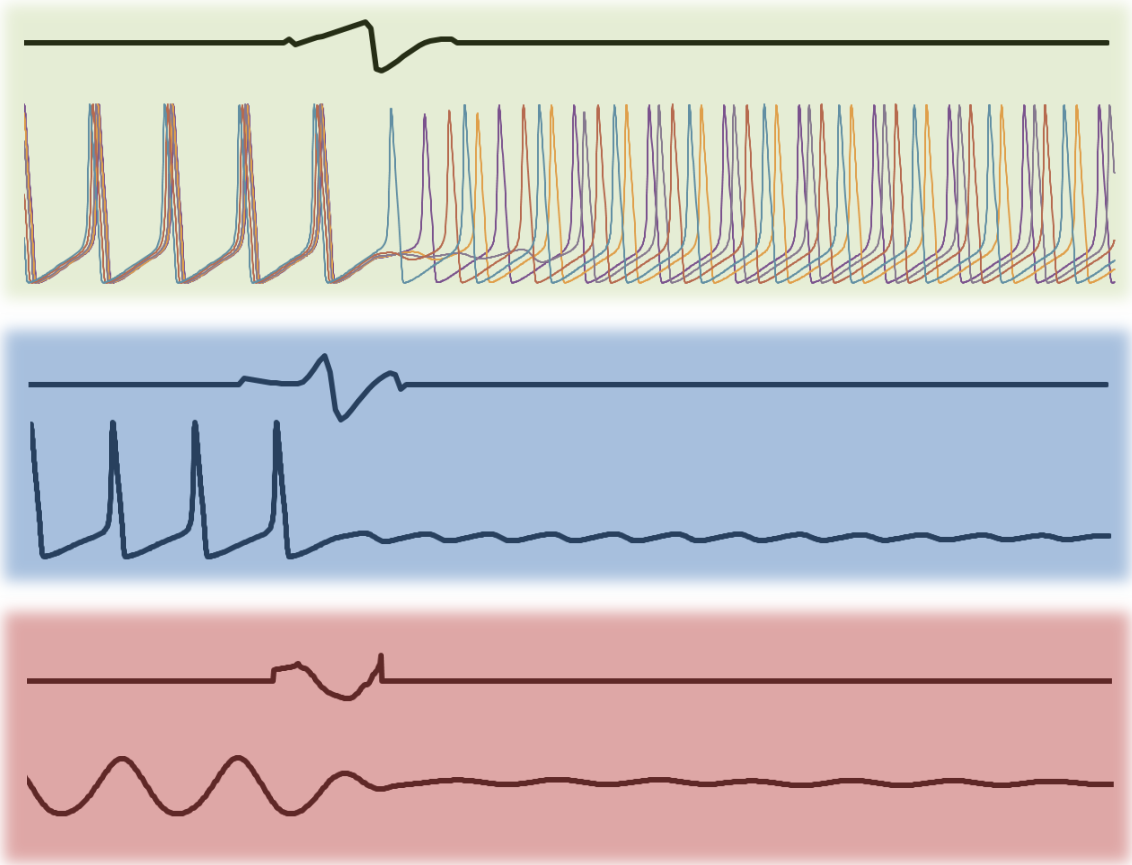
Optimized stimulus: 24.43 μJ/cm^2

Rectangular pulse: 154.88 μJ/cm^2



Chang J. Paydarfar D *Sci Rep* 2018;8:1-13.

