Identifying Mechanisms Underlying the Emergence of Cortical Network Dynamics Using Control Theory

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Abstract

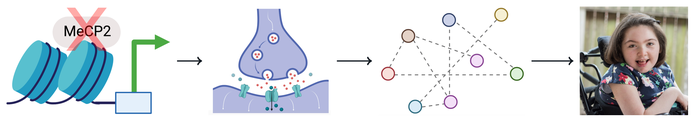
Despite the advances in understanding the architecture of neural networks, the study of their dynamics remains a major challenge. Analysis of such complex dynamical systems is also at the heart of control engineering, where it is central to the design of robust control strategies. Here, we apply the recent developments in the field of structural controllability [1, 2] to the study of microelectrode array (MEA) recordings from in vitro cortical cultures [3]. This will enable us to examine how neural network dynamics are shaped by neurodevelopment in health and in a mouse model of Rett syndrome.

Aims

1. Compare and validate spike detection methods for in vitro cortical cultures.
2. Infer functional connectivity of cortical networks from the spontaneous activity.
3. Investigate control theoretical approaches for the analysis of neural network dynamics.
4. Elucidate the effects of developmental age and Mecp2 deficiency on the dynamical properties of developing cortical circuits

Background

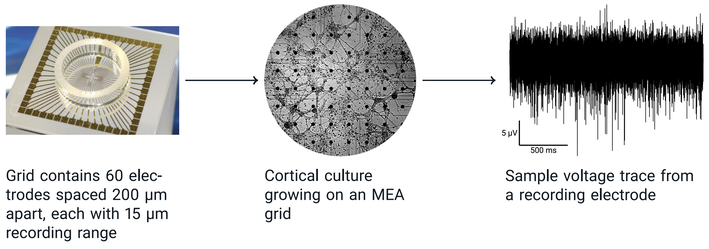
Rett syndrome is a childhood neurodevelopmental disorder that leads to severe impairments, affecting nearly every aspect of the child's life. It currently remains without cure [4]. Findings of this project might help elucidate the mechanisms underlying the disruption in brain function, identify strategies for therapeutic intervention and establish a pipeline for the testing of possible drug candidates.



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 chips (MultiChannel 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).



Grid contains 60 electrodes spaced 200 µm apart, each with 15 µm recording range | Cortical culture growing on an MEA grid | Sample voltage trace from a recording electrode

Network controllability

The core of network control theory is the structural network of neurons and their connections. To model the temporal evolution of network dynamics as a function of its architecture, we consider a continuous-time linear time-invariant (LTI) system,

$$\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}_K\mathbf{u}_K(t)$$

where the column vector $\mathbf{x}(t) = [x_1(t), x_2(t), \ldots, x_N(t)]^T$ represents the state (the neuronal spiking activity) of the system of N neurons at time t. The adjacency matrix $\mathbf{A} \in \mathbb{R}^{N\times N}$ denotes the functional connectivity between each pair of neurons. $\mathbf{B} \in \mathbb{R}^{N\times m}$ is an input matrix whose columns define the directions along which time-varying inputs $\mathbf{u}(t) \in \mathbb{R}^{m\times 1}$ actuate the system.
The central question of this investigation is: Can the state $\mathbf{x}(t)$ of the network be steered along any direction $\mathbf{v}$ in state space, using control inputs $\mathbf{u}(t)$ that can only actuate the network along a restricted set of directions (defined by the columns of $\mathbf{B}$)? Answers can be found in the controllability Gramian:

$$\mathbf{W}_c = \int_0^\infty \exp(\mathbf{A}\tau)\mathbf{B}_K\mathbf{B}_K^T \exp(\mathbf{A}^T\tau)d\tau.$$

