Computational Modeling of Closed-loop Peripheral Nerve Block Based on Halorhodopsin (NpHR)

BIOMEDE 599-003 Neural Engineering Prof. Cindy Chestek
Winter 2016 Final Project

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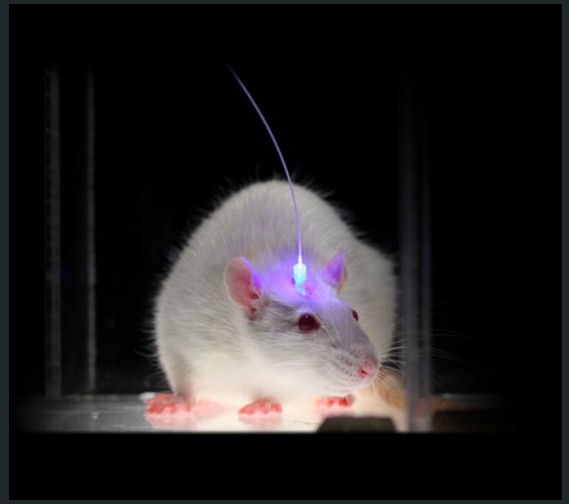
Objectives

- Introduction to optogenetics and neural inhibition solutions;
- Methods of computer finite element simulation
- Results of relations among modeling variables
- Discussion of findings and real world application
- Future work and conclusion

Introduction



Optogenetics = Optics + Genetics

Optogenetics: “the branch of biotechnology which combines genetic engineering with optics to observe and control the function of genetically targeted groups of cells with light, often in the intact animal.”[1]

Optogenetic actuators or opsins: “Light sensitive agents present in or injected into the neuron to achieve effective neuron control”[2].

Commonly used opsins:

Channelrhodopsin (ChR-2), **halorhodopsin (NpHR)** and archaerhodopsin[3]

Research in Optogenetics:

Chronic pain, Parkinson’s disease, epilepsy, depression, obsessive-compulsive disorder (OCD), etc.[2]

Halorhodopsin (NpHR) - Deactivation

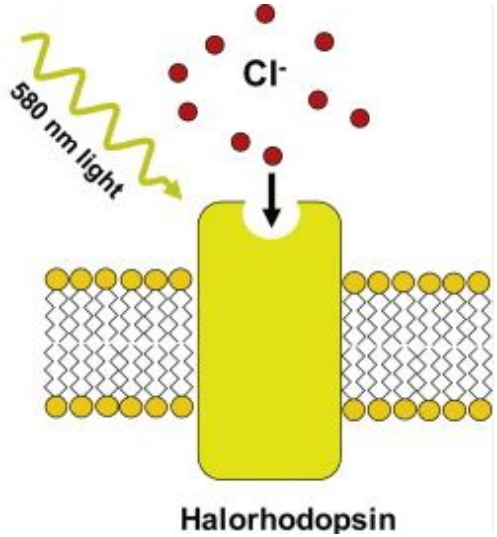
Light gated chloride pump commonly found in halobacteria.

Vesicles that expand the volume of the channel, when exposed to 590-nm light.

Effect: Inward flow of Cl^- accompanied with cation uptake (K^+ or Na^+), leading to hyperpolarization similar to electrical stimulation[4].

Research on Halorhodopsin (NpHR):

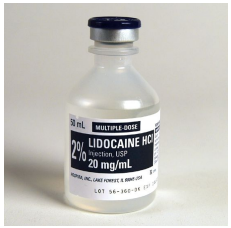
1. NpHR mechanism in subthalamic nucleus of Parkinson's[5].
2. Modelling of locomotive neural circuits using NpHR activation[6].
3. Relationship between the neural circuit models and photochemical models[7].



Conduction Block - Current Solutions

Treatment for Neurological Disorders - Nerve blocking - Blocking of action potentials by specific deactivation of ionic channels

Pharmacological (Lidocaine[8], Procaine)[9]



High neurochemical specificity
Low temporal precision[10]

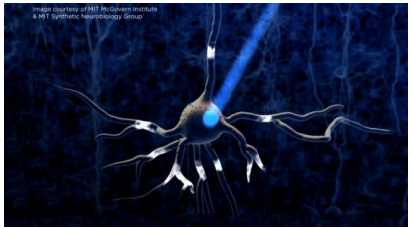
Electrical stimulation - (Spinal Cord Stimulator)[11]

High temporal precision
Low spatial accuracy[10].

http://www.nevro.com/physicians/senza-system/

Proposed Solution

Optical stimulation



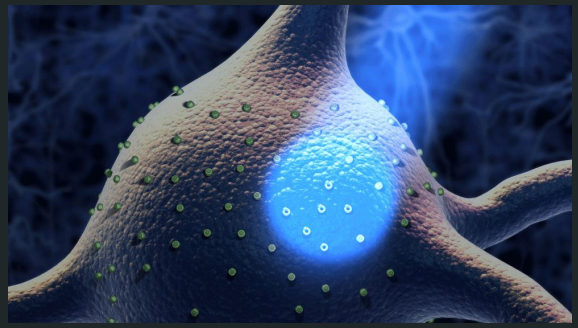
High spatial, subcellular and temporal precision[10]

Project Goals

To computationally model a device, that is capable of actively detecting action potentials propagating in a peripheral afferent neuron and blocking the propagation of the action potentials downstream from the recording site by activating NpHR with optogenetic stimulation.

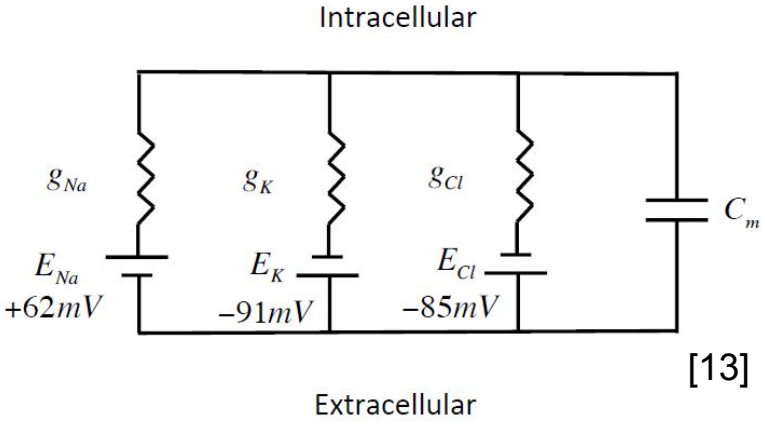
1. Establish a cable theory model adapted to neurons expressing NpHR based on the Hodgkin-Huxley equations.
2. To build a closed-loop integrated system that applies the aforementioned cable theory model to the inhibition of neuronal signal.
3. To optimize the system by adjusting the related parameters, to ensure effective inhibition under various physiological conditions.

