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Dr. Les Lee | M^4 Program

Biomolecular soft matter for tunable, low-power neuromorphic computing

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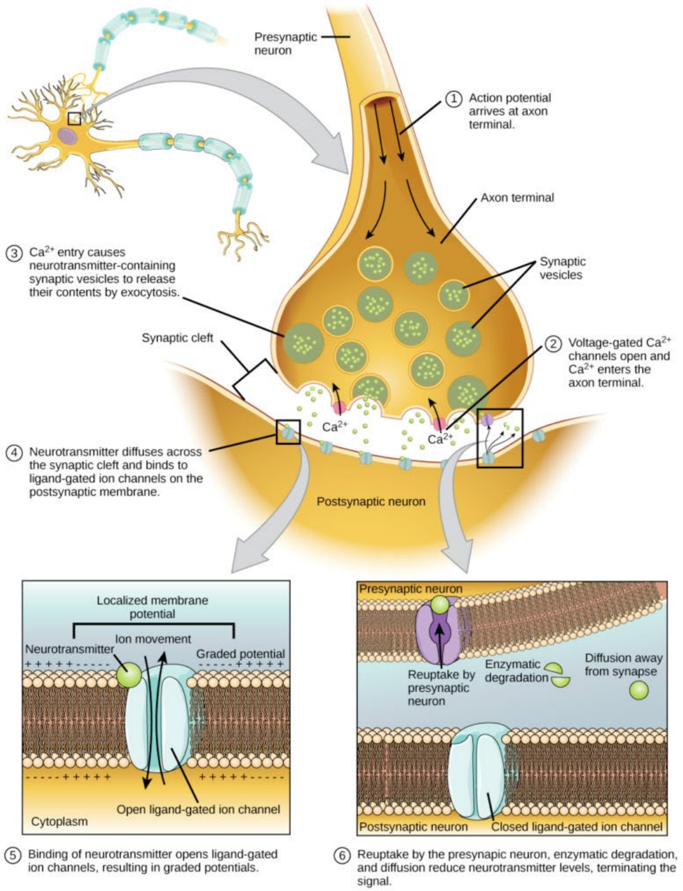
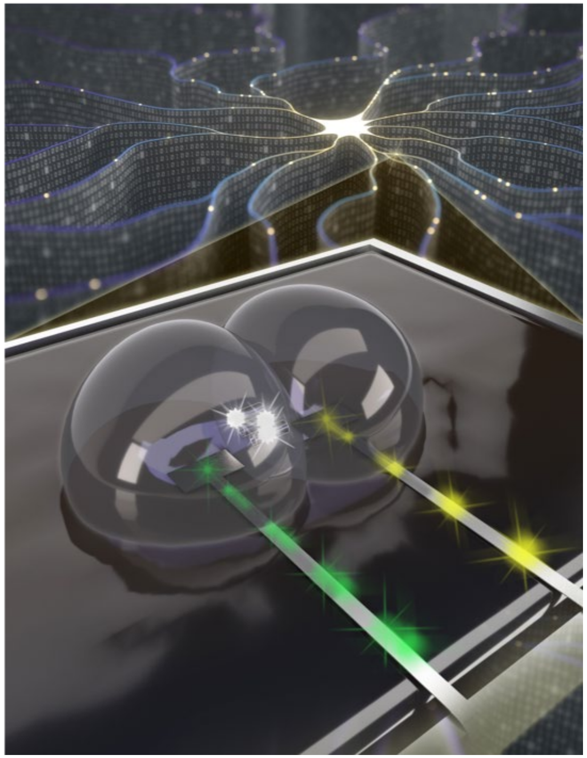


"The number of biological structures and functions that have been mimicked electrically using emerging devices is still very limited. To better emulate the brain's functions, it is believed that the fundamental basis of the brain, including its structure and components, as well as the behaviors and working mechanisms of neural circuits, needs to be re-visited and better understood in the context of neuromorphic computing."

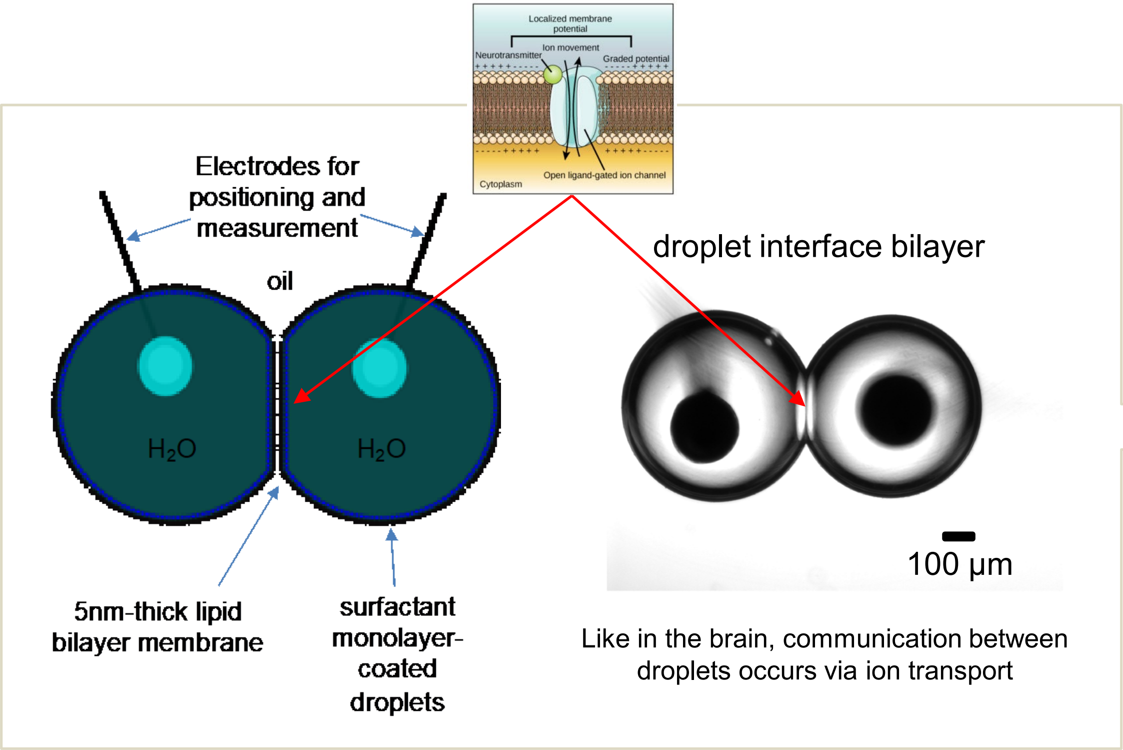
Tang, J.; Yuan, F.; Shen, X.; Wang, Z.; Rao, M.; He, Y.; Sun, Y.; Li, X.; Zhang, W.; Li, Y.; Gao, B.; Qian, H.; Bi, G.; Song, S.; Yang, J. J.; Wu, H., Bridging Biological and Artificial Neural Networks with Emerging Neuromorphic Devices: Fundamentals, Progress, and Challenges. *Advanced Materials* **2019,** *31* (49), 1902761.



We aim to advance the understanding and development of tunable synapse and neuron-inspired devices and materials for embedded signal processing, memory, and learning.

Hypothesis: Emulating composition, structure, and transport properties of neuronal membranes will yield new functionalities in modular, low-power brain-inspired synapses and neurons.

Unique Approach: nm-thick insulating biomimetic membranes doped with voltage-activated biomolecules



