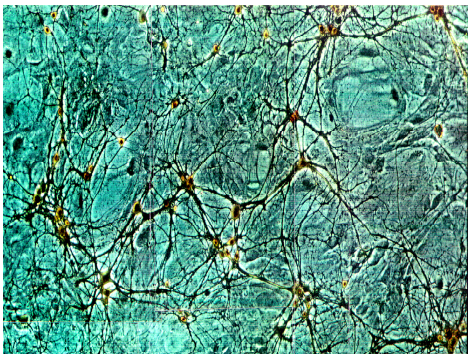
Cultured Thoughts:

(Questions on) The structure and dynamics of mammalian neuronal networks *ex vivo*

Work in progress and in collaboration with Guenter Gross (Texas) and Luis Bettencourt (Los Alamos)

Los Alamos NATIONAL LABORATORY



Center for Network Neuroscience
UNIVERSITY of NORTH TEXAS

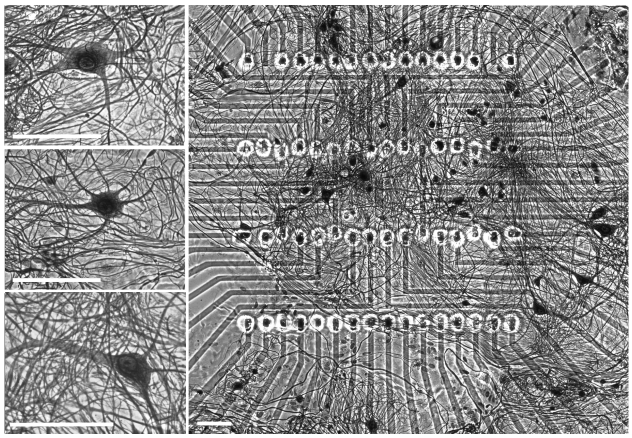
Outline

How do we understand the complex interplay between network structure and network dynamics that provides the functional neural basis for behavior?

(e.g *in vitro* imaging of dendritic spines…)

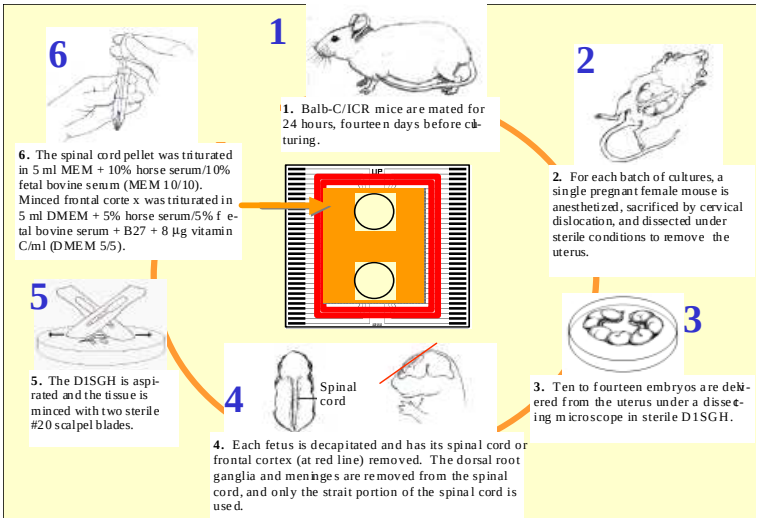
I. Introduction to Cultured Networks
II. Exploration of Network Dynamics. Coordinated bursting, pharmacological control and modelling
III. Connectivity through Correlation. Analyzing the global pattern of synaptic connections
IV. Conclusions

Spinal Cord Network Grown on 64-electrode Array



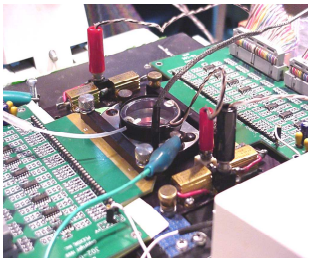
Cultured network shown 95 days after seeding. The indium-tin-oxide conductors are 10 μm wide. Horizontal electrode spacing is 40 μm, vertical spacing is 200 μm. *Insets*: close-ups of neurons within the network. Bars: 80 μm. Loots-modified Bodian stain.

