IDENTIFYING MECHANISMS UNDERLYING THE EMERGENCE OF CORTICAL NETWORK DYNAMICS USING CONTROL THEORY

Jeremi Chabros
Department of Physiology, Development and Neuroscience,
University of Cambridge

pdn
Department of Physiology, Development and Neuroscience

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synapse & network development

Abstract

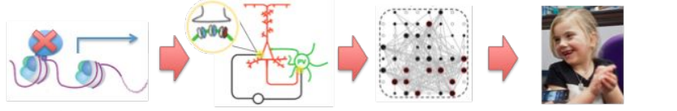
Despite the advances in understanding the architecture of neural networks, the study of their dynamics remains a major challenge. Analysis of such complex dynamical systems is also at heart of control engineering. The aim of this project is to bridge control- and graph-theoretical approaches in the study of microelectrode array (MEA) recordings from in vitro cortical cultures [1]. This will enable us to examine how dynamics of neural networks are shaped by neurodevelopment in health, and in a mouse model of Rett syndrome.

Aims

1. Compare and validate spike detection methods in in vitro cortical cultures.
2. Identify best method for inferring functional connectivity from neural activity.
3. Investigate control-theoretical approaches for the analysis of neural dynamics.
4. Elucidate the effects of age and genotype on cortical network dynamics.

Motivation

Rett syndrome is a childhood neurodevelopmental disorder and currently remains without cure [2]. Findings of this project might help establish a pipeline for testing of drug candidates in vitro.



Loss of Mecp2 changes gene expression | Disrupts synaptic function | Alters network development | Decline in cortical function in human disease

Experimental methods

Murine primary dissociated cortical cultures were grown directly on MEA chip (Multi-Channel Systems 60MEA200/30iR-ITO-gr). The 60 electrodes were arranged in an 8x8 grid (without corners) with 59 recording electrodes and 1 reference electrode. Changes in voltage (µV scale) were sampled at 25 kHz frequency, and sent through an amplifier to the acquisition software (MC_Rack).

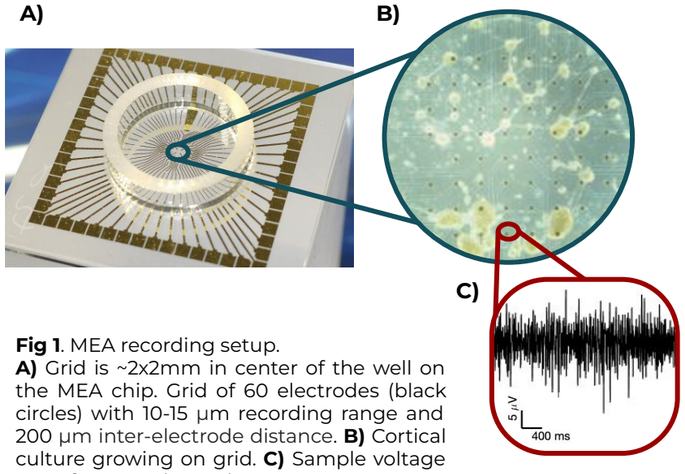


Fig 1. MEA recording setup.
A) Grid is ~2x2mm in center of the well on the MEA chip. Grid of 60 electrodes (black circles) with 10-15 µm recording range and 200 µm inter-electrode distance. **B)** Cortical culture growing on grid. **C)** Sample voltage trace from an electrode .

Spike detection

Accurately identifying neuronal activity in MEA recordings is paramount for the downstream analysis. Accuracy of spike detection was improved by developing a novel method based on continuous wavelet transform [3] with data-driven templates.

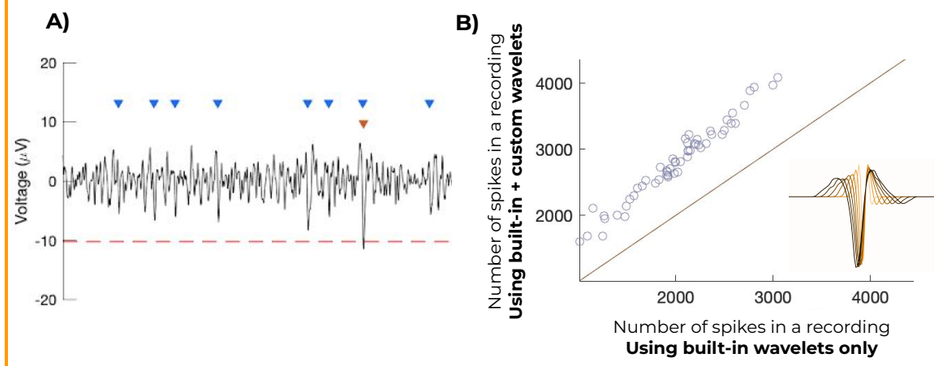


Fig 2. A) Example 30 ms filtered voltage trace with spike markers; threshold method (red), custom wavelet method (blue); voltage threshold (dashed line). **B)** The effect of custom wavelet on spike detection. Wavelet families: bior1.5, bior1.3, db2. Additional sensitivity: 39.1%. Sample custom wavelet across scales (bottom right).