Electrodes for positioning and measurement

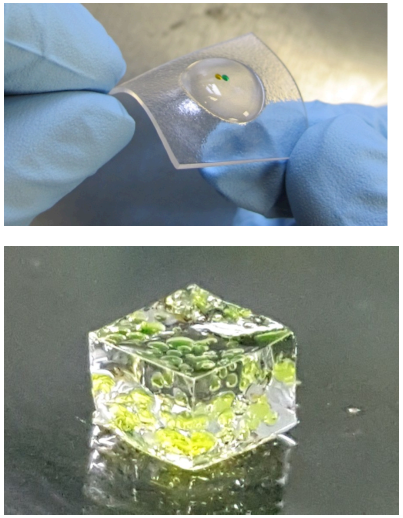
droplet interface bilayer

5nm-thick lipid bilayer membrane

surfactant monolayer-coated droplets

Like in the brain, communication between droplets occurs via ion transport

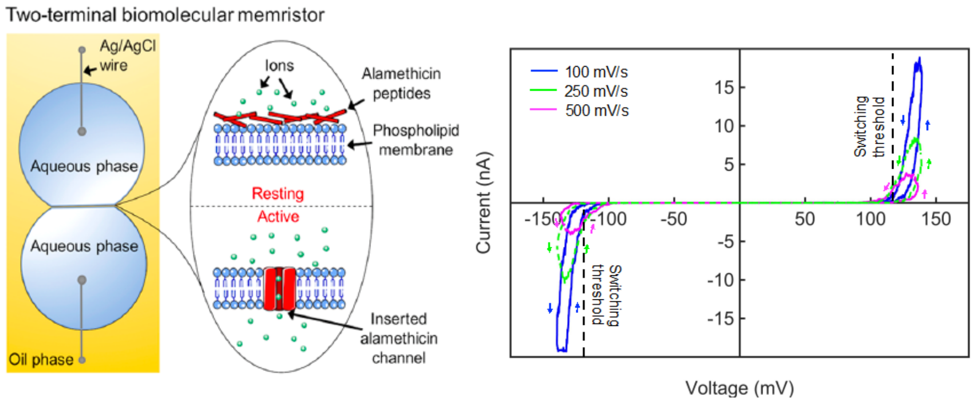
Printable biomolecular soft materials



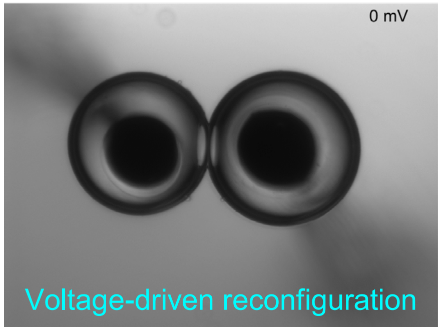
Specific MURI Objectives

- Study plasticity/memory in membranes containing voltage-dependent biomolecules.
- Tune memory retention and switching dynamics.
- Assemble and characterize modular biomolecular synapses and neurons.

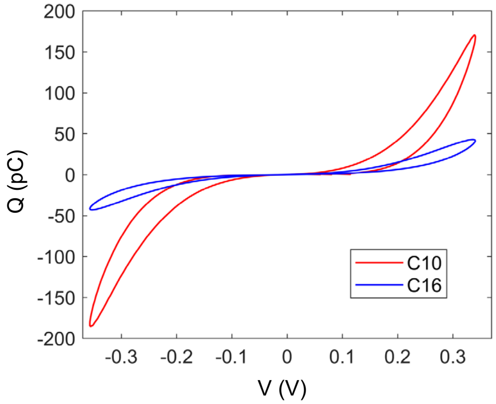
Biomembrane-based synapses exhibit volatile memristance and memcapacitance



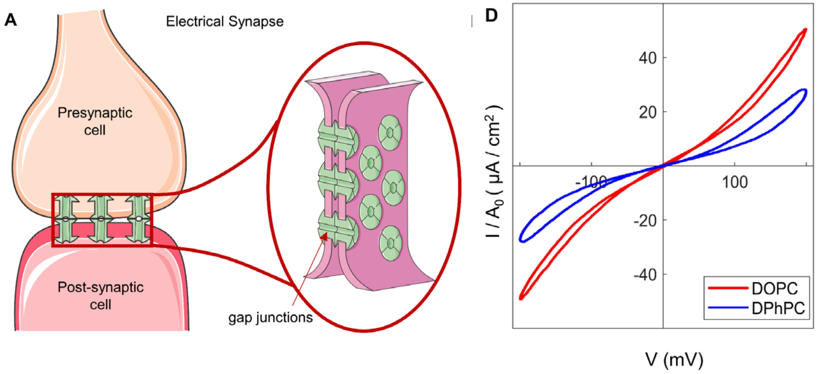
Najem, J. S., et al., *ACS Nano* 2018, *12* (5), 4702-4711.



$$C(R,W) = \frac{\varepsilon\varepsilon_0\left(a\pi R(t)^2\right)}{W(t)}$$



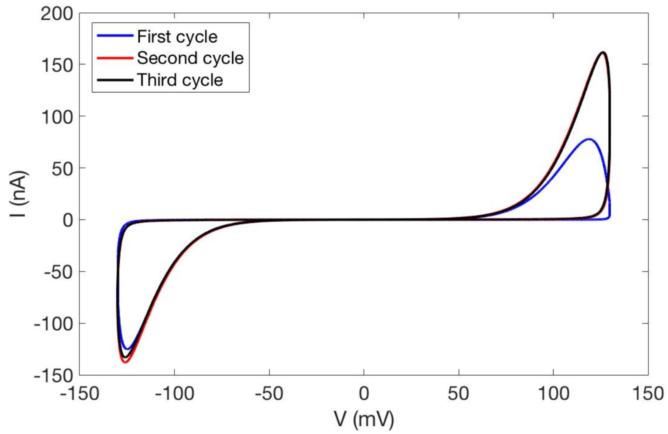
Najem, J. S., et al., *Nat Comm* 2019, 10 (1), 3239.



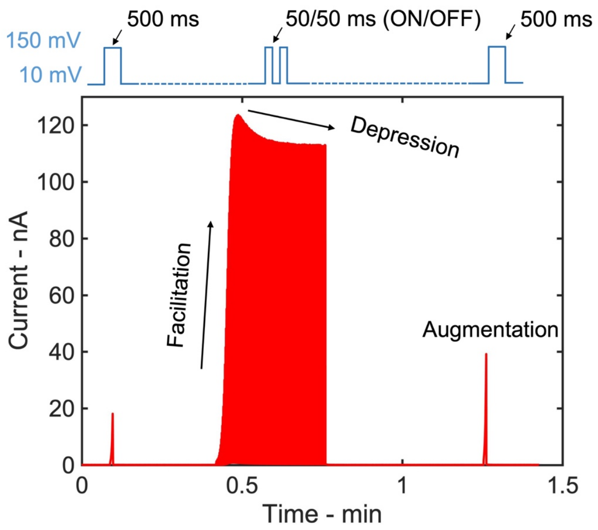
Koner, S., et al., *Nanoscale* 2019, 11 (40), 18640-18652.

Gaps: 1) channels with memory; 2) long-term (non-volatile) memory; and 3) neuron-like spike generation

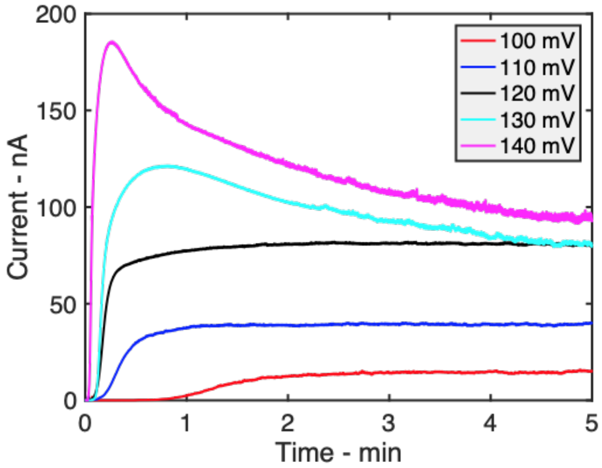
Voltage-activated plasticity and hysteresis across multiple time scales in monazomycin (Mz)-doped DIBs



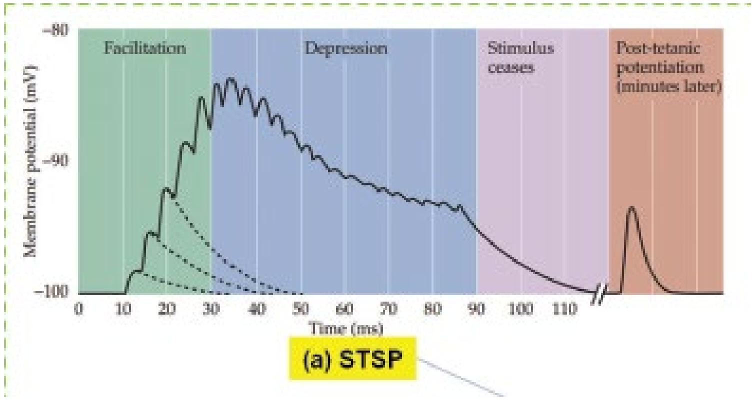
Memristance in Mz-doped membranes



Multiple time scales of memory



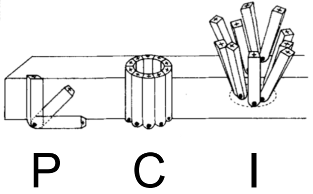
Bi-directional plasticity



Tang, J., et al., *Adv. Mat.* **2019,** *31* (49), 1902761.