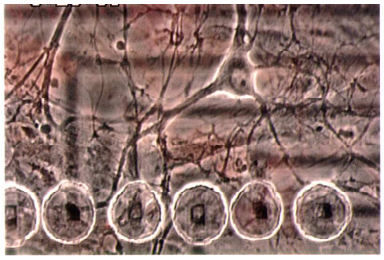
Sugar, Spice and Everything Nice: What are Cultured Networks Made of?



Culture Preparation Advantages

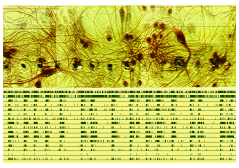
- Hundreds to thousands of neurons. Substantial (possibly complete) sampling of 2D mescoscopic network.
- Dynamical timescales ranging from milliseconds to months with 2-3 weeks in *ex vivo* development.
- Electrodes can stimulate and record. Learning and adaptation (Etyan et. al. 2003).
- Simple pharmacological manipulation of network activity.

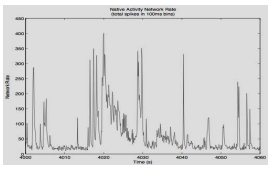




Culture Dynamics

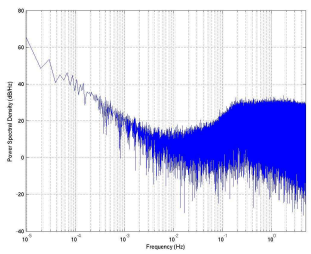
(to what class of dynamical systems do cultured networks belong?)

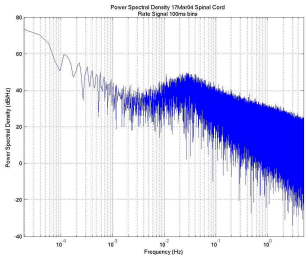




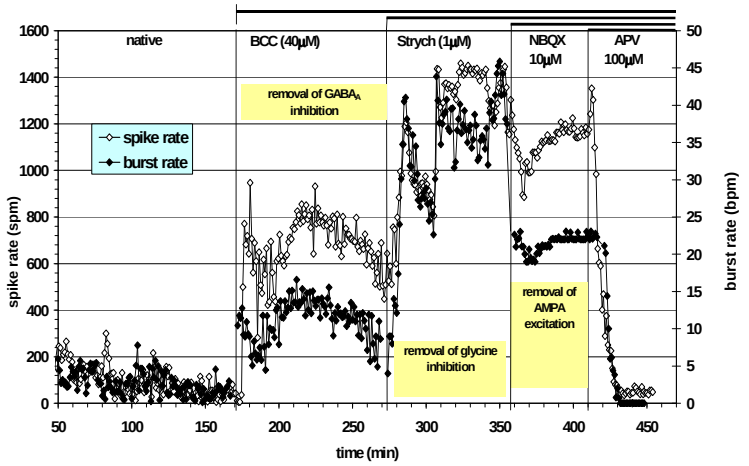
Network bursts are easily recognizable dynamical patterns. Others are certainly possible (e.g. synfire chains).

Bursting Networks as a Self-Organized Critical System
(organotypic cultures, Beggs et. al. 2003)

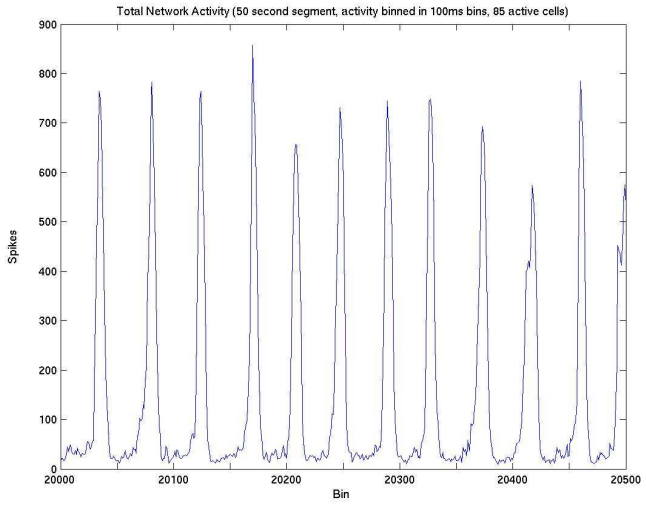




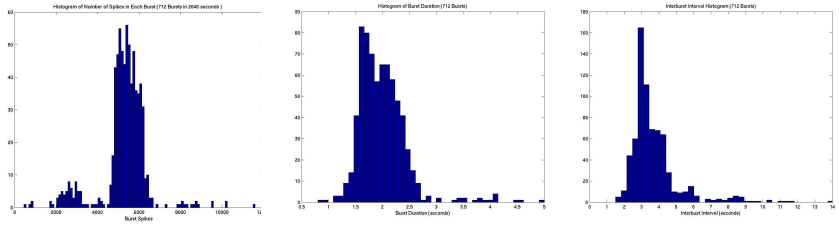
The Culture Clock:
An NMDA-only mediated excitatory network