Network controllability

Average controllability quantifies the ease with which given node can steer the network into different states *on average*, establishing *driver* and *follower* node subpopulations [4].

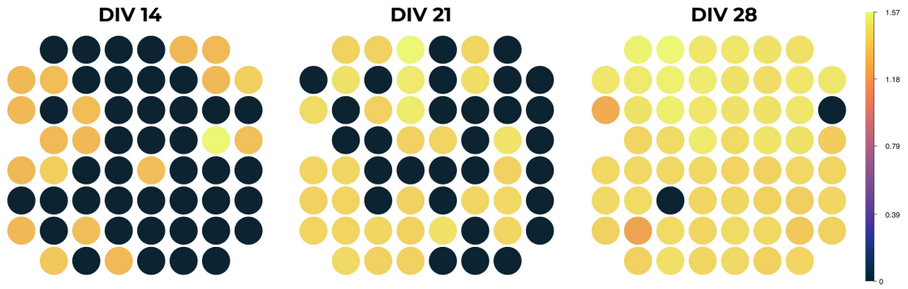


Fig 3. Heatmaps of nodal controllability in a sample wild-type culture across development (DIV = days in vitro). Larger controllability values mean easier control.

Dimensionality of network dynamics

Network complexity can be expressed as the effective dimensionality of its dynamics. Effective rank quantifies the number of dimensions of state-space by which the observed neural activity can be described [5].

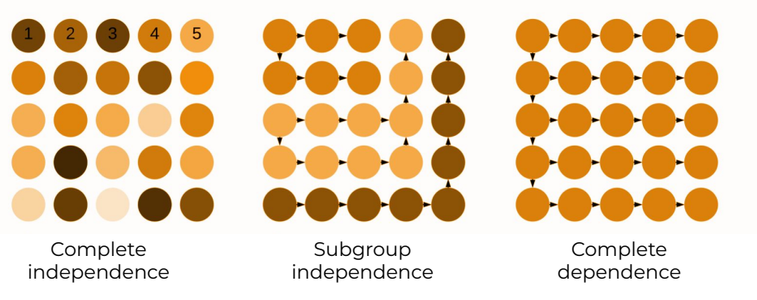


Fig 4. Toy network exemplifies different patterns as quantified by the effective rank. NB: these do not pertain to the network structure but rather to the dependences in dynamics

Extracting patterns of neural activity

Effective rank combined with non-negative matrix factorization (NNMF) enables identification of interdependencies in nodal dynamics retrieved from neuronal patterns of activity.

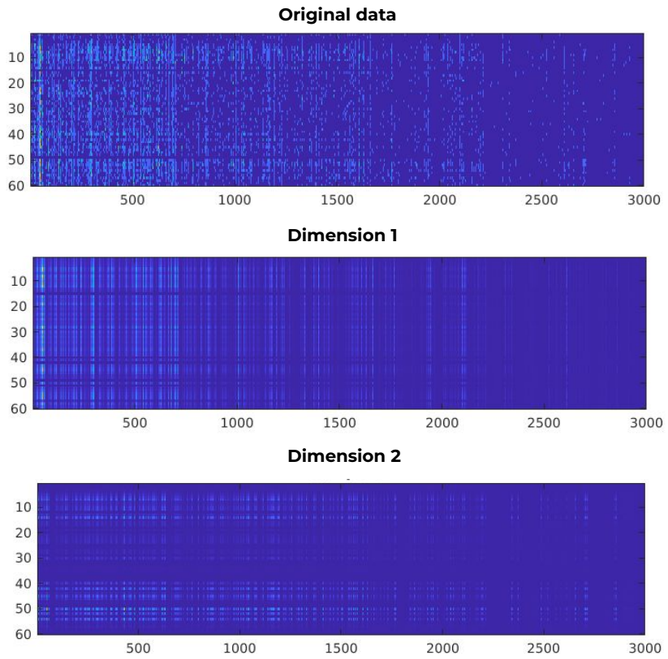


Fig 5. Patterns of neural activity extracted with NNMF.

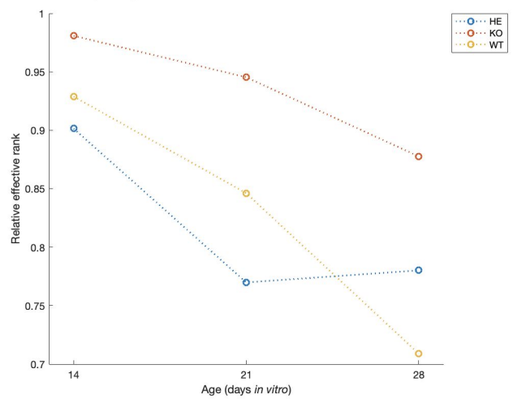


Fig 6. Age and genotype effects on network effective dimensionality as quantified by relative effective rank ($p < 0.05$).

Further directions

- Compare distribution of driver nodes across ages and genotypes.
- Effective rank for identifying subcommunities in network from patterns of activity.
- Neural activity reversibility analysis - Sequential Component Analysis.
- Identifying nodes with the highest controllability and testing these predictions using optogenetics.
- Role of putative pyramidal vs. parvalbumin +ve neurons