Year 1 Aims: quantify, model, and tune Mz-based synapses and investigate neuron-like behavior in biomembranes

Physical states



Transition Schemes

$$P \underset{k_{1r}}{\overset{k_{1a}}{\rightleftarrows}} C \underset{k_{2r}}{\overset{k_2}{\rightleftarrows}} I$$

$$C + P \xrightarrow{k_{1b}} 2C$$

Kinetics

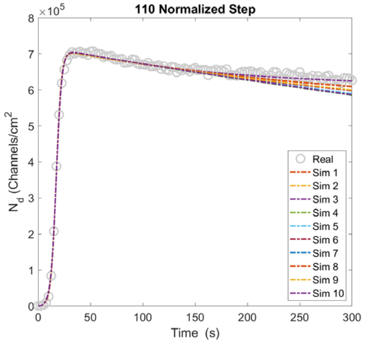
$$\frac{d[P]}{dt} = -k_{1a}(v)[P] - k_{1b}(v)[C][P] + k_{1r}[C]$$

$$\frac{d[C]}{dt} = k_{1a}(v)[P] + k_{1b}(v)[C][P] - k_{1r}[C] - k_2(v)[C] + k_{2r}[I]$$

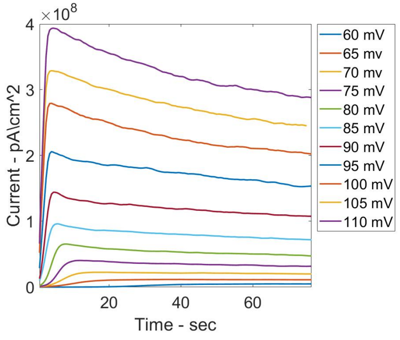
$$\frac{d[I]}{dt} = k_2(v)[C] - k_{2r}[I]$$

Modeling Mz

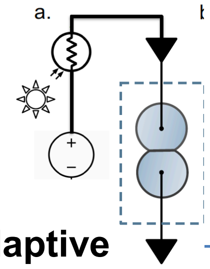
Fitting of model parameters

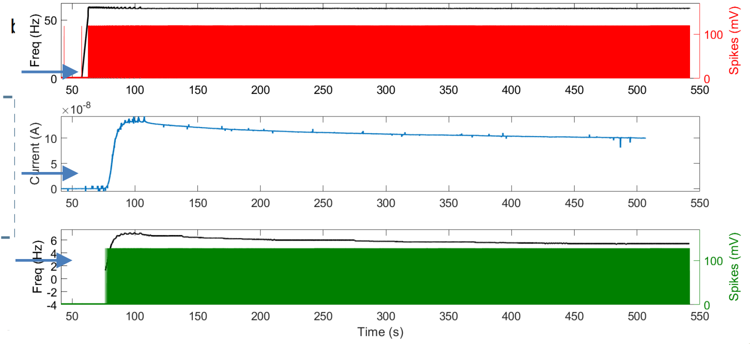


Tuning dynamics



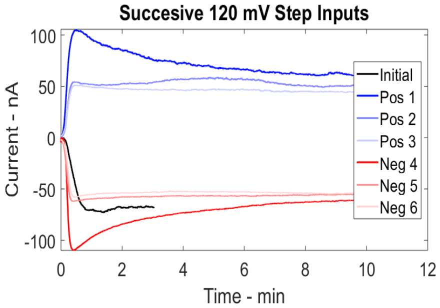
Quantifying Mz kinetics and tuning responses