Methods



Neural Circuits Review

Hodgkin & Huxley[12][13]:



[13]

$$I_K = g_K(V_n - E_K)$$

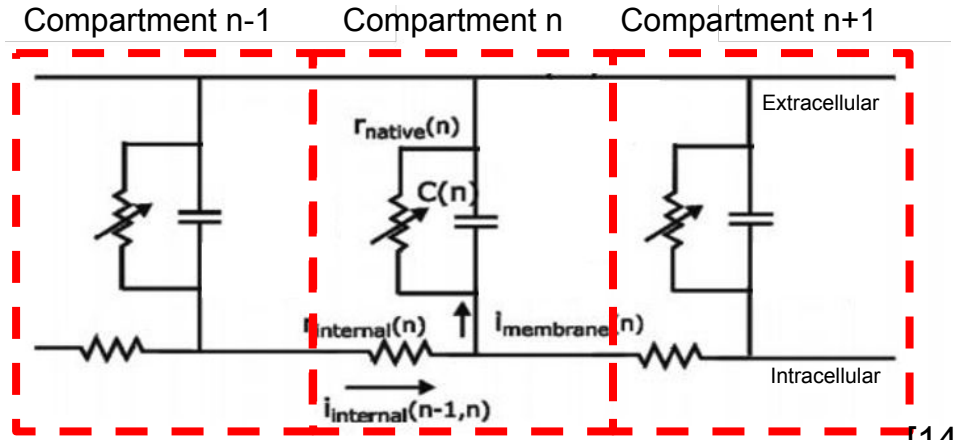
$$g_K = \bar{g}_K n^4$$

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n$$

$$I_{Ionic} = I_K + I_{Na} + I_{Cl}$$

Same for m and h!

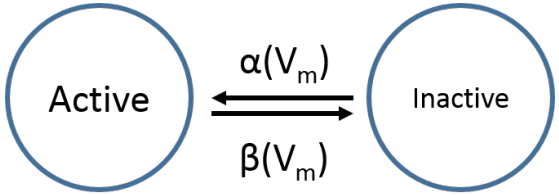
Cable Theory[14]:



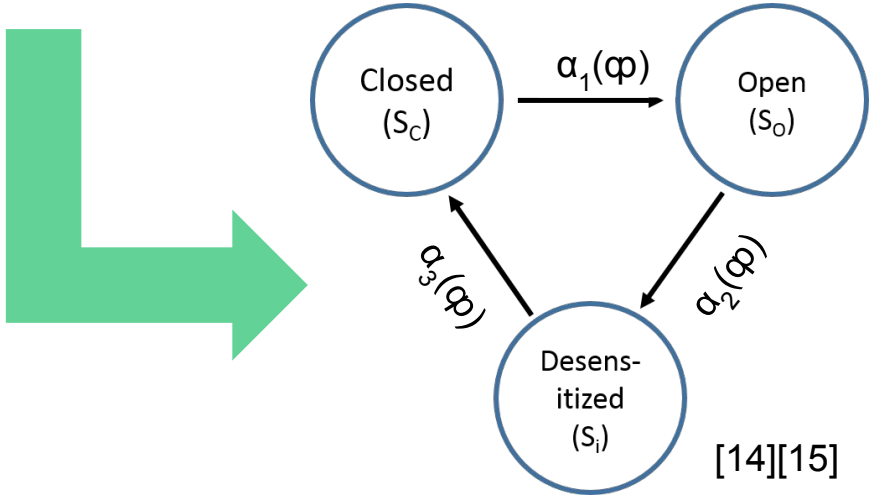
[14]

$$\frac{dV_n}{dt} = -\frac{1}{C_m}[I^n_{Ionic} + \gamma(V_n - V_{n-1}) + \gamma(V_n - V_{n+1})]$$

NpHR Kinetics



m, n & h kinetics[13]



[14][15]

$$\frac{ds_o}{dt} = s_c\alpha_1 - s_o\alpha_2$$

$$\frac{ds_c}{dt} = s_i\alpha_3 - s_c\alpha_1$$

$$\frac{ds_i}{dt} = s_o\alpha_2 - s_i\alpha_3$$

$$\alpha_1 = a_1(\varphi(t)/\varphi_0)$$

$$\alpha_2 = a_2$$

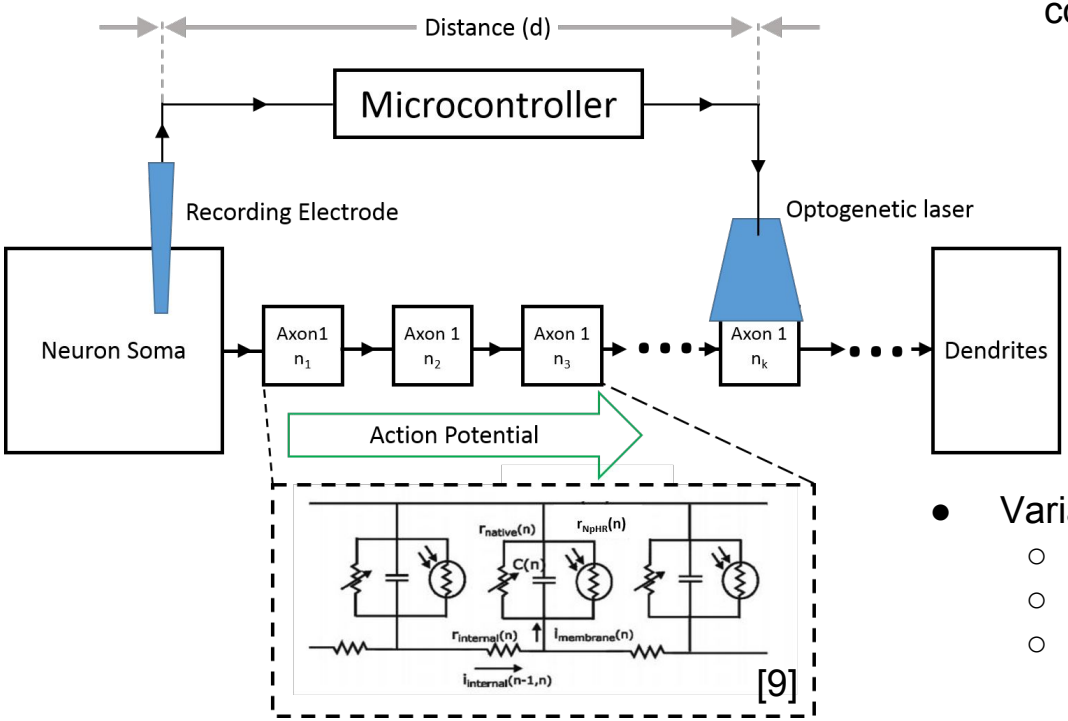
$$\alpha_3 = a_{3d} + a_{3l}\log(\varphi(t)/\varphi_0)$$

