Simultaneous multiwell optogenetic stimulation and microelectrode array recording for disease modeling and toxicological assays

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**Multiwell MEA Technology**

- **Why use in vitro microelectrode arrays?**
  - Thrue neural experimentation often requires analysis of both single cell activity and network function. Patch clamp techniques provide detailed single cell analysis but lose sight of how cell behaves in a population.
  - Microelectrode array (MEA) provide a high-throughput, high precision method for evaluating the activity of cultured neurons. MEAs collect data simultaneously from many discrete locations in a cultured neural population, delivering information on both cellular activity and network connectivity.
  - MEAs provide a powerful approach to modeling in-vivo neural behavior and can be applied to disease modeling, stem cell characterization and phenotyping, neurotoxicity, and safety.

- **Why use the Maestro?**
  - **Simplified design and implementation with multi-simulation capacity**
    - A user-friendly interface allows for the easy setup of experimental protocol.
    - A variety of stimulation options can be selected through the Maestro software.
    - The Maestro interface allows for the easy setup of experimental protocol.

- **Neural network activity profiles**
  - Neural action potentials are detected as changes in voltage above a defined threshold.
  - A simple view of this activity is a raster plot where each detected action potential is represented by a "tick" mark to indicate the time at which the event occurred.

- **Why add stimulation?**
  - While neural cultures exist spontaneously active, stimulation provides control over cellular activity that can be used to:
    - Evaluate measures of evoked activity
    - Reduce variability across wells
    - Create application specific protocols to assess behavior of network connectivity
    - Reduce assay duration by increasing activity levels.

**Multiwell optical stimulation for optogenetic control**

- **Why apply optogenetics to cultured neural networks?**
  - Cell-specific modulation of neuronal sub-types through genetic targeting
  - Bi-directional control of activation and suppression of neural activity by utilizing of stimulatory and inhibitory opsins

- **Design and validation of the Lumos system for multiwell optical stimulation**
  - Four LED in-well illumination for high-intensity light delivery to an integrated array of microelectronic devices. Light emission and timing are programmable at both the well and cell level for the independent delivery of light to each MEA well, and minimizing cross-talk from adjacent well-walls.

**MEA / optogenetic assay for disease-in-a-dish modeling**

**Organotypic neural cultures modelled as Disease in a Dish Models**

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- **Optically-evoked network activity differs between diseased and healthy networks**
  - Using optogenetics to modify network states
    - The Maestro multiwell MEA platform enables functional modular analysis in the screening with 96 electrodes across 8 plate formats.

**Conclusions**

- The Maestro multiwell MEA platform enables functional characterization of neural cell culture activity and connectivity, and the Lumos optical stimulation system enables precise optogenetic modulation. Both systems are provided in a flexible, easy-to-use, benchtop format.
- Viral vectors, concentrations, and delivery techniques can be efficiently optimized in parallel, using the Maestro and Lumos systems.
- Human-derived iPSC networks were effectively modulated by multiple optically-evoked network states.
- Optogenetic stimulation provides enhanced metrics for evaluating drug response and mutation phenotypes in models of neural diseases.
- These findings demonstrate the potential of optically-integrated multiwell MEA systems to enable high throughput drug screening and phenotypic modeling of neurological diseases.