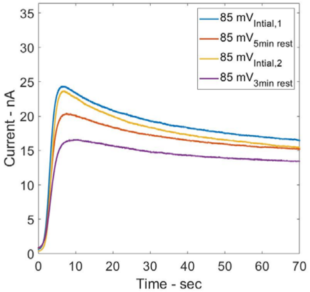


Adaptive filtering

Mz inactivation = stored memory



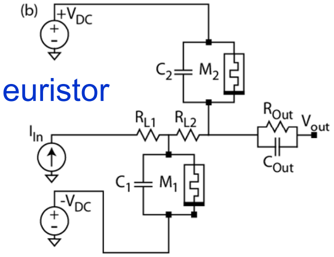
Passive recover after inactivation

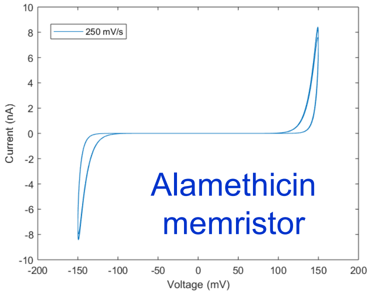


Linking channel kinetics to stored memory

Low voltage spike generation

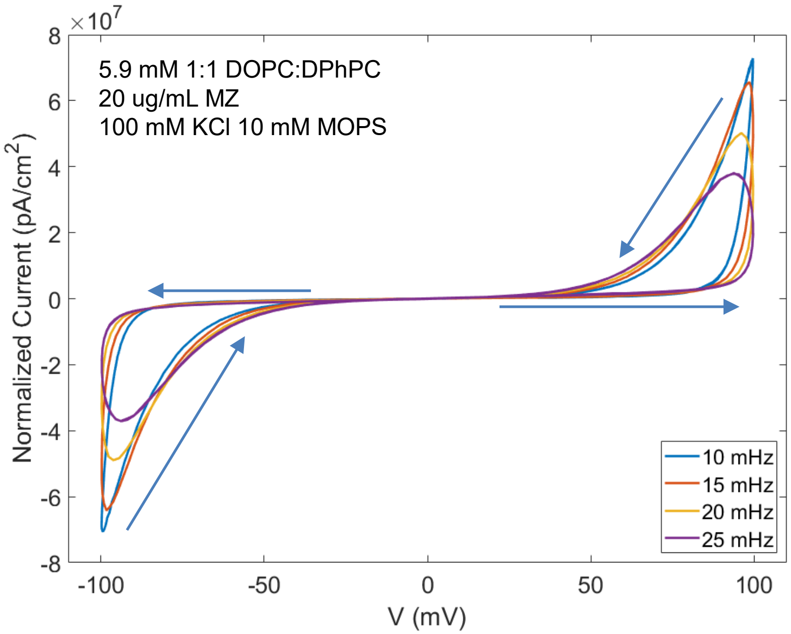
Neuristor

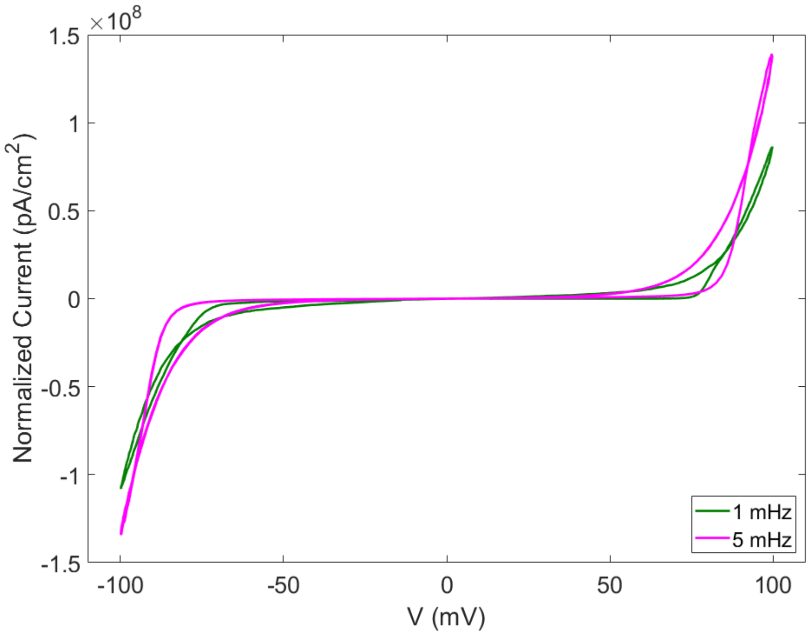


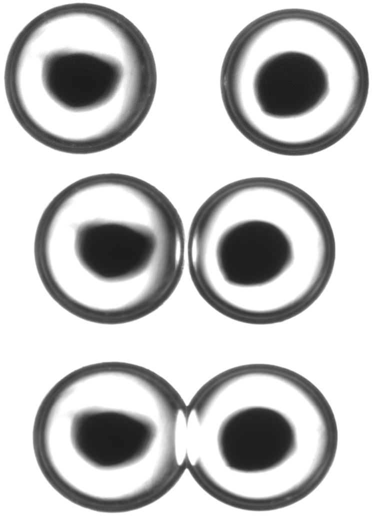


Alamethicin memristor

Monazomycin (Mz) based memristance

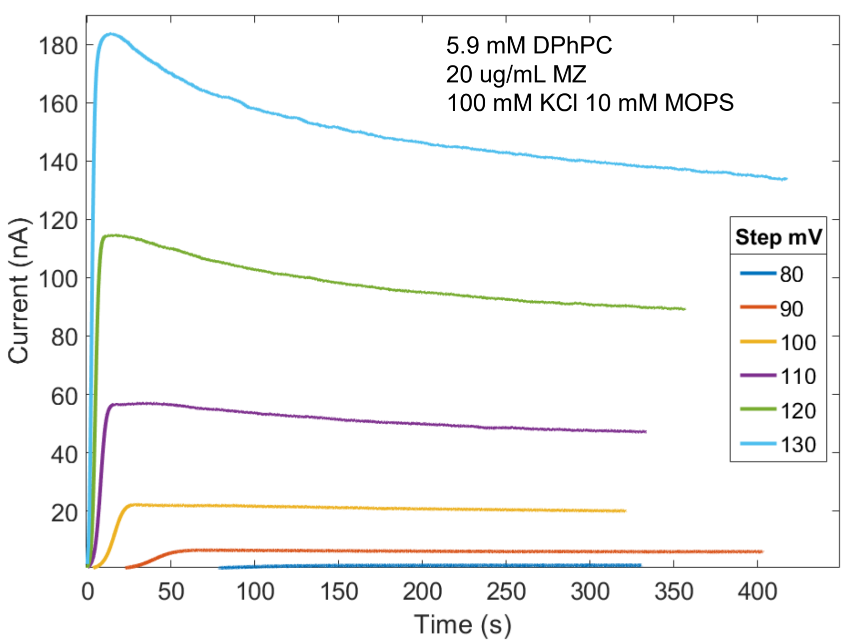


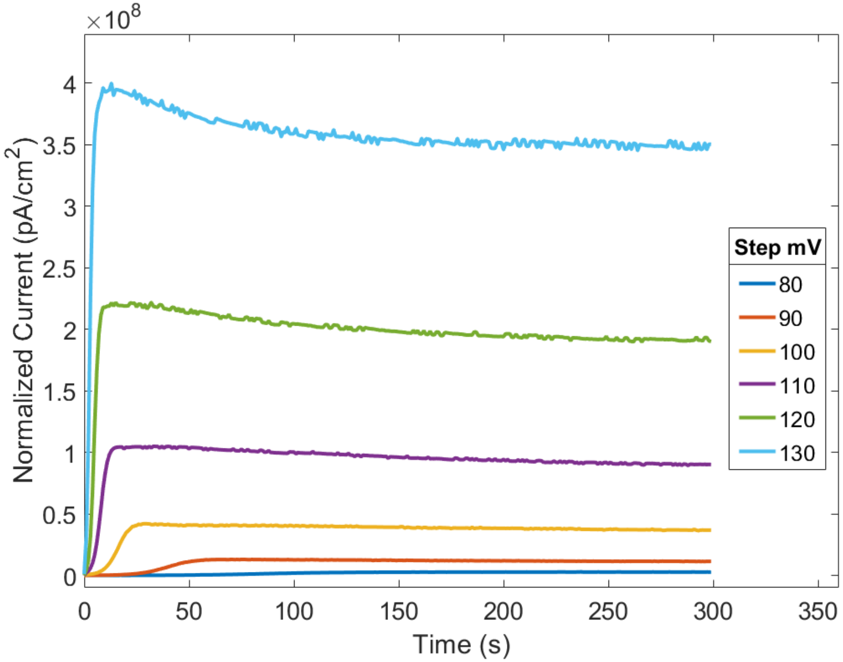


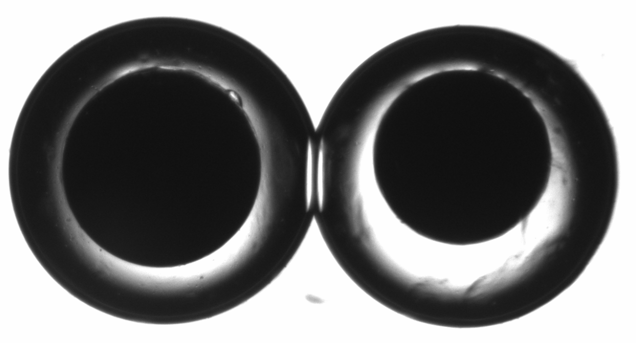


- Mz channels open as voltage approaches |100 mV| and close as voltage returns to zero.
- Thus, pinched hysteresis observed indicates volatile memristance.
- Hysteresis varies with frequency: including some interesting double-pinching at extremely low frequencies due to channel inactivation at large potentials.

Monazomycin based memristive behavior



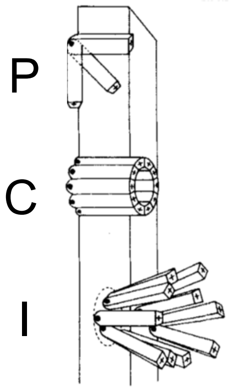




- Quasi-static step inputs show facilitation followed by depression.
- Normalized currents are used to represent these due to droplet electrowetting, which happens simultaneously.

Physical States and Kinetics Modeling

Physical states



P = Pre-inserted Mz density
C = Mz channel density
I = Inactivated Mz density

Transition Schemes

(noncatalytic) $P \underset{k_{1r}}{\overset{k_{1a}}{\rightleftarrows}} C$

(autocatalytic) $P + C \xrightarrow{k_{1b}} 2C$

(inactivation) $C \underset{k_{2r}}{\overset{k_{2}}{\rightleftarrows}} I$

Kinetics

$$\frac{dP}{dt} = -k_{1a}P - k_{1b}(V)CP + k_{1r}C$$

$$\frac{dC}{dt} = k_{1a}P + k_{1b}(V)CP - k_{1r}C + k_{2r}I$$

$$\frac{dI}{dt} = k_2C - k_{2r}I$$

$$N_b(V) = P + C + I$$

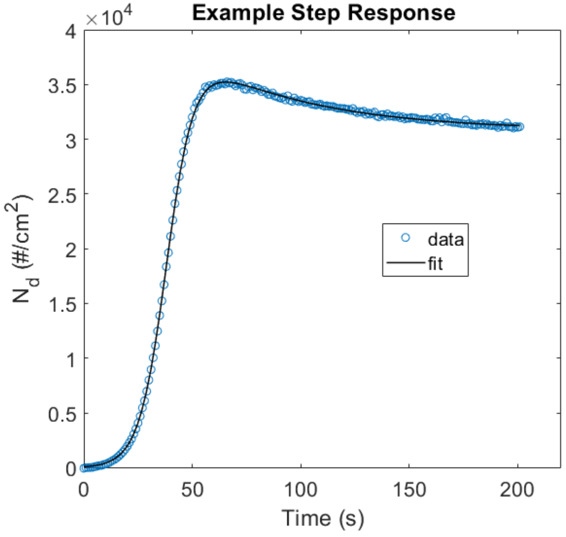
Goals

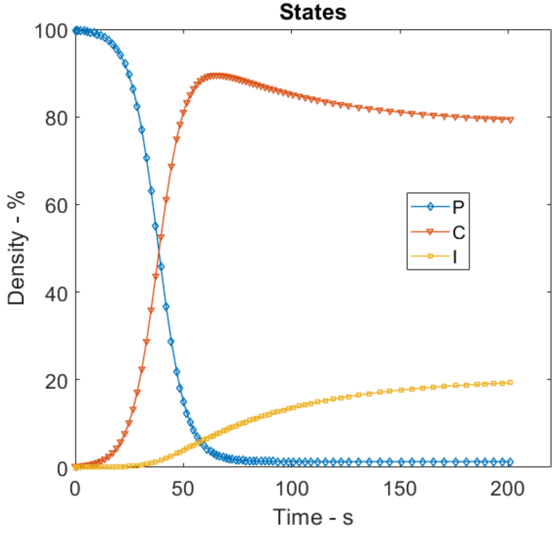
- **Develop a sufficiently accurate model and estimate unknown rate constants by fitting Mz step response data**
- **Assess channel kinetics versus membrane composition**

i vs *t* Fitting Procedure

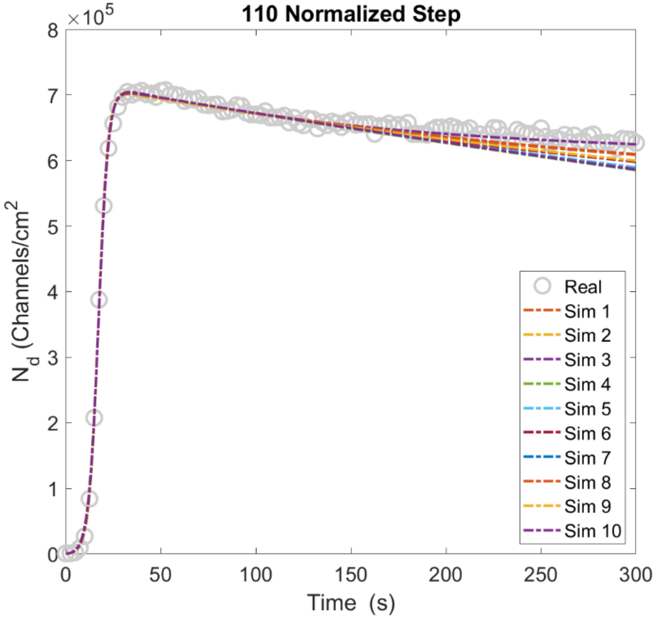
- Convert nominal ion current to channel density (C) by normalizing by membrane area and single channel conductance
- Randomize initial guesses for reaction rate constants, between 0 and 1
- Iterate rate constants and N_b using Matlab's fminsearch to minimize least-squares error w.r.t. C vs. t for each voltage step.