$$I_{NpHR} = \overline{g_{NpHR}} * s_o(\varphi) * (V_m - E_{Cl})$$

[14][15]

*: Parameter Values in Appendix.

Full System Simulation



- Combines cable theory, Hodgkin & Huxley, NpHR channel kinetics, and device feedforward control

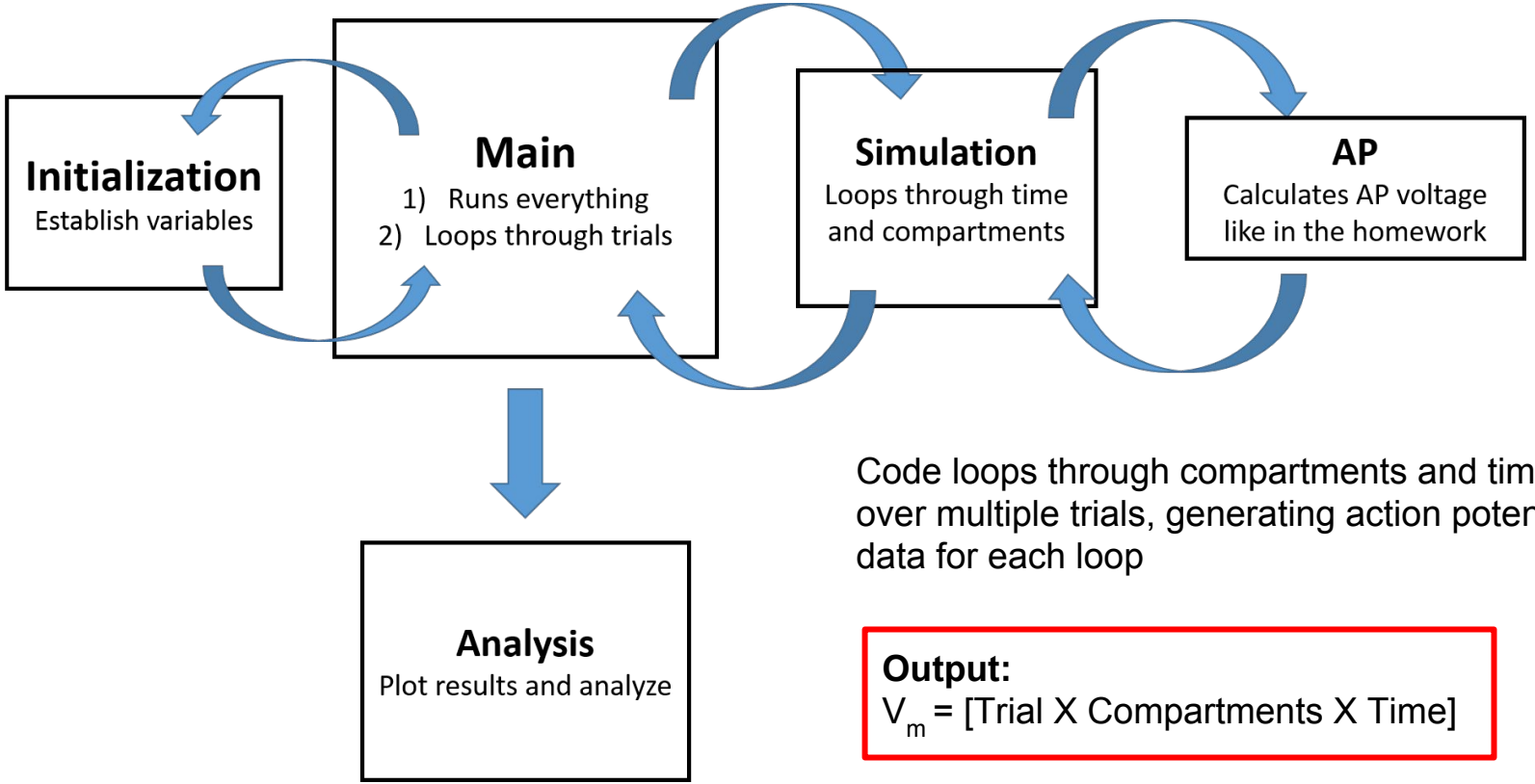
Unifying Equation:

$$\frac{dV_n}{dt} = -\frac{1}{C_m}\left[I^n_{Ionic} + I^n_{NpHR} + \gamma(V_n - V_{n-1}) + \gamma(V_n - V_{n+1})\right]$$

[14]

- Variables to explore:
  - Length of region exposed to light
  - Intensity of light
  - Distance between recording electrode and laser
  - Pulsed light application

