MODELING PLASTICITY: FROM SINGLE CELL AXONAL TRAFFICKING TO NEURAL NETWORKS

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ABSTRACT:

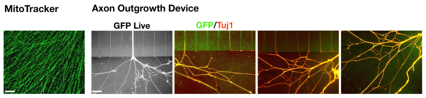
The role of individual neurons in neural plasticity is affected by both its underlying compartmentalized infrastructure of axons and dendrites as well as by communication between neurons and neural regulating cells. We present two models to address plasticity from alternate perspectives. Mathematically neuron axon structure has largely been ignored in terms of its nano to microscale components that impact macroscale outcomes. The first model demonstrates the ability of integrated roles of the axonal microtubule network and trafficking to internally define a neuronal 'barcode'. This model establishes a mechanism by which individual neurons of a given type have expanded diversity and opportunity for functional plasticity. We apply a totally asymmetric simple exclusion process (TASEP) and Langmuir kinetics combined modified model to track equilibrium and non-equilibrium dynamics of kinesin motors on the staggered infrastructure of the axonal microtubule network and partial differential equations for the motor density profile. The second model presents a neural network simulation for the transfer of impulses between the post-synaptic and pre-synaptic compartments for digital implementation. For calcium dynamics we consider the lipophilic retrograd signaling model. The hebbian learning rule for synaptic plasticity is used including the antisymmetry Tsodyks and Markram proposed form where the time interval of potentiation and depression are comparably similar. The model reproduces relevant biological behaviors with appropriate feedback control. The system architectures and simulation outcomes are presented for both models. .

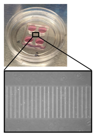
NEUROSCIENCE MODELING PROJECTS:

GENERAL PROBLEM STATEMENT: In order to interpret the neuronal contribution to information processing, synaptic plasticity, and normal or disease states we must create mathematical models that expand into the underlying neuron infrastructure. Our current models incorporate molecular complexity in axons and synapses to reveal new insights and expandable detail.

- **Modeling the Neuron as a Nanocommunication System to Identify Spatiotemporal Molecular Events in Neurodegenerative Disease.** Intern. J. Nanomedicine 2018
- **Motor Traffic and MT Organization Regulate Axonal Identity Along its Length.** *Manuscript in preparation*
- **Neural Network with Post-synaptic Internal Feedback System.** *Manuscript in preparation*

NEURAL CHAMBER ANALYSIS & DEVELOPMENT:

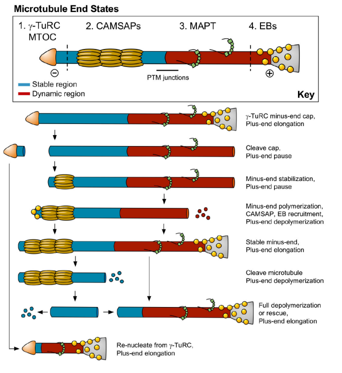




Need to advance axon imaging/transport tracking

- Images use Sigma Axonal Chamber
- Human stem cell derived neurons shown
- SUNY Poly has capabilities for custom lithography and generation of MEMS/NEMS
- Exploring application of CNTs, Graphene and electrochemical detection

Neuronal Axons: MT end states and Regulators

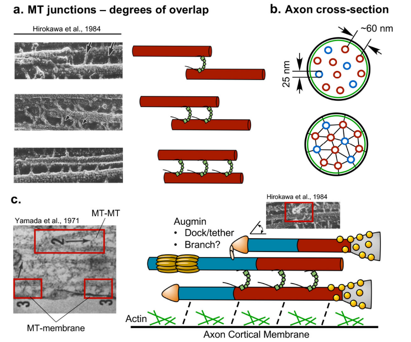


PALUH LAB NEURAL STEM CELL PROJECTS:

- **NYSCIRB: NY Spinal Cord Injury Review Board**
  Healing the contusion injury microenvironment with stem cells and nanotechnology.
- **NYSTEM: NY Stem Cell Research Board**
  Neural Cell-Cell Interaction Microchip (NCCIM) for TBI Biomarkers
- **NIH AREA R15 (revising)**
  Neuronal Microtubule Cytoskeleton Signaling Contributions
- **NSF SBIR Phase I pitch (submitted)**
  Microchip-Based Opioid Biosensor