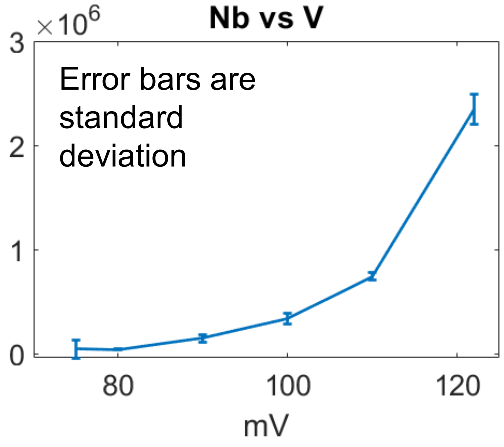
The 3-state model captures Mz kinetics; fitting yields estimates of rate constants

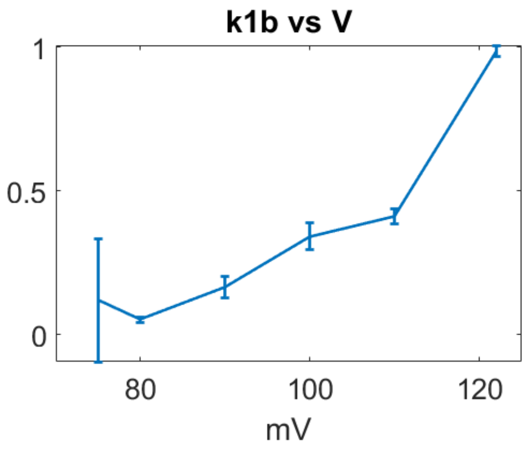




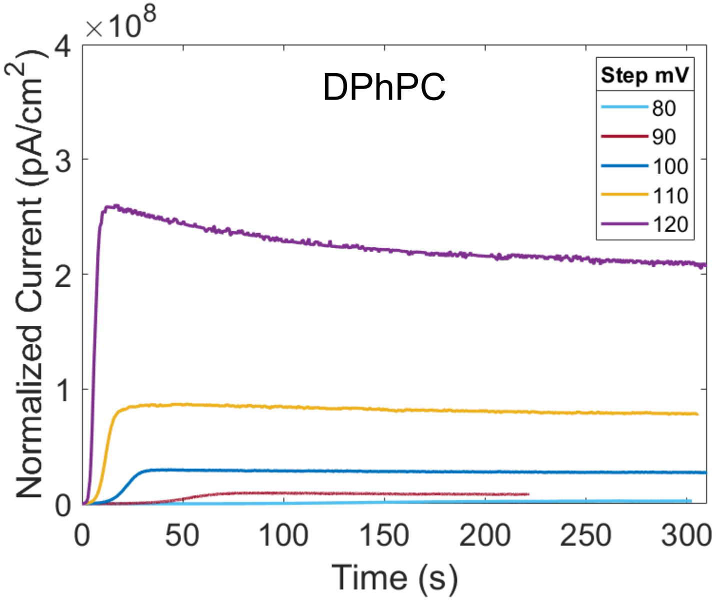
- Iterations that do not meet a normalized root-mean-square error cutoff are rejected until 10 are acquired.
- Parameter averages are plotted versus step voltage to identify trends in rate constants.

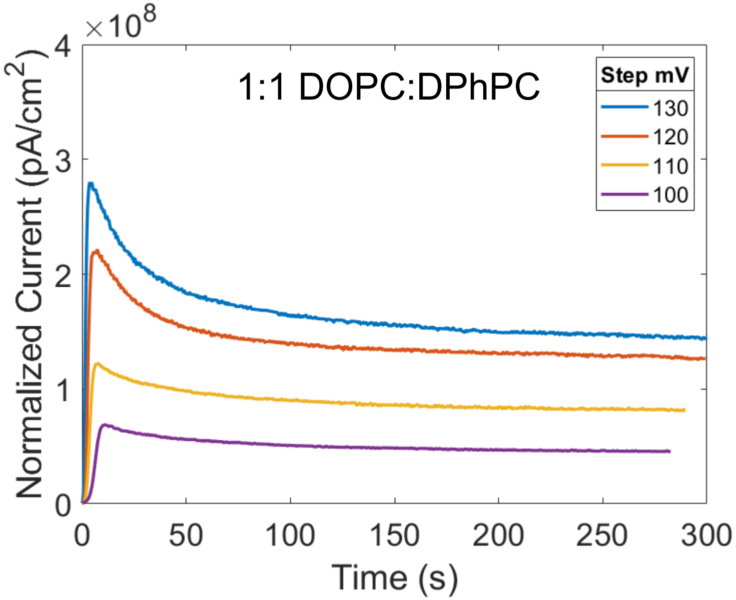


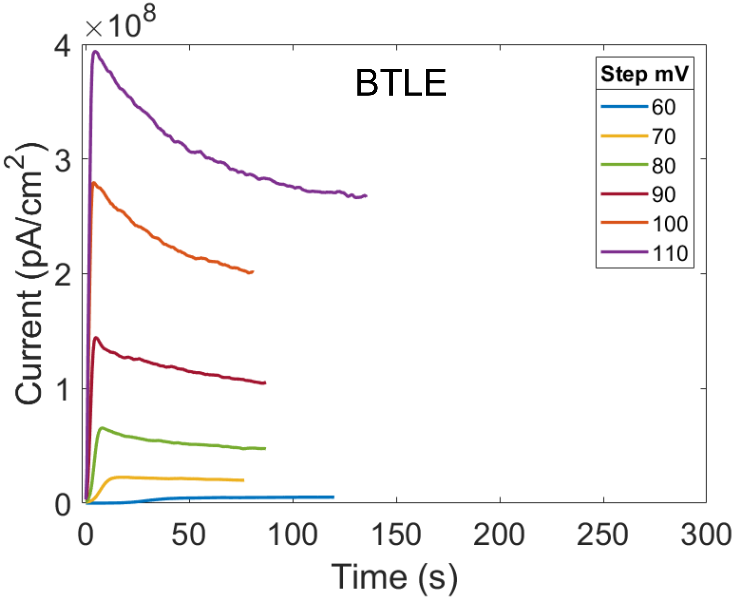

Error bars are standard deviation



Tuning Mz kinetics with membrane composition







$k_{1b}(V)=a*\exp(b*V)$

Mz channel formation

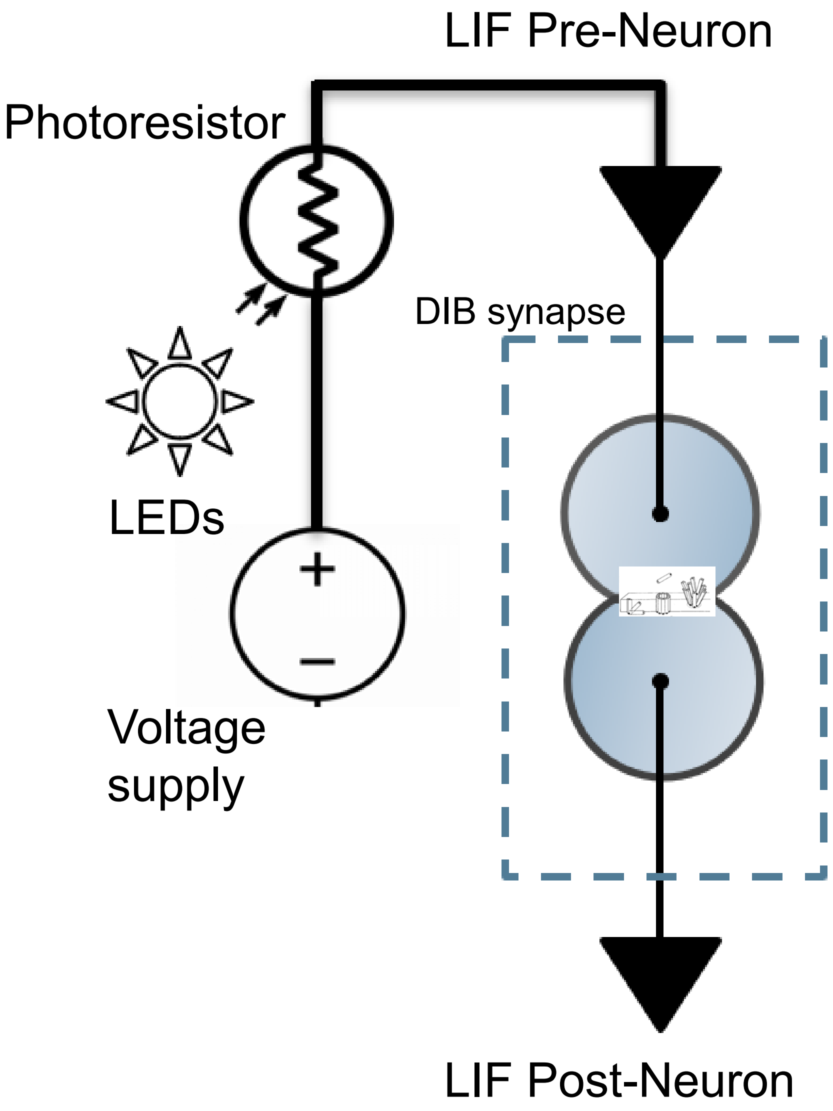
Membrane	a (1/chan*s)	b (1/mV)
DPhPC	0.00093	0.05694
DOPC:DPhPC	0.0587	0.02851

