Enhanced Performance of Engineered Neural Networks using Microfabricated Guidance Cues and Predictive Computational Modeling

LABORATORY DIRECTED RESEARCH & DEVELOPMENT

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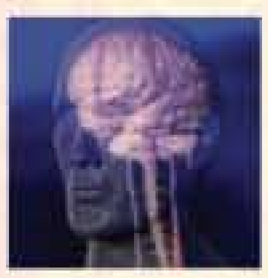
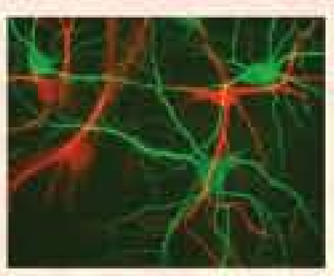
Problem

Functional enhancement and/or repair of nervous tissue circuitry requires the ability to engineer, measure, and modify living networks. Current neural engineering efforts only organize large populations of neurons into grossly-defined networks with minimal success at organizing the individual synaptic connections that are key to network function.

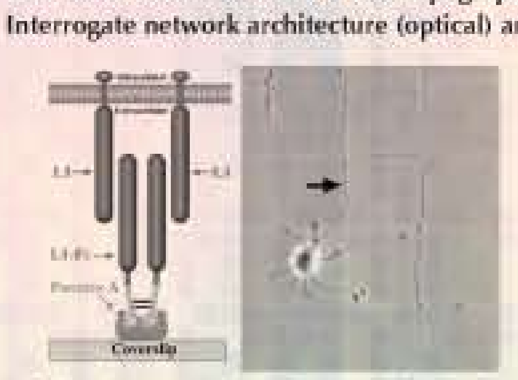
Our objective is to precisely organize dissociated primary neurons into functional networks. The network structure will be controlled with microfabricated cues to examine the role of network architecture on the development of synaptic memory in the form of long-term potentiation (LTP) and depression (LTD). Experimental data will then be used to train a computational model to predict network functionality.

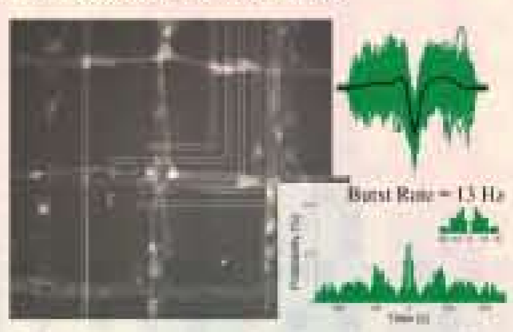
Background

Engineered networks can be user-defined, replicated, and readily interrogated at single cell and sub-cellular levels:

Utilize microfabrication to create topographical and chemical guidance cues
Interrogate network architecture (optical) and function (electrophysiology)



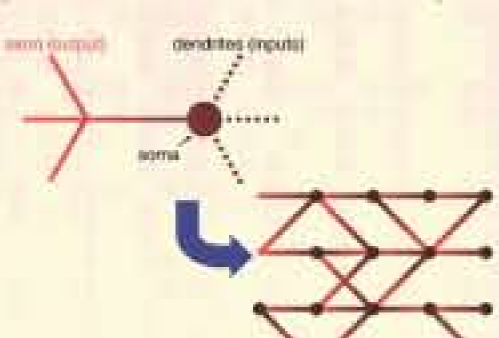
Chimeric proteins for biofunctional organization of neurons with control of polarity - *Oliva et al., Neurochem. Res. 2003*



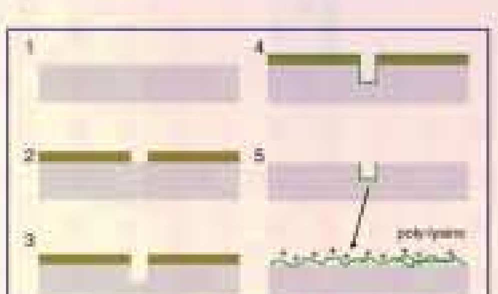
Protein patterns on microelectrode arrays for monitoring network activity - *C.D. James et al., IEEE Trans Biomed Eng 2000, 2004.*

Approach

- Utilize geometrically confined chemical cues to guide soma (neuron cell body) attachment & neurite polarity (signal inputs and outputs)
- Topographical cues provide increased surface area contact with neurons for quasi-3D guidance — more robust network engineering