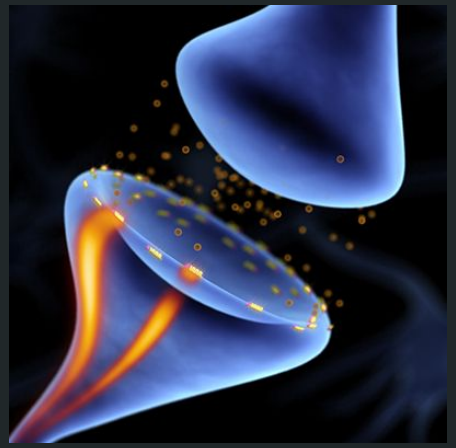
MATLAB Code Description



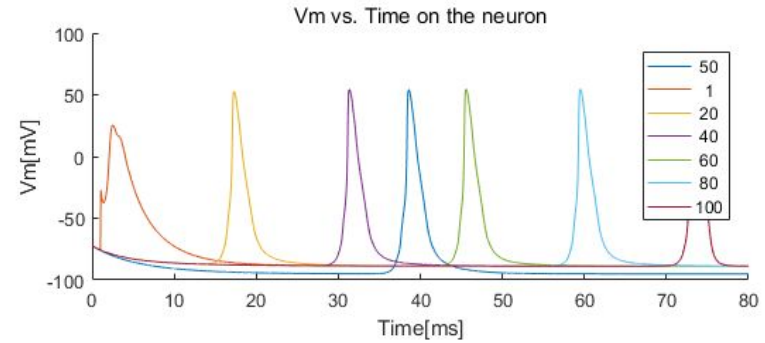
Code loops through compartments and time over multiple trials, generating action potential data for each loop

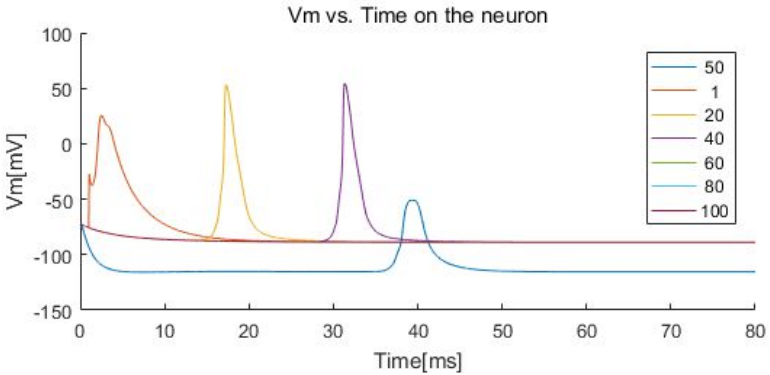
Output:
V_m = [Trial X Compartments X Time]

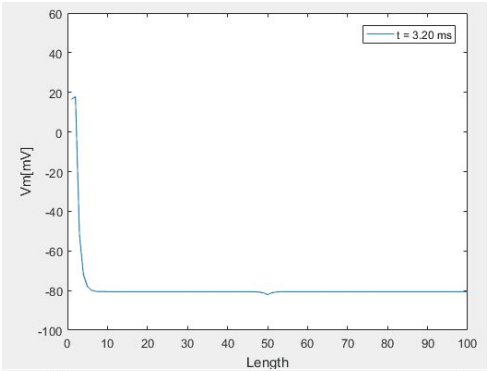
Results

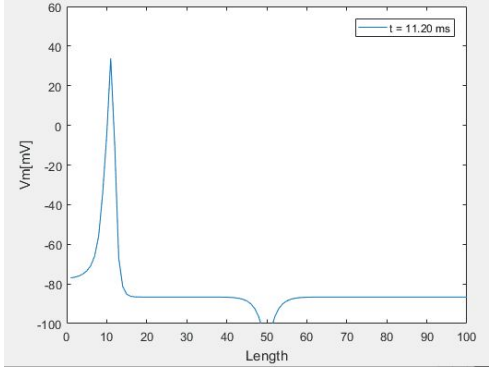


Action Potentials









IA = light intensity relative to subthreshold irradiance in mW/mm^2;

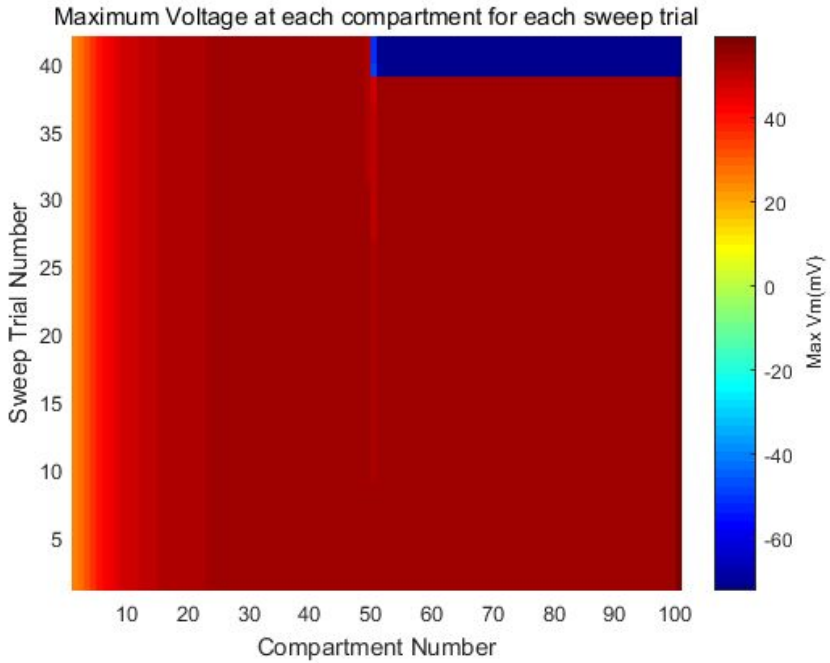
lleng = light exposed region length in compartment number;