Mz channel inactivation

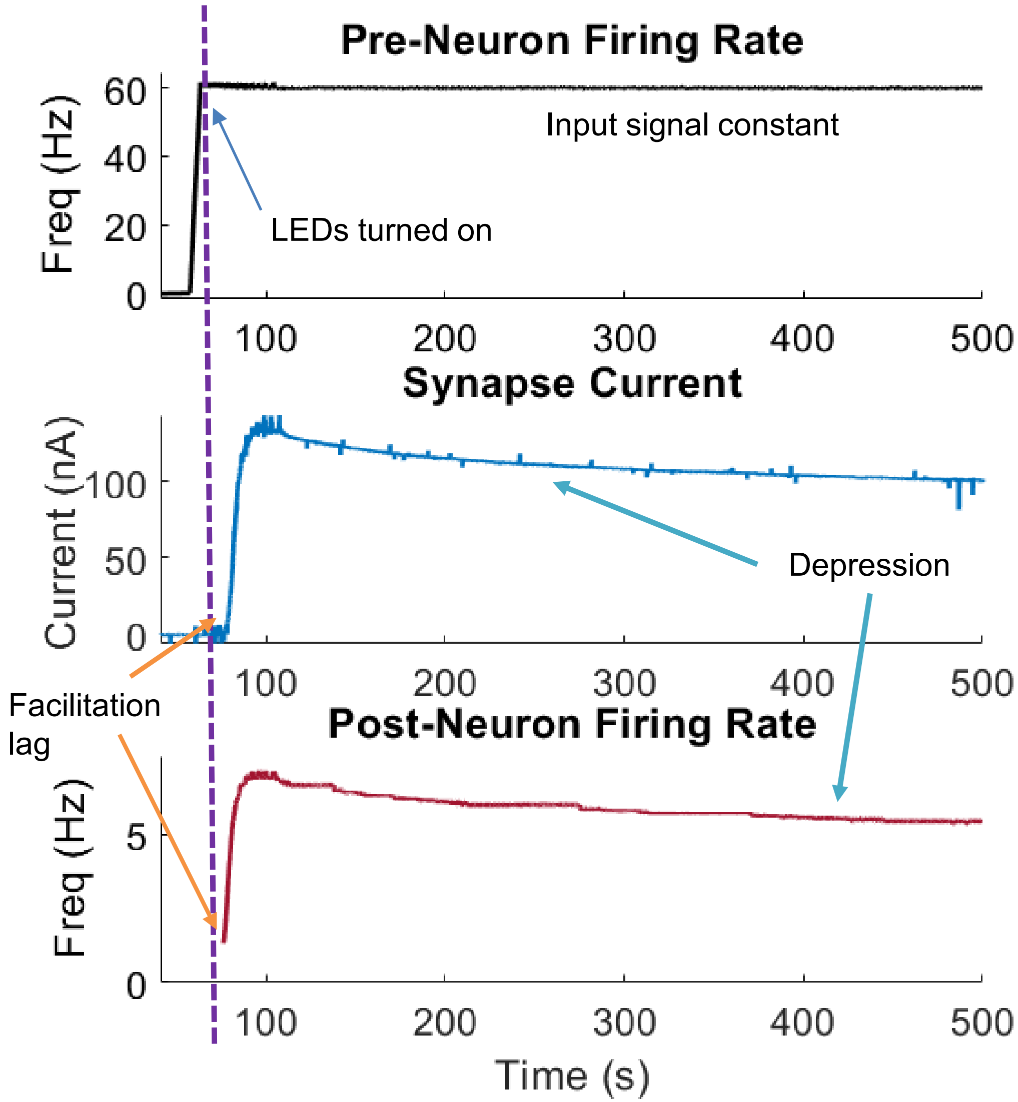
Membrane	k_2 (1/s)
DPhPC	0.0013
DOPC:DPhPC	0.0026
BTLE	0.0488

Mz synapse integrated with solid-state neurons

- A Mz containing DIB acts as a synapse between 2 identical, hardware implemented leaky integrate-and-fire (LIF) neurons
- When the LEDs turn on, the photoresistor's conductance rapidly increases, allowing more current to enter the Pre-Neuron, increasing its spiking rate up to a constant, light-dependent value
- Voltage pulses from the Pre-Neuron facilitate the formation of Mz pores, increasing the conductance of the synapse.
- The Post-Neuron is activated by the synapse current, whose output frequency is directly related to the synapse current