TRANSPORT & AXON MTs = BARCODED COMPLEXITY

Staggered Axonal MT Packing & MT Junctions



Modified TASEP and Langmuir Kinetics

Parameters	Non-BDNF Kin 3 (A)	BDNF Kin 1 (B)
Velocity	v_a = 1000 nm/s (5 steps)	v_b = 600 nm/s (3 steps)
Processivity	8000 nm	1250 nm

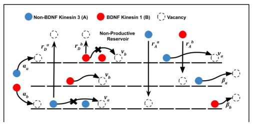


Fig. 3. Illustration of Modified TASEP-LK model:
The loading and delivery sites are at the minus and plus end of the one-dimensional lattice are given by α_a, α_b and β_a, β_b respectively.
r_A^a, r_A^b and r_D^a, r_D^b denote the local attachment and detachment rates for Non-BDNF and BDNF motors.

The TASEP and LK can be considered as two of the simplest paradigms which contrast equilibrium and nonequilibrium dynamics and stationary states. Langmuir kinetics evolves into a steady state well described in terms of standard concepts of equilibrium statistical mechanics. In the TASEP the number of particles is conserved in the bulk of the one-dimensional lattice. It is only through the particle reservoirs at the system boundaries that particles can enter or leave the system. In LK the particle number is not conserved in the bulk. Particles can enter or leave the system at any site with attachment and detachment rates, r_A^a, r_A^b and r_D^a, r_D^b, which are independent of system size N.

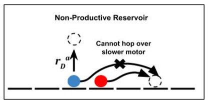


Fig. 6: Special Case
If two motors of different velocities try to occupy the same unoccupied sites, then the motor nearer, i.e. slower motor moves to the unoccupied neighbouring site while the faster motor being restricted from hopping over the slower motor in front of it, gets detached from the system at a detachment rate r_D^a.

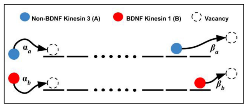
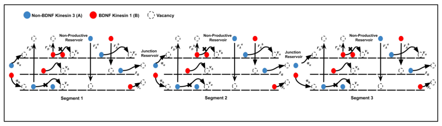
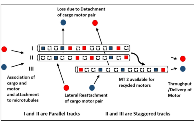


Fig. 8: Boundary Conditions
Left boundary (Loading):
a) Particle A loads on track at rate α_a
b) Particle B loads on track at rate α_b
Right boundary (Delivery):
c) Particle A gets delivered at rate β_a
d) Particle B gets delivered at rate β_b





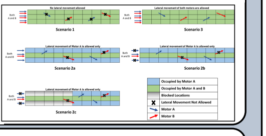
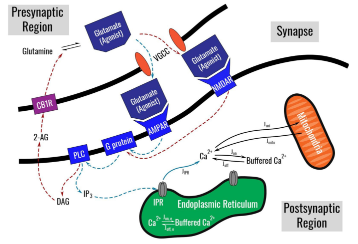


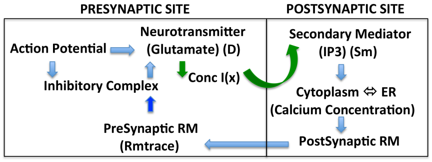
Table 4: Summary of Different Scenarios considered for simulation and outcomes

Scenario number	Loading Section	Transport Section (TASEP)		Detachment and Reattachment (Langmuir Kinetics)	Hypothesis
		Allowances for Lateral movement	Organization of MTs		Observations
Scenario 1	Fast and Slow motors have access to all MT tracks.	No lateral movement	Parallel	The detached motors in non-productive reservoir have access to all MT tracks.	• Crowding plays a greater role at Axon loading than further down the axon. • Without lateral movement a slow motor forces fast motor into non-productive reservoir.
Scenario 3	Fast and slow motors have access to all MT tracks.	Lateral movement of both motors, any direction	Parallel	The detached motors in non-productive reservoir have access to all MT tracks.	• Lateral movement allows an equal distribution of motors in non-productive reservoir
Scenario 2a	Slow motor restricted to the middle MT track. Fast motor has no track restrictions and load simultaneously on all of the three tracks.	Lateral movement of fast motor only, any direction.	Parallel	The detached Fast motors in non-productive reservoir have access to all MT tracks while Slower motor is restricted to middle track.	• Dedicated adjacent tracks allow faster motor to move out at a quicker rate. • Lateral movement and dedicated tracks allow faster motor to move freely without crowding.
Scenario 2b	All motors initially restricted to load only on middle MT track	Lateral movement of fast motor only, any direction.	Parallel	The detached Fast motors in non-productive reservoir have access to all MT tracks while Slower motor is restricted to middle track.	• Dedicated track results in easier movement of faster but affects the slower motor very much resulting in huge loss.
Scenario 2c	All motors initially restricted to load only on middle MT track	Lateral movement of fast motor only, any direction.	Staggered at 50% distance	The detached Slow motors is restricted to middle MT track, while Faster motor has access to staggered track.	• Dedicated track results in easier movement of faster but staggered tracks compensate over that movement. Staggering affects both the motors equally. • Restricted Lateral Movement due to staggering and crowding creates higher wait both motors at initial 50%