Computed optimal stimulus waveforms

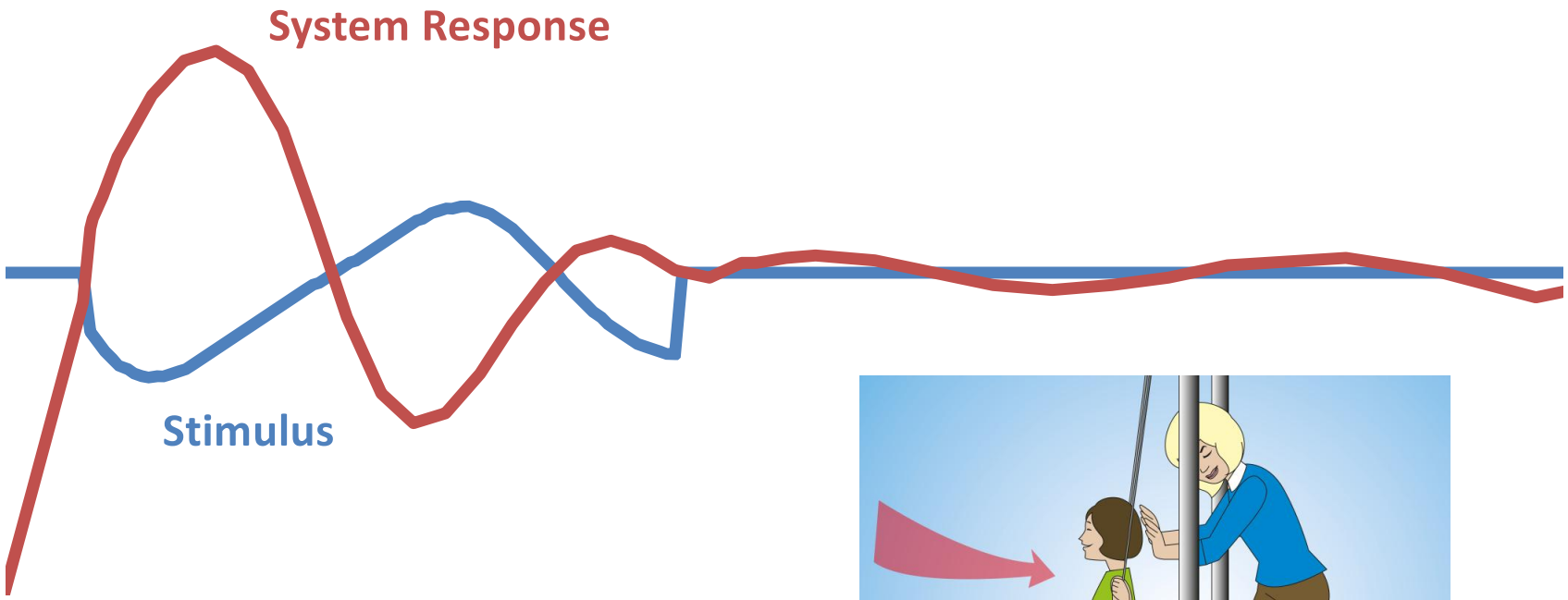


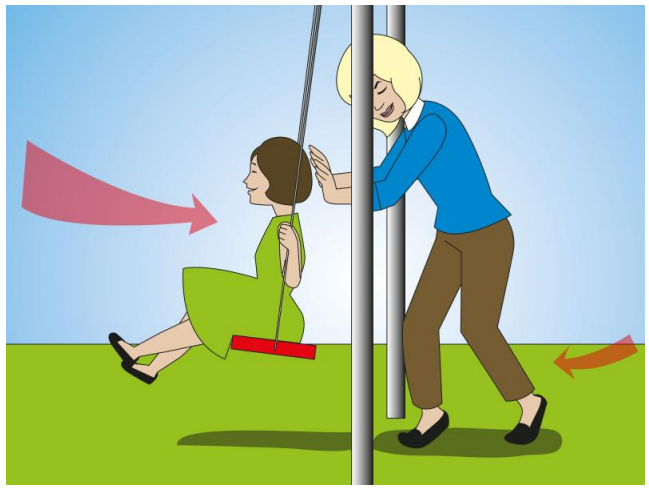
Desynchronization

Bistable Single Cell

Bistable Population

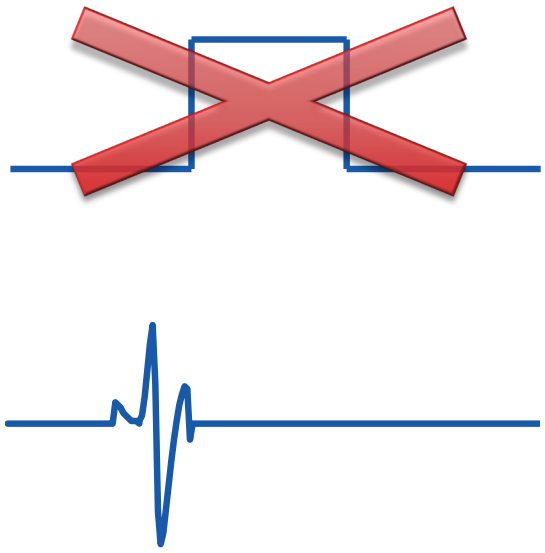
Illustration of counterbalancing mechanism



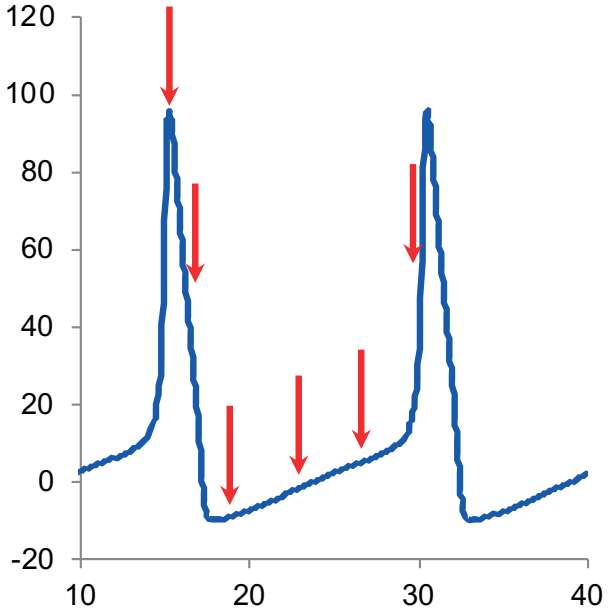


Tailoring therapy to the dysfunctional circuit

Waveform shape

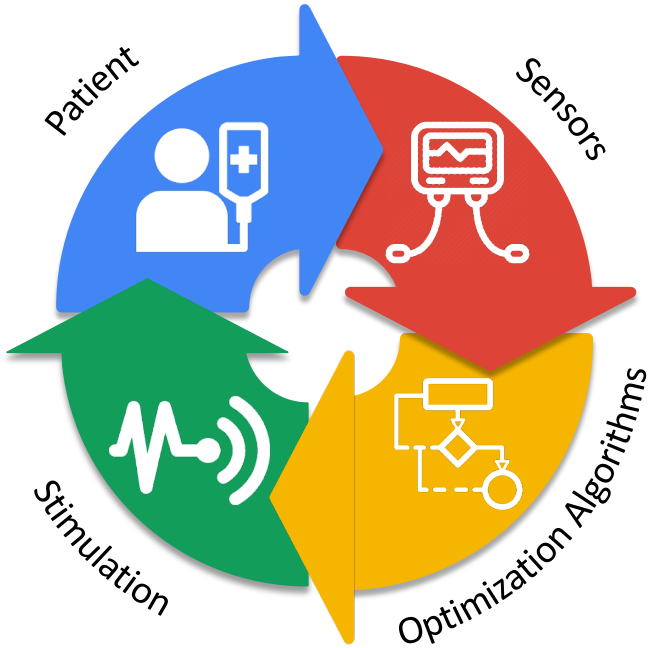


Stimulus timing



Electroceutical Principles

- Mechanisms of action
- Spatial and temporal scales of effect
- Optimal dose profile



Special Thanks!

Varun Sridhar, BSEng
Computational Research Fellow
Clayton Foundation

Software Engineering

Joshua Chang, MD/PhD
Assistant Professor
UT Austin

Machine Learning in Health Care

Sara Hackett, BSEng
Research Engineer
UT Austin

Biomedical Instrumentation

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.