NMDA-only Network Rate



NMDA-only Burst Statistics



What controls the **onset**, duration and magnitude of these quasi-regular bursts?

$$I_i^{syn}(t) = \sum_j g_{ji}^{max} s_{ji}(t)(V_i - V_{ji}^{rev})$$

$$g_{ji}^{max} = \frac{\bar{g}_{ji}}{1 + \frac{[Mg^{2+}] \exp \frac{-V_i}{16.13mV}}{3.57mM}}$$

Connectivity through Correlation

The complex computational processes implicit in even simple behavioral tasks rely on the ability of elaborate neuronal networks to code, process and store information.

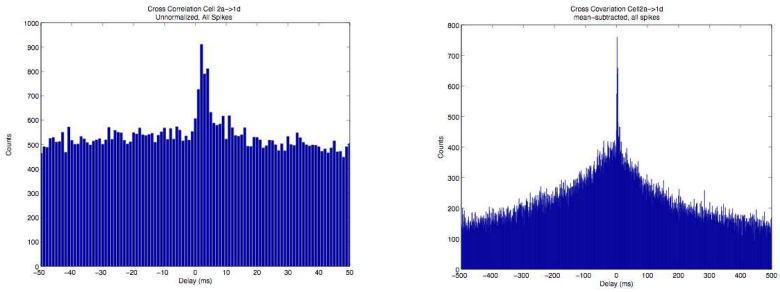
Unfortunately, current understanding of even relatively small networks is limited and a number of important questions remain open or only partially answered.

- What are the rules by which a complex neural circuit develops?
- How are the resulting networks classified (are they random or structured)?
- How does ongoing neural activity sculpt the network (plasticity and learning)?

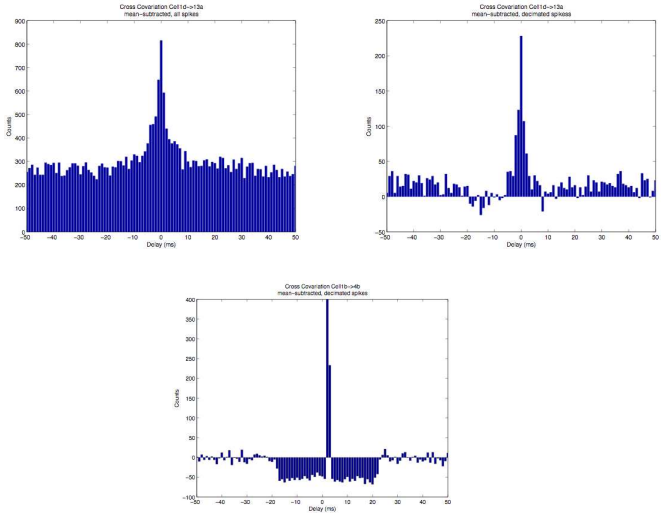
Synaptic Correlations in Spinal Cord Cultures