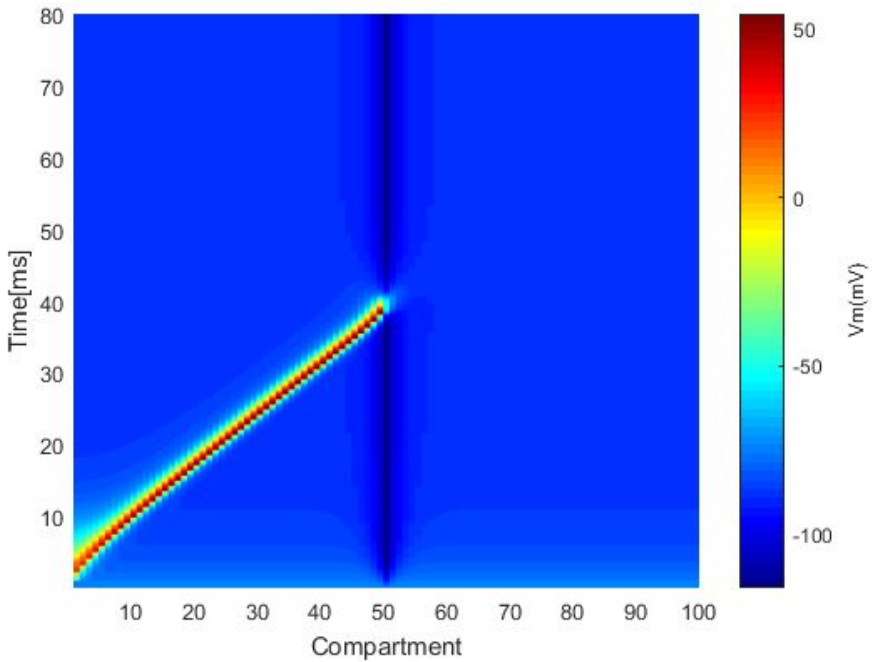
lcent = light inhibition central position in compartment number (relative to the first compartment);

lst = inhibition patterns in ms;

For later sides, L = 1 cm, dt = 0.01 ms.

Light Irradiance

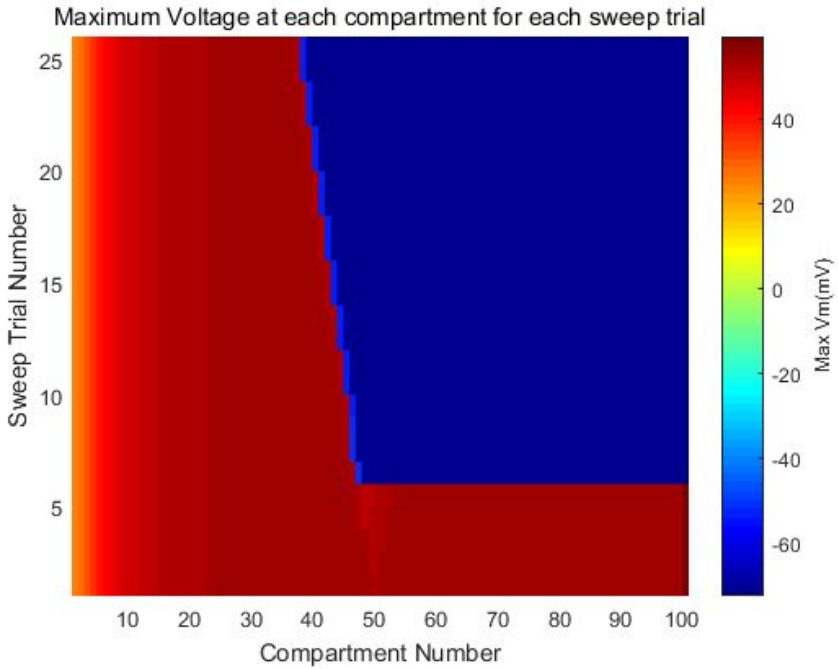


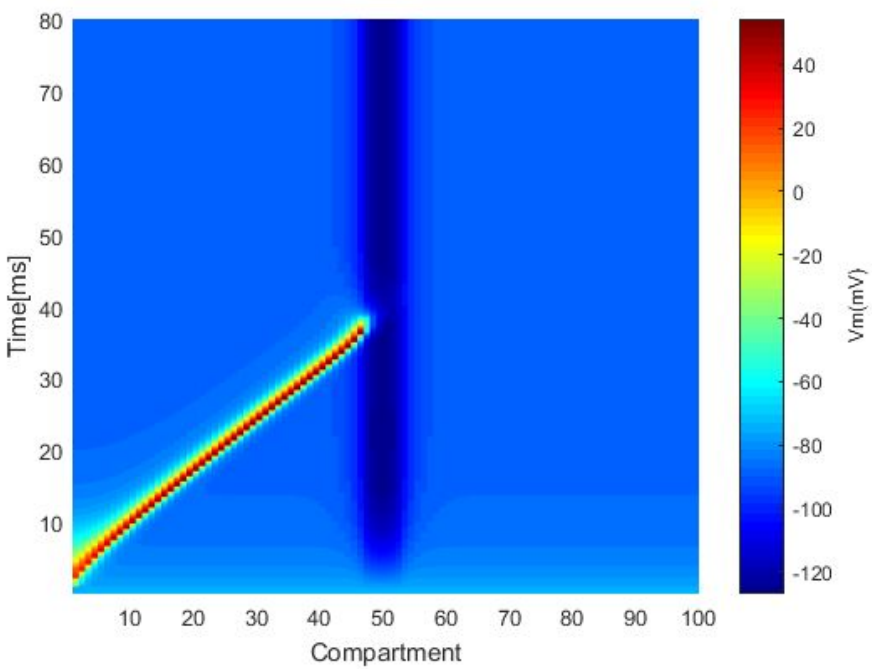


IA logarithmic sweep from 1 to 1000, Icent = 50, Ileng = 1, Ist = [0,∞].

Blocked at IA ≥ approx. 790.