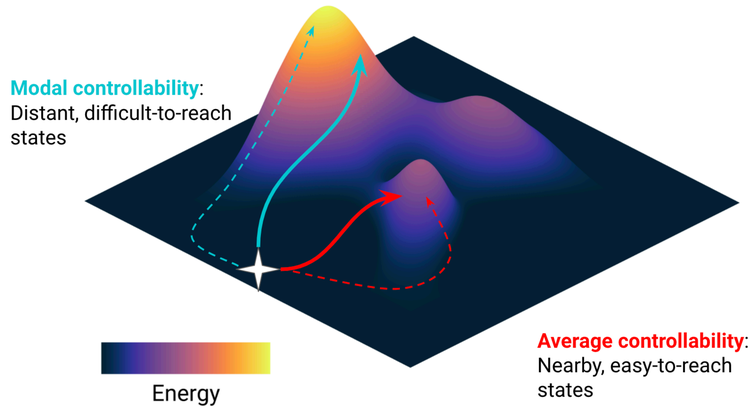


Fig. 1: Controllability in an energy landscape

Derived from $\mathbf{W}_c$, nodal controllability metrics describe which nodes in the network are most influential in constraining or facilitating changes in state trajectories. Each of these diagnostics captures a different goal [5].

- **Average controllability** identifies nodes that, on average, can steer the system into different states with little effort (that is, input energy). In other words, nodes with high average controllability are able to drive the network towards many easily reachable states.

$$\text{ctrb}_{\text{ave}} = \text{Tr}(\mathbf{W}_c)$$

- **Modal controllability** identifies nodes that can push the network into difficult-to-reach states (states that require substantial input energy).

$$\varphi_i = \sum_{j=1}^{N}(1 - e^{\lambda_j(\mathbf{A})})\mathbf{v}_{ij}^2$$

where $\lambda_j(\mathbf{A})$ and $\mathbf{v}_j$ are the j-th eigenvalue and eigenvector of $\mathbf{A}$.

Drivers and followers

The extent to which a given node can drive the network around the state space, as quantified by average controllability, enables us to establish *driver* and *follower* node subpopulations.

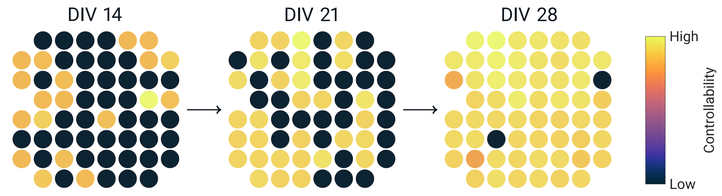


Fig. 2: Heatmaps of nodal controllability in a sample wild type culture across development (DIV – days in vitro). Larger controllability values mean easier control. Drivers in yellow, followers in navy blue.

Results

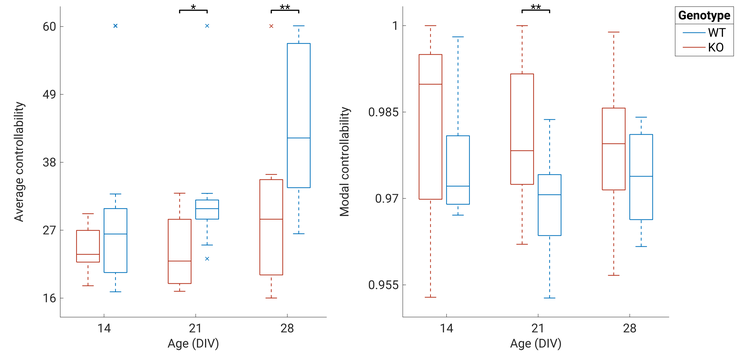


Fig. 3: Box plot (median, interquartile range, minimum and maximum) of effects of age and genotype on network controllability (n = 15). WT – wild type, KO – Mecp2 knockout. Outliers are plotted separately using the '+' symbol. * $p < 0.05$, ** $p < 0.01$ (Welch's t-test)

We found that in vitro cortical networks support a diverse range of possible dynamics which increases with age. An overall increase in average controllability was expected to reflect the increase in connectivity over development. This supports the notion that cortical circuits become increasingly structured in a manner highly optimized for network control, as postulated by [6]. These results suggest key neurophysiological changes that may be occuring during development, driving the system towards an increasing capability to traverse a larger surface of the energy landscape.

References

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