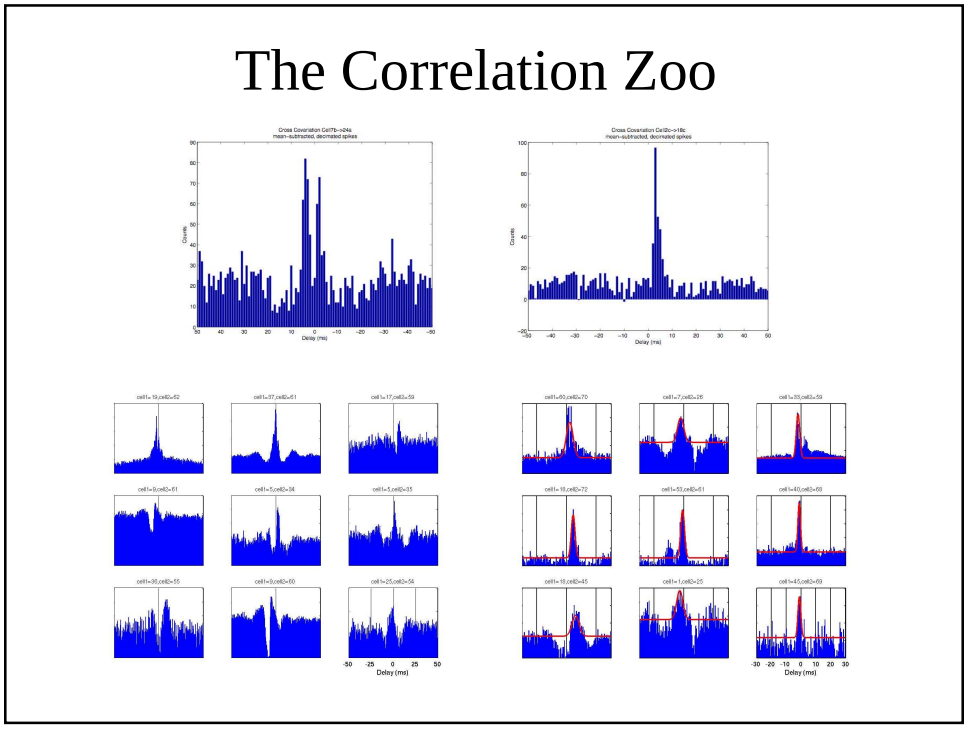
The Cross-Covariance Function

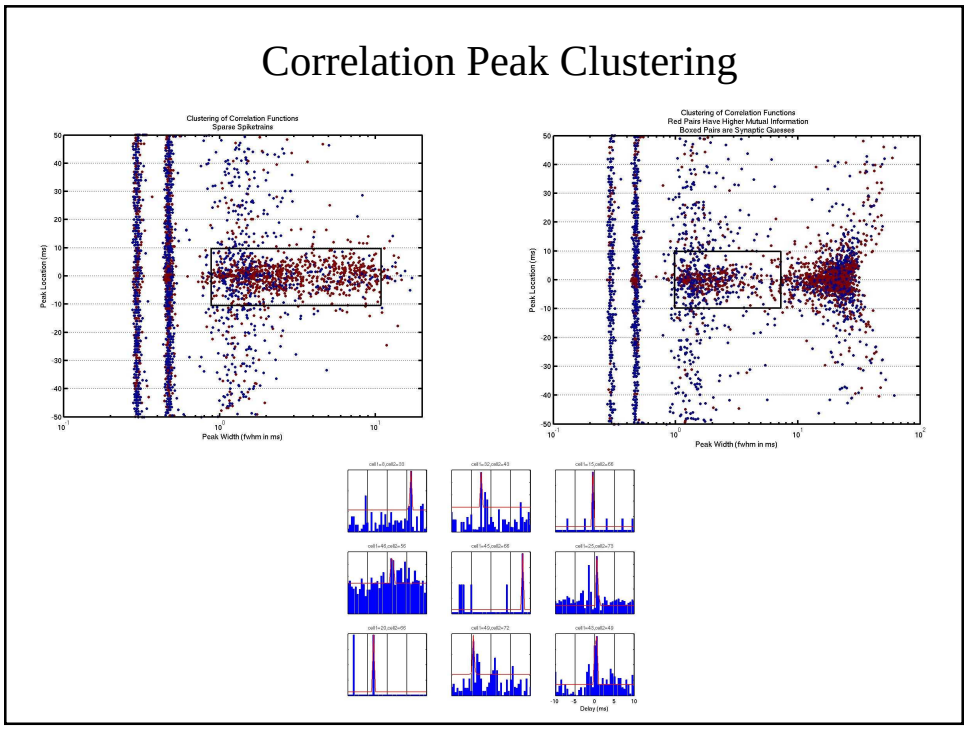
$$\tilde{c}_{12}(j) = \sum_{i=1}^{N} s_1(i) * s_2(i+j) - < s_1 >< s_2 >$$