NEURAL CODE AND SYNAPTIC PLASTICITY



LIPID-DERIVED RETROGRADE SIGNALING MODEL



System Architecture: Neural Network with PostSynaptic Internal Feedback System

The goal is to design a mathematical framework for an artificial neural network with a postsynaptic internal feedback system that mimics CNS cortical neurons while enabling significantly lower cost-effective digital implementation. The modeled synapse includes the presynaptic and postsynaptic neurons and the synaptic vesicle transport channel and control elements of natural neural networks: electrical action potential, chemical neurotransmitter (NT-glutamate, Glu) release, binding of Glu to postsynaptic membrane glutamate ionotropic receptors (AMDAR, NMDAR) and depolarization, opening of presynaptic VGCCs and flow of synaptic current. Glutamate receptors coupled to membrane G-protein complex and calcium activation triggers PLC beta processing of PIP2 into IP3 and DAG. IP3 controls release of calcium from the ER, while DAG processing to 2-AG provides feedback control to regulate the pre-synaptic compartment. Formation of DAG is the rate-limiting and calcium-sensitive step in 2-AG production. NMDARs are calcium permeable and when activated allow influx of calcium needed for the induction of LTP.

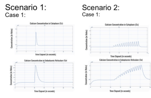
Model framework: Lipid-derived retrograde signaling.
Hebbian Plasticity: In which potentiation of an excitatory postsynaptic potential (EPSP) occurs if a presynaptic spike is accompanied by an increase in the probability of a postsynaptic spike during the period of association. We apply an antisymmetric form of Hebbian Plasticity (Tsodyks and Markram) where the time interval of potentiation and depression are comparably similar.
Hardware with field programmable gate arrays (FPGA)

Simulation Cases: Scenarios 1,2,3

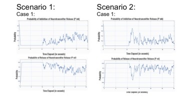
Frequency of Impulse = 0.01s (SCENARIO 1) ; 0.1s (SCENARIO 2); 1.0s (SCENARIO 3)
All simulations conducted for 30 seconds

Case	Variables Considered	Range of values	Constant values assigned to other parameters
1	α	0.0000003	β=0.01; r=0.000005; P_{init}=0.25; I_{Sm}=0.01
2	β	Yet to Define	α=0.0000003; r=0.000005; P_{init}=0.25; I_{Sm}=0.01
3	r	Yet to Define	α=0.0000003; β=0.01; P_{init}=0.25; I_{Sm}=0.01
4	P_{init} Initial probability of release of neurotransmitter	Yet to Define	α=0.0000003; β=0.01; r=0.000005; I_{Sm}=0.01
5	I_{Sm} Frequency of impulse	Yet to Define	α=0.0000003; β=0.01; r=0.000005; P_{init}=0.25

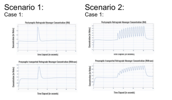
Calcium conc cytop (top); ER (bot)



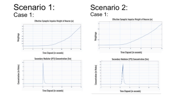
NT release (Pinh) vs (Prel bot)

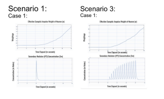


Rm conc (top); RM trace conc (bot)

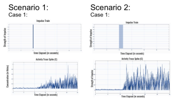


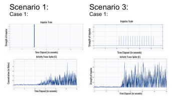
Synaptic Impulse Weight; Sm conc (bot)





Impulse Train; Activity Trace Spike (bot)





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