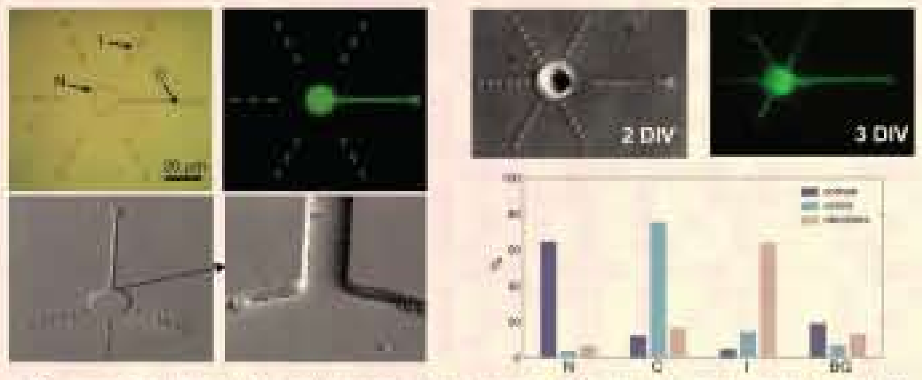
Neuron polarity: orientation of neurons affects information flow and function in a complex network



Dual guidance cues: CHF_3/O_2 reactive ion etching of fused silica for topographical cues; lift-off patterning of a polyamino acid for chemical cues

Results

- Culture pyramidal hippocampal primary neurons from rats on substrates
- Cell attachment, axon growth, and dendrite growth are promoted differentially with simple changes in the geometry of the guidance cues

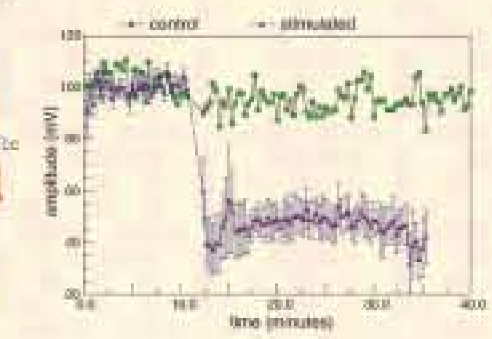


15 μm nodes (N) guide cell somae attachment; 1-2 μm wide continuous lines (C) promote rapid neurite growth to develop axons; interrupted lines (I) delay neurite growth to promote dendrite development; Background (BG) is unmodified glass.

Electrophysiology

- Field potentials and patch clamp recordings on multiple and single neurons in engineered networks; Measure LTP/LTD and compare to measurements in brain slices
- Examine the characteristics of LTP/LTD as a function of synaptic architecture – recreate in vivo architecture and optimize functionality

LTD in corticostriatal networks – high frequency stimulation in the cortex depresses activity in the striatum



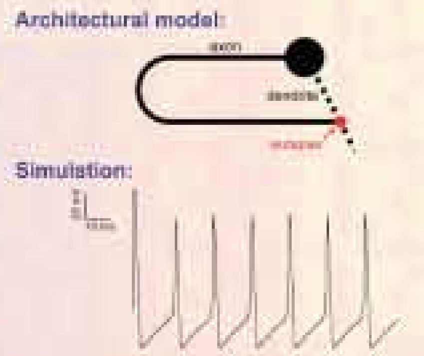
Michael Baca with D. Partridge (UNM)

Computational Modeling

- Implemented basic Hodgkin-Huxley dynamics in Xyce; Xyce will scale to larger networks, and interfaces directly to Dakota for optimization/tuning
- Synaptic connections: kinetic model release and uptake with nonlinear gating functions for signal transmission

HH Model: $C_m \frac{dV_m}{dt} = I_{stim} - \sum_{ion} g_{ion}(V_m - E_{ion})$

Conductances	Soma	Dendrites	Axon
Na (pS/μm2)	200	200	400
K (pS/μm2)	250	250(1+d/100)	50
K (pS/μm2)	100	100	100
I (pS/μm2)	0.5	0.5(1+3d/100)	0



Autapse – neuron connected to itself; oscillatory spiking after input stimulus

Significance

- First effort to measure LTP/LTD phenomena in engineered networks, and to examine how network architecture affects these phenomena.
- Represents a revolutionary effort in engineering multiple cell types (e.g. cortical and striatal neurons) into functional networks.
- DOD applications in augmented memory, learning, and visual perception for the war-fighter.
- Short-term applications in the restoration of motor function in peripheral nervous system injuries in soldiers.
- Long-term applications in developing treatments for traumatic brain injuries and to repair neural circuitry defects that lead to psychological phenomena such as post-traumatic stress disorder.

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SAND 2008-3292 P CreativeArts 98429.LW8.08

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