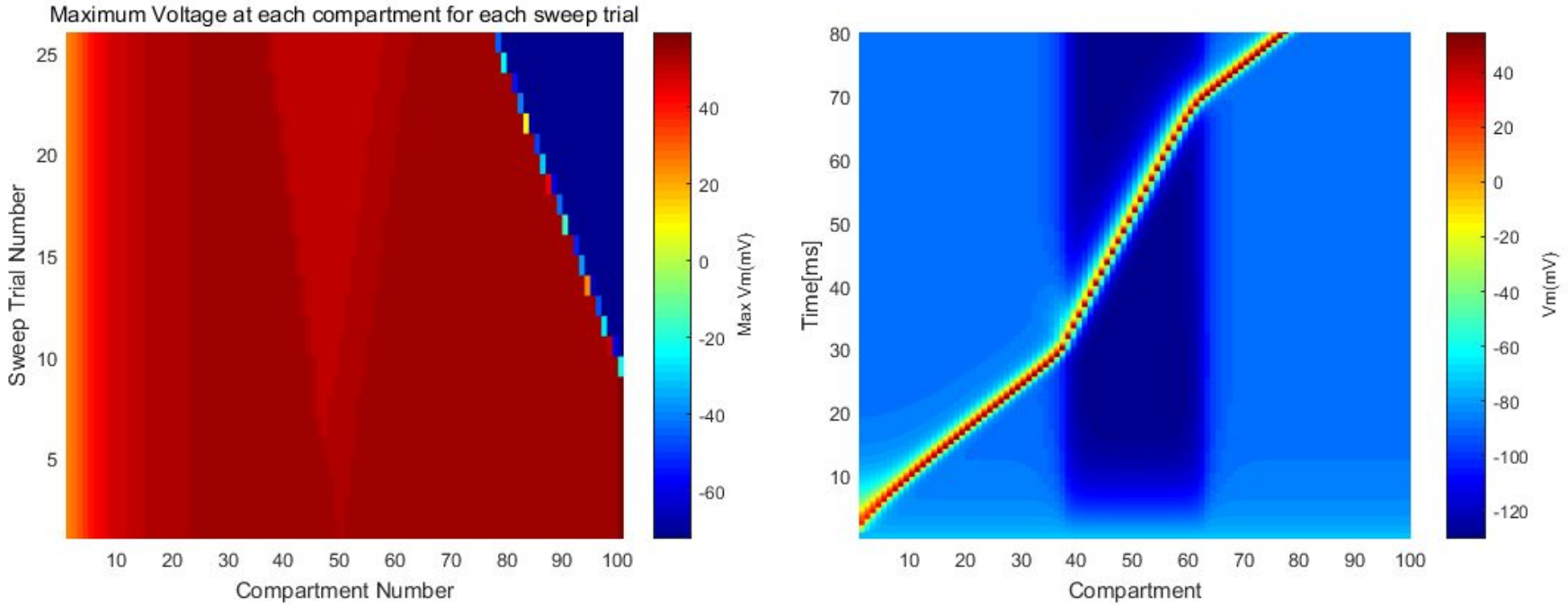
Light Inhibition Region Length (1 of 2)





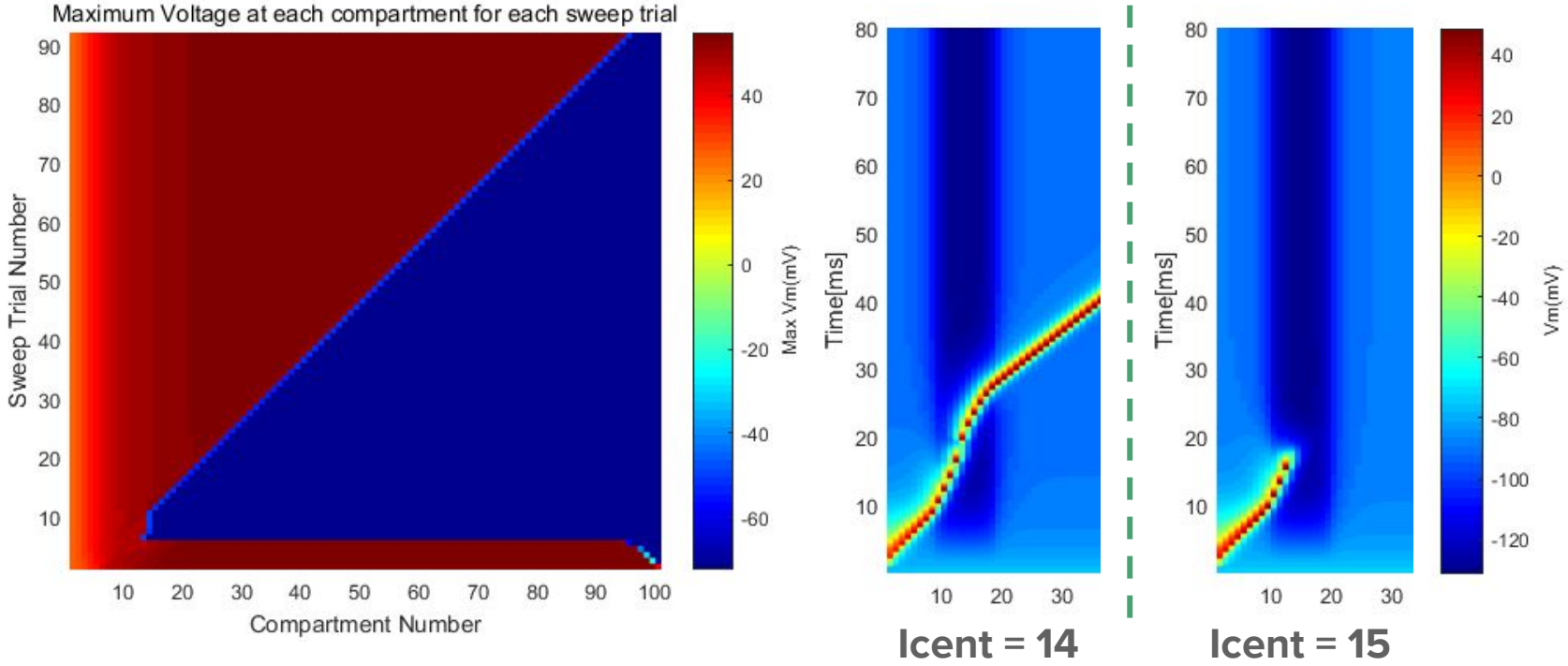
Ileng linear sweep from 1 to 25, Icent = 50, **IA = 30**, Ist = [0,∞]. Blocked at Ileng ≥ 6.

