**Lumos™**: A multiwell optical stimulation device for precise control of cell activity

Axion BioSystems, Atlanta, GA

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**Maestro: Multiwell MEA system for analysis of cell network activity**

**Why use microelectrode arrays?**
Microelectrode arrays (MEA) provide high-throughput, benchtop method for evaluating cellular behavior and physiology. MEAs measure extracellular action potential activity simultaneously from many discrete locations in a cultured neuronal population, delivering information on both activity 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?**
- Label-free and non-invasive recording of extracellular voltage from cultured neurons
- Environmental control provides a stable benchtop environment for short-and long-term studies
- Fast data collection (≈ 15 sec/kHz) concisely quantifies the magnitude of depolarization events
- Sensitivity voltage resolution detects subtle extracellular action potential events
- Industry-leading array density provides high quality data through the integration of information from multiple locations in the culture
- Scalable format (15-, 48- and 96-well plate) meets all throughput needs in a single system
- Example applications:
  - Assess safety and toxicity through functional evaluation of drug-induced toxicity
  - Optimize stem cell differentiation and culturing protocols by incorporating network development with functional endpoints
  - Perform phenotypic drug discovery utilizing functional cell-based models in a high-throughput MEA assay
  - Design disease-in-a-dish models for phenotypic characterization of patient-derived cells or genetic variants

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**Lumos: Multiwell optical stimulation for control of cell activity**

**Why use optogenetics?**
Optogenetics is the integration of light, light-activated channels (opsins) that allow targeted, precise manipulation of cellular activity. Upon incident light of the correct wavelength, the opsins produce currents that directly hyperpolarize or depolarize the cell.

**Why use Lumos?**
- Lumos is the first commercial multiwell light delivery device designed to excite the majority of our opsin array. It operates independently and also integrates seamlessly with the Maestro and Axion, offering an array of features:
  - Increased throughput – 152 LEDs per 48 wells
  - Maximal intensity – High-powered LEDs coupled with optimized pulse materials and custom LED optics for robust performance and reliability
  - User any opsins – wavelength options cover 445-575nm, with four wavelengths per well, allowing the use of any opsins and multiple opsins per well
  - Precision control – fully user-configurable through an intuitive interface in Axolite software, providing precision and finely adjustable intensity for each LED – independently and simultaneously

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**Applications in Screening**

**Getting Started**
The following simple steps may be used to achieve optically-evolved activity in vitro:
1. Obtain viral vector encoding desired opsin
2. Add viral vector directly to thawed cell pellets
3. Incubate briefly harvested cells
4. Evaluate optically-driven functional activity

**Control Cardiac Beating**
Cardiac repolarization is intrinsically linked to the beating frequency, both of which are sensitive to pharmacological manipulation. Optogenetic stimulation allows tuning of beating frequency and removes its influence on the physiology, leading to increased reliability and sensitivity of the repolarization measurement.

**Quantity Arrhythmic Risk**
Arrhythmic indicators, like EADs and APDs, are also sensitive to the beating frequency of cardiomyocyte networks. Optogenetic stimulation can be used to control for emergent arrhythmic events or more precisely quantify cardiac arrhythmias.

**Induce or Suppress “Seizures-in-a-dish”**
Optogenetic stimuli may be used to induce or suppress specific activity phenotypes, such as seizure-like activity. Induction of seizure-like activity may be used to screen for proconvulsant liability in the efficacy of anti-epileptic drugs, while suppression of seizure-like activity may be used to tune activity states in “disease-in-a-dish” models of epilepsy.

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**Conclusions**
- Optogenetics enables cells to be controlled by light, offering the opportunity to precisely control or manipulate complex in vitro cell models.
- Lumos, the first commercial multiwell optogenetic stimulation device, enables high-throughput optogenetics with precise control over light delivery in an easy-to-use format.
- The Maestro multiwell MEA platform connects key biological variables to cellular and network function by extracting information from complex biological systems in vitro.
- Together, Lumos and Maestro improve the reliability and sensitivity of existing assay screeing and enable new directions in high throughput network electrophysiology.
- Lumos also operates independently, enabling chronic light delivery experiments for influencing cellular processes such as gene expression, cell growth, and differentiation.

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**Challenges and Opportunities in MEA Applications**

**Challenge:** Combining primary neuronal cultures may be at different spontaneous rates across well, complicating analysis
**Opportunity:** Reducing variability across wells will significantly improve the reliability and sensitivity of the assay

**Challenge:** Mixed neuronal populations incorporate important complexity into the model, but make interpretation difficult
**Opportunity:** Understanding how components interact in a biological system adds significant impact to model interpretation

**Challenge:** Some networks are not very active, requiring long experiments to get sufficient data for analysis
**Opportunity:** Increasing activity levels in a controlled manner may reduce assay times and simplify analysis

**Challenge:** The model exhibits a phenotype of interest, but it’s buried within noisy biological activity
**Opportunity:** Methods to target and evoke a specific phenotype will heighten the sensitivity of an assay

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**Why use stimulation?**
While neural or cardiac cultures are often spontaneously active, stimulation allows the user to control the input to the cells.

Stimulation can be used to:
- Evaluate measures of evoked activity
- Assess variability across wells
- Create application-specific protocols to assess features of network connectivity
- Reduce assay duration by increasing activity levels

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**AxiosMEA: Fast optical stimulation using ArchT™, Lumos™ and Maestro™**

Axion’s fast optical stimulation using ArchT™, Lumos™ and Maestro™ platform enables functional cellular analysis on the benchtop with 100-electrode across all plate formats.

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**Optogenetic Stimulation**

Each opsin has been designed for a specific functionality. For example, channelrhodopsin-2 (ChR2) can be used to activate neurons or cardiomyocytes in response to blue light, whereas ArchT™ suppresses neural activity upon incident green light. These techniques provide unprecedented control over electrophysiological activity, with negligible artifacts.