Common Input and Data Corruption

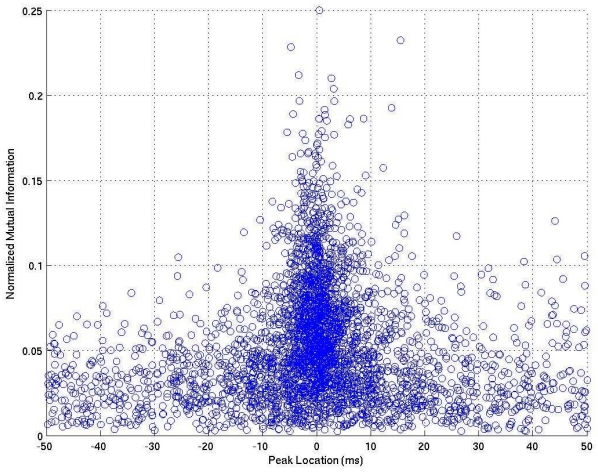



The Correlation Zoo
Delay (ms)


Correlation Peak Clustering
Clustering of Correlation Functions
Sparse Spiketrains
Peak Location (ms)
Peak Width (fwhm in ms)
Clustering of Correlation Functions
Red Pairs Have Higher Mutual Information
Boxed Pairs are Synaptic Guesses
Peak Location (ms)
Peak Width (fwhm in ms)
Delay (ms)

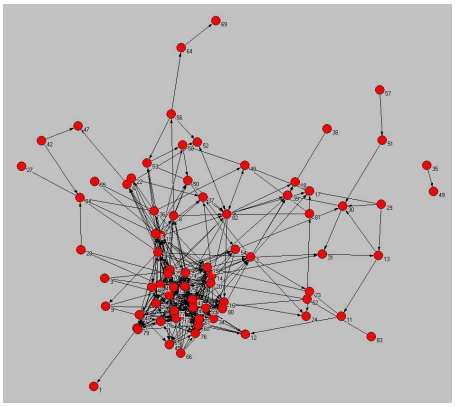
Beyond Cross-Correlation

(rephrase functional connectivity using information theory, London et. al. 2002)

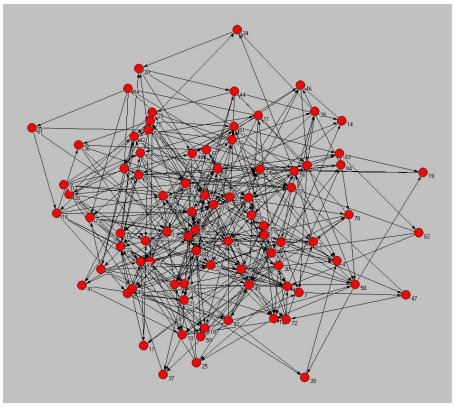


From Local to Global

(the small world of cultures?)

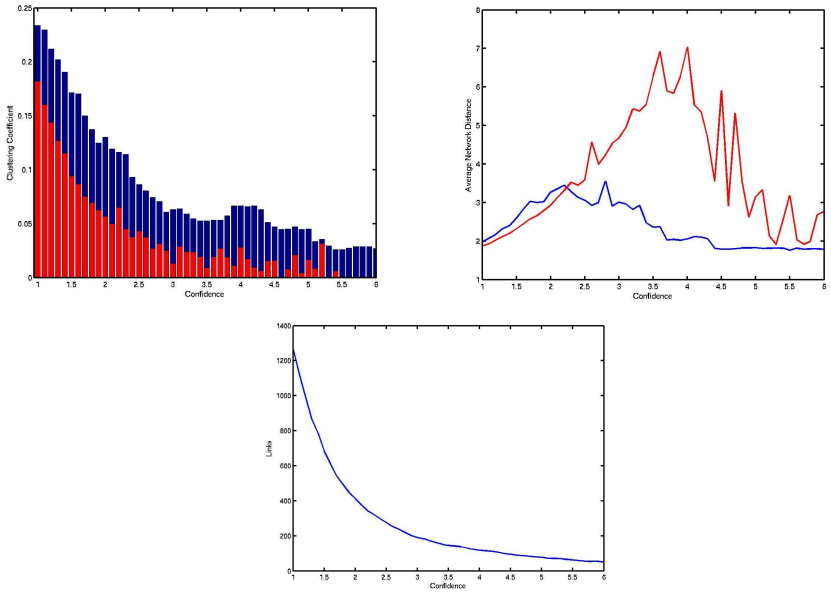


Cultured Network



Random Network

Network Statistics



Conclusions

- Neurons cultured on multi-electrode arrays provide a unique and powerful tool for understanding the interplay between the structure and dynamics of complex neuronal networks.

- As a compromise between the simplicity of a single neuron and the daunting complexity of an intact neural system, cultured networks offer an opportunity to productively combine physiological and computational approaches.

The Art of Culture