Light Inhibition Region Length (2 of 2)



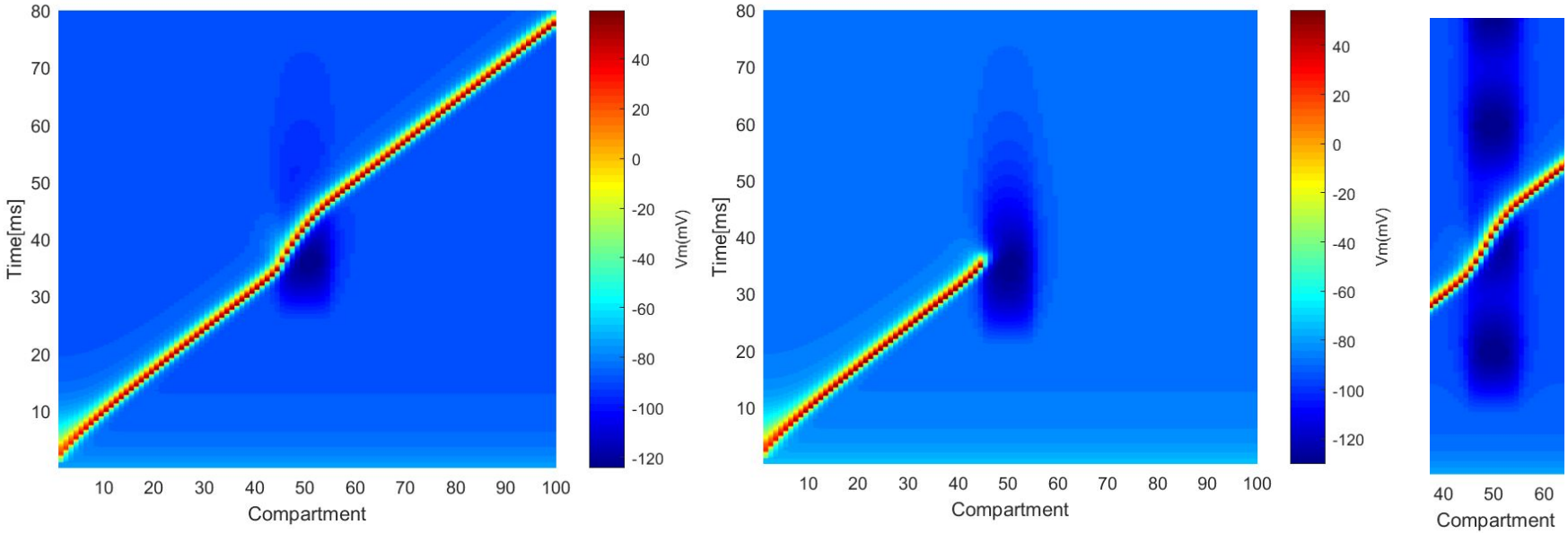
lleng linear sweep from 1 to 25, lcent = 50, **IA = 25**, lst = [0,∞]. No blockage.

Light Inhibition Position (Delay Time)



Icent linear sweep from 10 to 100, Ileng = 10, IA = 30, **Ist = [after AP stabilized,∞]**. Blocked at Icent ≥ 15.

Light Pulses and Patterns



Ileng = 10, IA = 30, Icent = 50

Pulse = 25~35 ms Failure **Pulse = 20~35 ms Success**

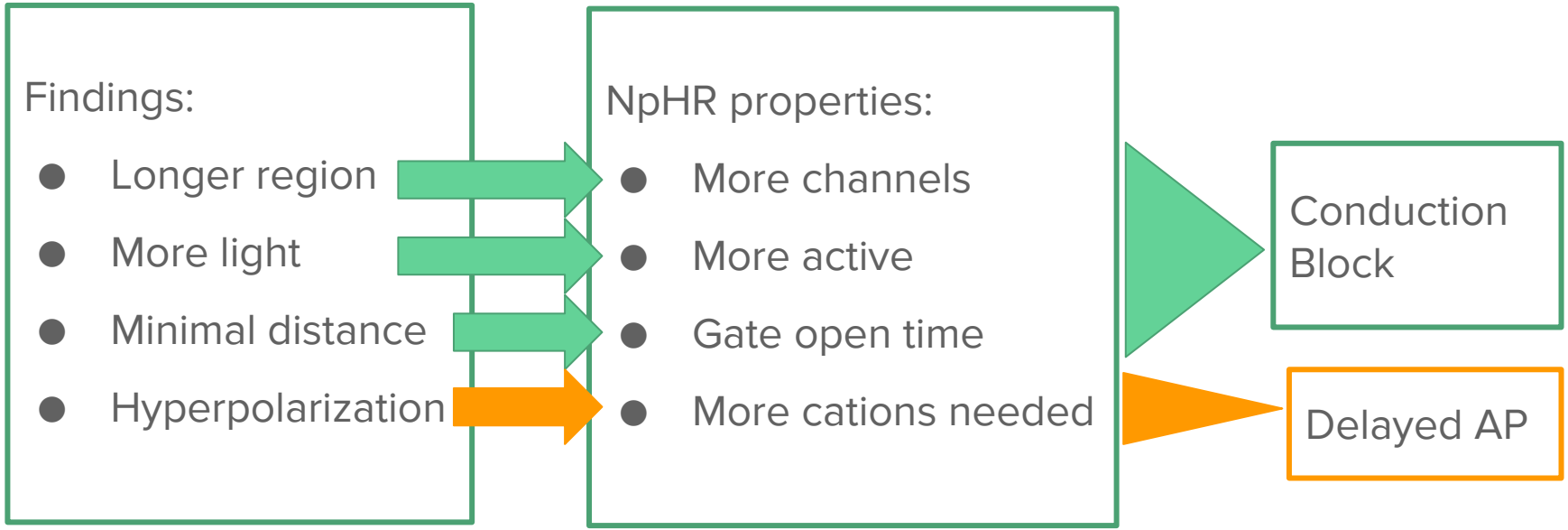
Modulations that produce single pulse / patterns are possible, e.g. 50 Hz pulses.

Discussion

Summary of Findings

1. It is necessary to reach a **threshold light intensity** to block an AP.
2. **Light inhibition region length** matters:
    a. A larger light inhibit region buttresses AP blockage.
    b. A longer region compensates the decrease in intensity up to a point.
    c. If blocking is unsuccessful (long region with dim light), the AP will be delayed.
3. **A minimal separation** between detection site and inhibition site is required to account for the response time of light stimulation.
4. It is feasible to control on-demand using light pulses.

Causal Explanations



Connection to Real World Application

Loads of design requirements for an implantable device before marketing:

Effective, low-power, small, cheap, etc.

Tradeoffs:

➔ Closed loop: on-demand, but extra microcomputer processing and chip cost;

➔ Open loop: simple, but potentially battery-eating as sources always on.