Mz-based plasticity provides adaptive filtering of neuron spikes

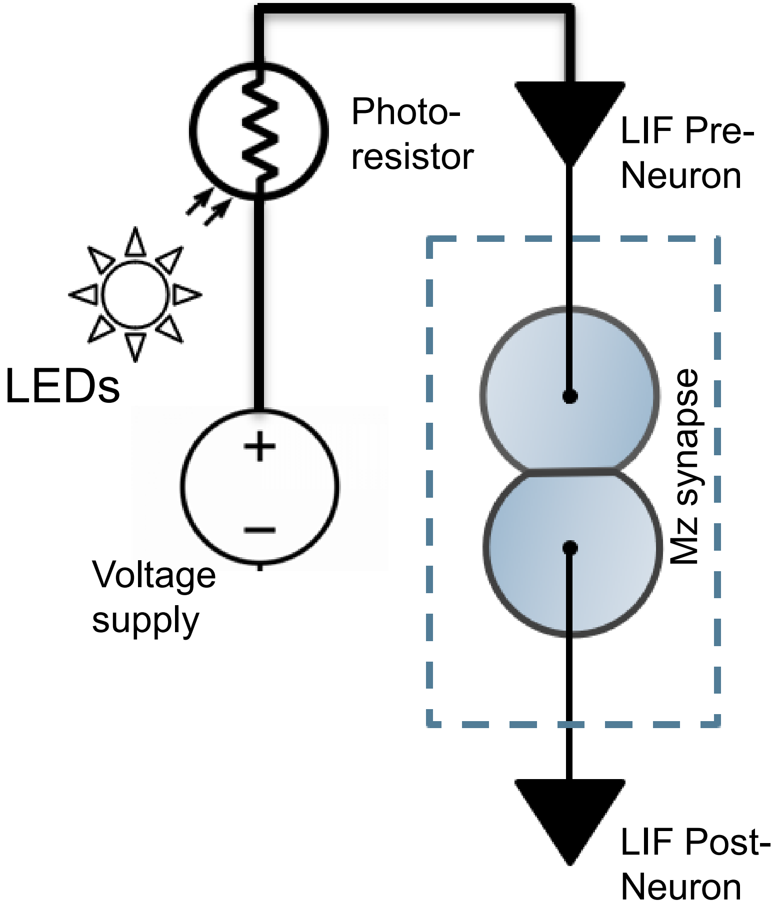


Input signal constant

LEDs turned on

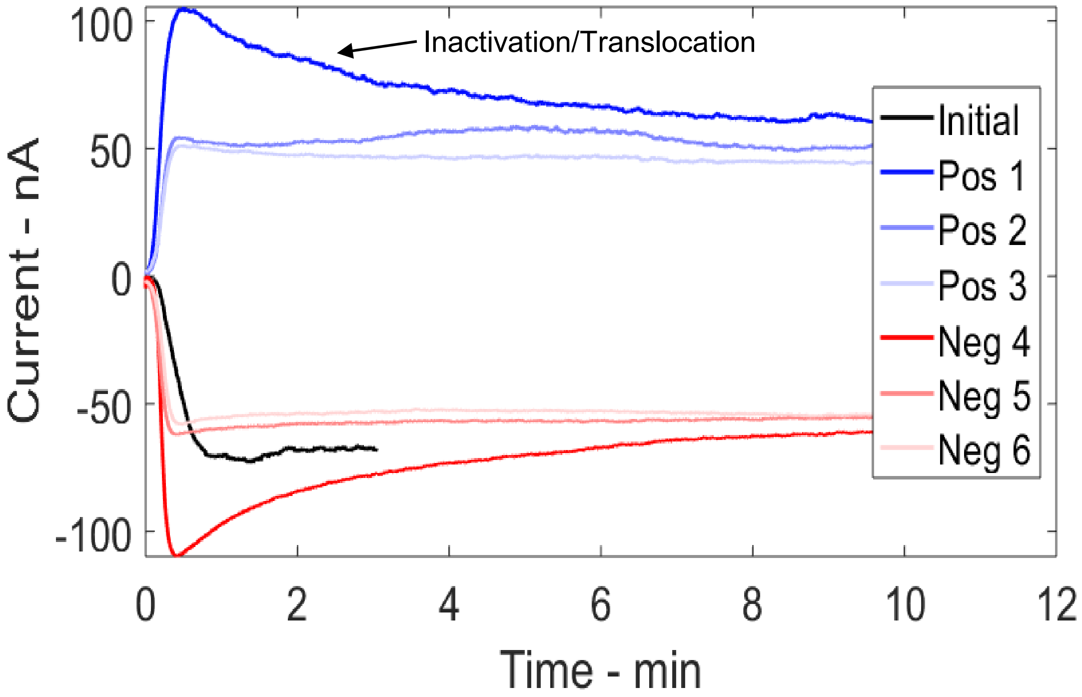
Depression

Facilitation lag

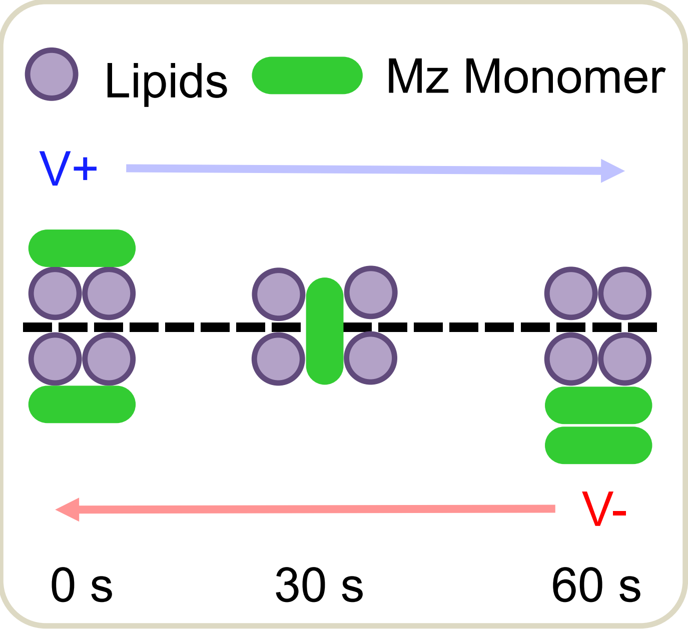


Initially, no signal is passed because Mz is inactive. After a brief delay, the firing rate of the post neuron is facilitated by current through the stimulated Mz pores, then slowly decays over time as Mz pores are inactivated.

Voltage-induced accumulation and resetting of long-term Mz memory

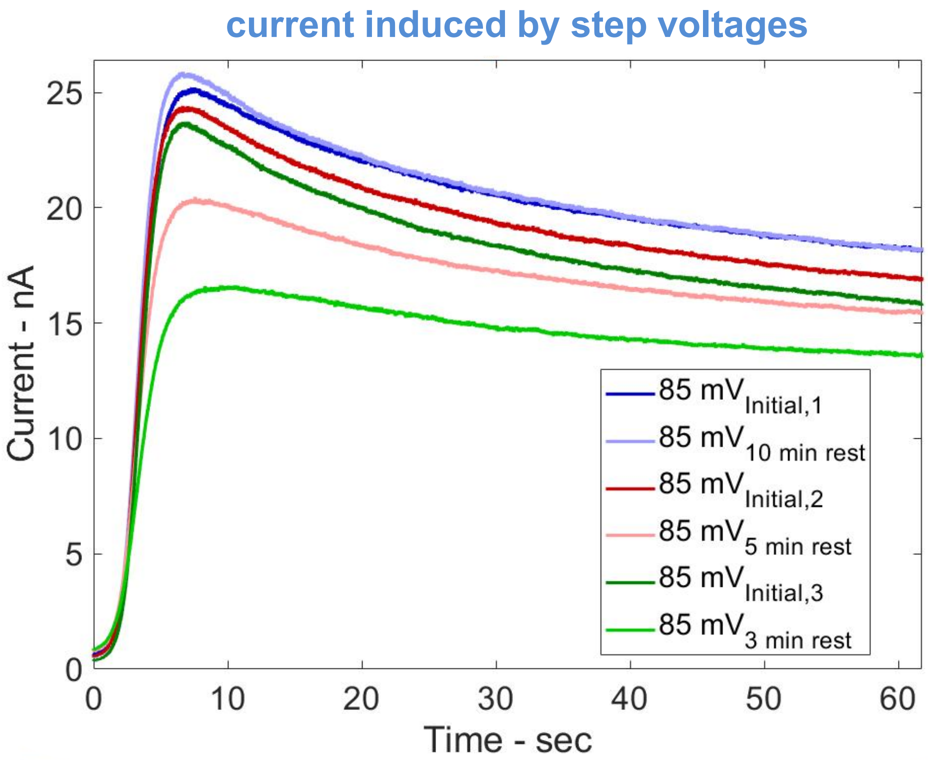


current induced by step voltages

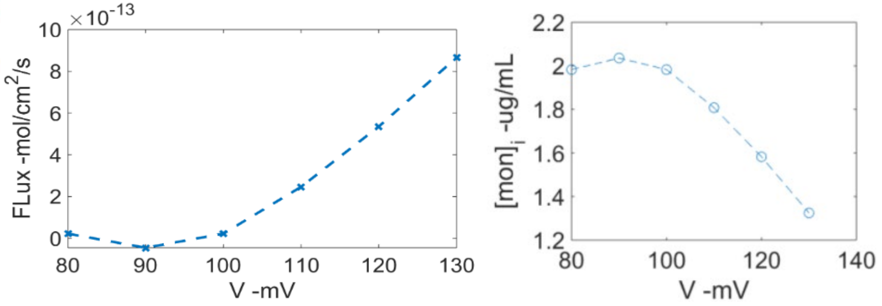


- Inactivation of Mz due to translocation increases its concentration on the *trans* (opposite) side of the membrane for when + voltage is applied on the *cis* side. This is a form of storable memory in the system.
- Active recovery, demonstrated by changing input polarity, can re-amplify current the response.

Passive recovery of long-term Mz memory



- Passive recovery is achieved after 10 minutes between step inputs.
- We hypothesize that Mz replenishes the interfacial concentration from the bulk solution during passive recovery.



$$\phi_{mon} = \frac{D_{mon}A}{\Delta x}[mon]_{bulk}[1-\frac{g_{ss}}{g_{ideal}}]\ 1$$

$$[mon]_i = \left(\frac{g_{ss}}{g_{ideal}}\right)^{\frac{1}{s}}[mon]_b$$

Initial 1

Rest 10 min

Follow-up Step

Rest 10 min

Initial 2

Rest 5 min

Follow-up Step

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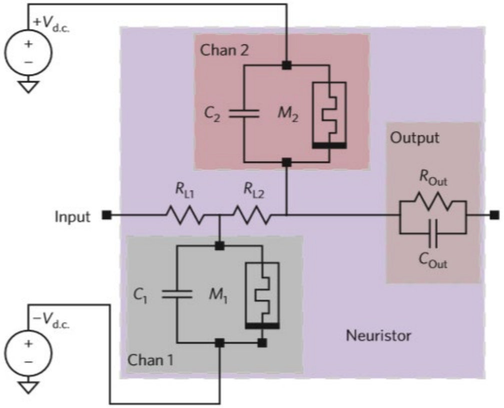
1. Heyer, R., Muller, R. & Finkelstein, A. Inactivation of monazomycin induced voltage dependent conductance in thin lipid membranes. II. Inactivation produced by monazomycin transport through the membrane. *J Gen Physiol* **67**, 731-748, doi:10.1085/jgp.67.6.731 (1976).

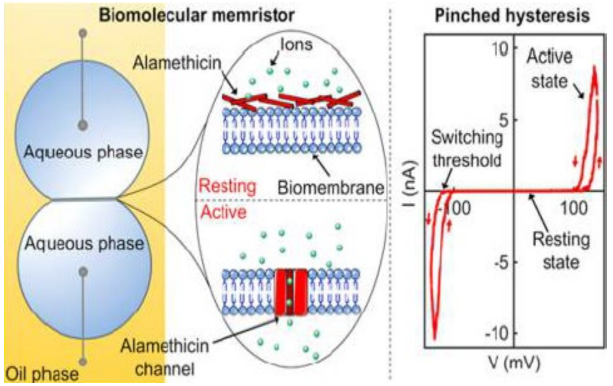
Shaping action potentials and activity-dependent plasticity in bio-molecular neuristors

Hypothesis: Neuristor circuits based on our bio-molecular devices that inherently integrate capacitance and volatile memristance, can shape and evolve the dynamic action potential in adaptive ways while operating at lower voltages.



Pickett, M. D., et al., *Nat. Mat.* 2012

Neuristor built using Mott memristor capable of generation and lossless propagation of action potential.



Najem, J. S., et al., *ACS Nano* 2018

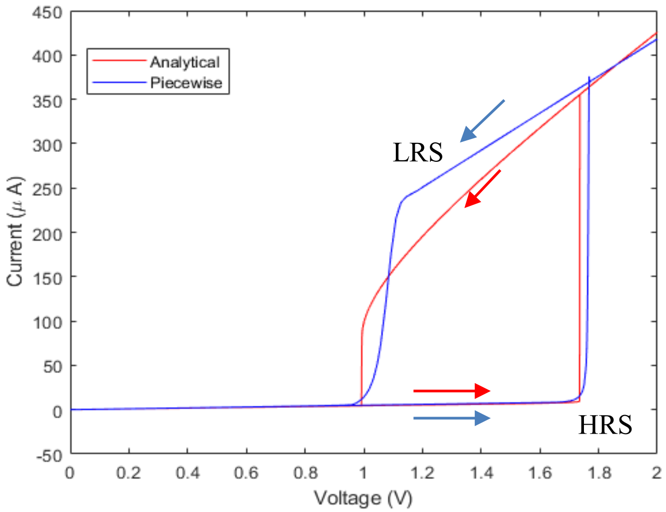
Bio-molecular memristor comprising insulating lipid membrane doped with voltage dependent alamethicin ion channels

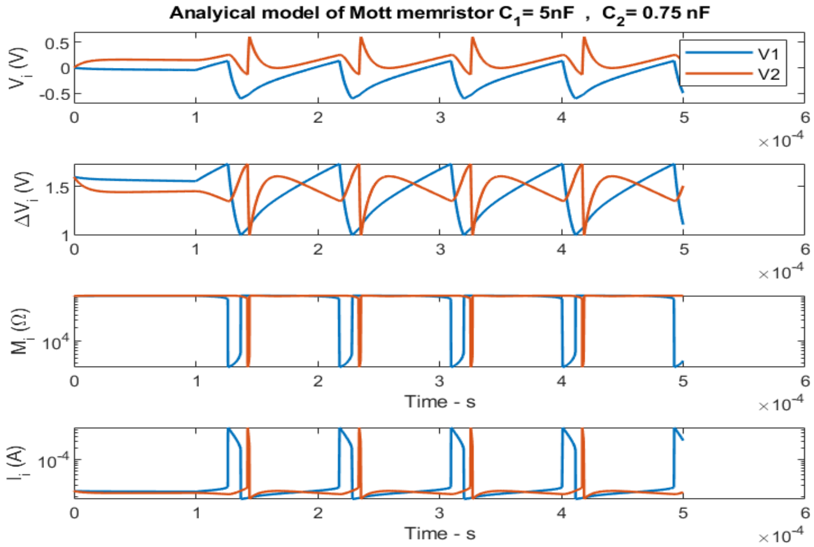
Functionality	Benefit
Threshold potential based actuation	Selective transmission of information
Activity dependent growth in connection strength	• Plasticity which can be tuned • Memory and learning
Operate at biologically relevant voltages (<|200 mV|).	Low powered device
Modularity in composition	Allow greater control in shaping the action potential

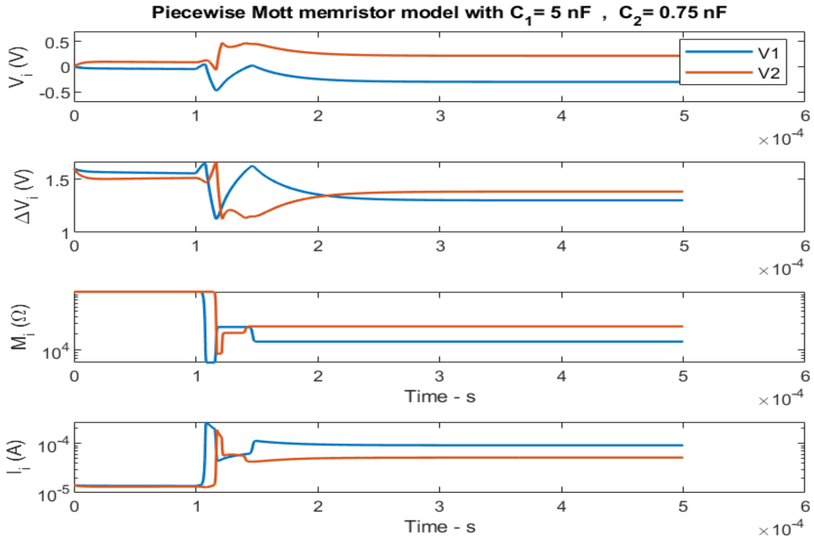
Research objectives:

- Fit a generalizable piece-wise empirical model to the *I*-*V* relationship of the Mott memristor.
- Simulate neuristor circuits and determine how I-V behaviors affect action potential generation.
- Tune *I*-*V* characteristics of bio-molecular devices for implementation in a neuristor circuit capable of working at biologically relevant voltages.

Piece-wise empirical model captures *I-V* behavior but not dynamics of Mott memristor in neuristor




Analyical model of Mott memristor C_1= 5nF , C_2= 0.75 nF


Piecewise Mott memristor model with C_1= 5 nF , C_2= 0.75 nF

Piece-wise empirical model

$$\frac{dM}{dt} = \begin{cases} C_{LRS}\left(\frac{V(t)-V_{tp}}{V_{tp}}\right)^{P_{LRS}} f_{LRS}(M(V,t)) & V > V_{tp} \\ -C_{HRS}\left(\frac{V(t)-V_{tn}}{V_{tn}}\right)^{P_{HRS}} f_{HRS}(M(V,t)) & V < V_{tn} \\ 0 & \text{otherwise} \end{cases}$$

where,

$$f(M(V,t)) = \begin{cases} \dfrac{1}{1+\exp\left(\dfrac{M(t)-\theta_{LRS}R_{LRS}}{\beta_{LRS}\Delta r}\right)} & V > V_{tp} \\ \dfrac{1}{1+\exp\left(\dfrac{\theta_{HRS}R_{HRS}-M(t)}{\beta_{HRS}\Delta r}\right)} & V < V_{tn} \end{cases}$$

and

$$C_i = \frac{\Delta r}{t_{si}}$$

Δr = HRS– LRS, t_{si} = switching time, V_{ti} = switching threshold.

Amer, S., et al. IEEE ISCAS 2017

Year 2 Focus

- Goal: Reveal mechanisms behind passive and active resetting of Mz step responses and quantify duration of stored memory (translocated Mz channels).
  - **Hypotheses: passive recovery is due to a combination of new Mz absorption and Mz diffusion across the membrane; active recovery is governed by voltage-driven translocation.**

- Goal: Study membranes containing multiple types of voltage-activated ion channels.
  - **Hypothesis: combining multiple types of voltage-gated species can enable a superposition of behaviors for tuning ionic memristance.**

- Goal: Explore neuristor circuits containing voltage-controlled memristors, including those from biomolecules. *[Williams and Yang]*
  - We've started process to synthesize voltage-gated potassium channels, like those in neurons—**hypothesize these will enable biomolecular neuristor response due to well-separated channel opening and channel closing potentials.**

- Opportunity: Interface biomolecular synapses and solid-state devices [*Chen, Williams, Yang*]
  - **Hypothesis: short-term plasticity of biomolecular memristor and long-term memory can yield spike-timing dependent potentiation.**

- Opportunity: Investigate how volatile biomolecular memory/plasticity can offer useful signal processing/control [*Chen, Williams, Inman*]

Publications and Products

Journal Papers:

1. Koner, S.; Najem, J. S.; Hasan, M. S.; Sarles, S. A., Memristive plasticity in artificial electrical synapses via geometrically reconfigurable, gramicidin-doped biomembranes. *Nanoscale* **2019,** *11* (40), 18640-18652.

Conference abstracts/presentations:

- 1 MRS Spring 2020 abstract accepted (conference canceled)
- 2 ASME SMASIS Virtual Conference presentations, Sept 2020

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