Restrictions:

➔ *The actual genetic therapy;*

➔ Device finite size;

➔ Light source limited output power;

➔ Accessibility of nerve for detection site and inhibition site.

=> Our nerve inhibition device is achievable in theory.

Future Work and Conclusion

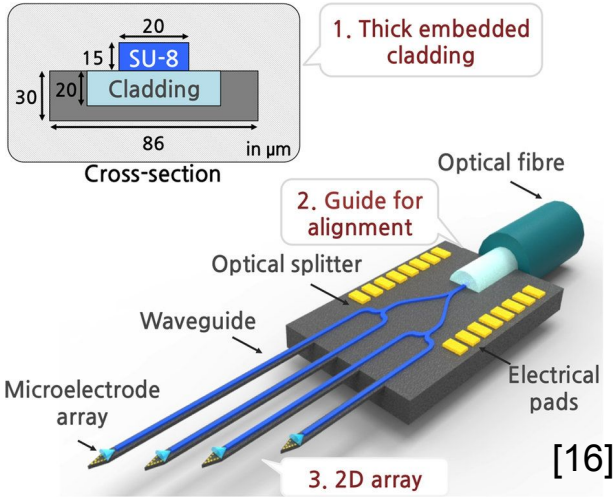
Future Work - For Our Model

- There are **compatibility issues of modeling parameters** due to multiple sources of neuron bioelectrical properties and model simplification.
  1. Use specific parameters for specific afferent axons in humans
     E.g. Sciatic nerve, amputation sites, etc.
  2. Fix propagation speed of APs: only 0.1 m/s, and should be independent to compartment number;
  3. Include the influence of neuron diameter to inter-compartment conductance (γ) and using better neuron geometry;

Future Work - For a Device

- Establish sensitivity of variables to blockage effect;
- Take into account the influence of surrounding tissue to the light using Finite Element Modeling tools:

  Diffraction, absorption at wavelength used, etc.
- Fast wireless device;
- Novel optrode system accounting for optimal recording and stimulating separation.



[16]

Conclusion

- We have devised a computer model that simulates a pain blocking device
- Effectiveness relies on light intensity, separation of light source to electrode, light application length, and pulse length
- NpHR demonstrates a robust mechanism for conduction block
- Future work relies on expanding of the simulation parameters and a better physiological model

Thank you!
Q & A

References

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Pocket Slide 1: Global Constants

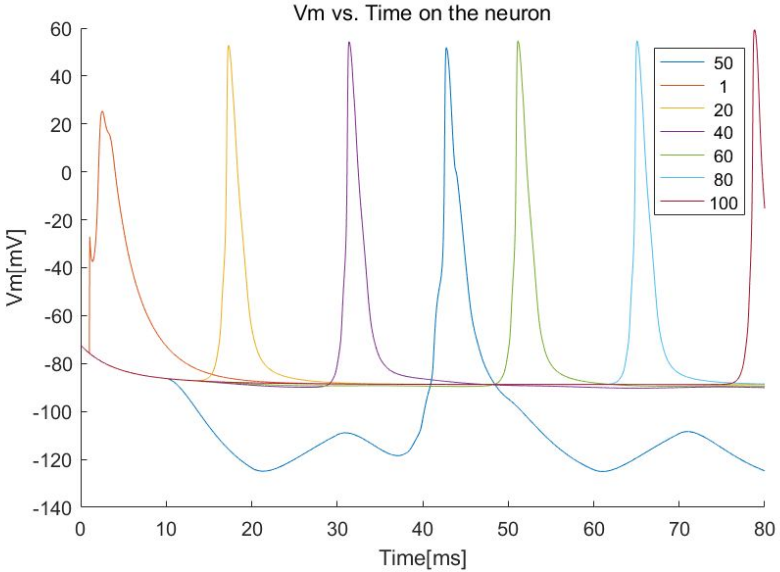
	K	Na	Cl	unit	meaning
Cout	4	145	120	mM	Extracellular Equilibrium Concentration
Cin	155	12	4	mM	Intracellular Equilibrium Concentration
g_bar	100	50	0.3	mS/cm^2	Total Conductance
z	1	1	-1	1	Ion Charge
P	1	0.04	0.45	1	permeability

	n	m	h
Aa	0.02	0.182	0.024
Ab	0.002	0.124	0.0091
Vha	20	-35	-50
Vhb	20	-35	-75
ka	9	9	5
kb	9	9	5

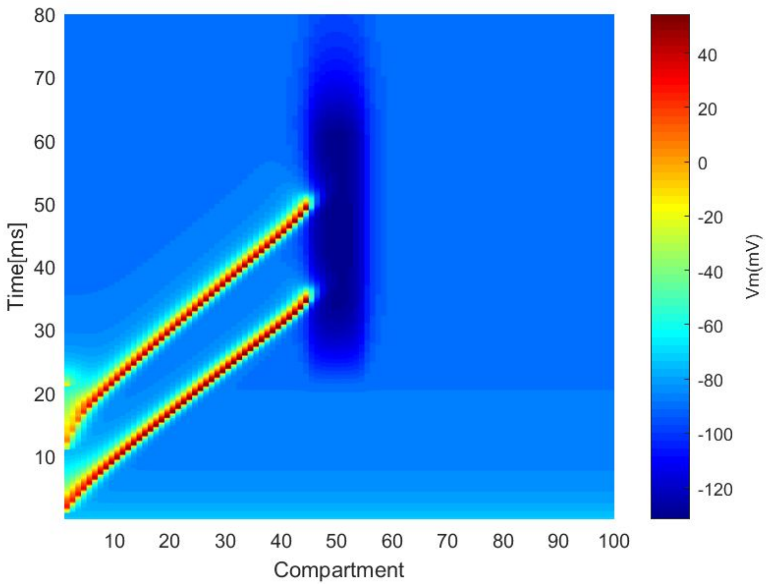
NpHR Characteristics			
E_0	0.0014	mW/mm^2	Sub-threshold irradiance
NpHR_a3d	0.1	1/ms	Light-insensitive recovery
g_NpHR	1	mS/cm^2	conductance
NpHR_a2	0.1	1/ms	Inactivation O to I

[12][13][15][17]

Pocket Slide 2: More Figures



Vm of 50 Hz pulse stimulation



Possible to simulate multiple APs