Innovation in Neural Interface Technology

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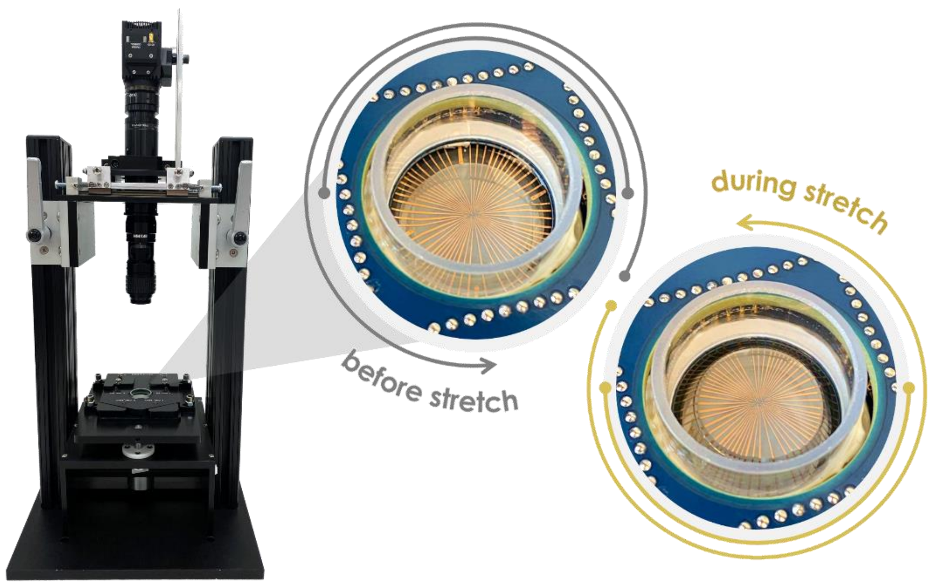

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1. MEASSuRE

MicroElectrode Array Stretching Stimulating und Recording Equipment

Cytostretcher, electrophysiology, imaging in one tool

MEASSuRE is a complete plug-and-play instrumentation that integrates three distinct laboratory methods into one system: (1) a cell stretching device, (2) a data acquisition system for electrophysiology, and (3) a live cell imaging system. MEASSuRE extends the capabilities of in vitro research and enables to perform in vitro research under in vivo-like conditions with respect to the mechanical and electrical environment of the cells.

MEASSuRE enables investigators to reproducibly and reliably study the effects of physiological and pathological mechanical stretch on the electrophysiology of biological tissue. The invention of proprietary stretchable microelectrodes was critical to enabling the capabilities of MEASSuRE. Stretchable microelectrodes for in vitro electrophysiology are only available at BMSEED.

Capabilities of MEASSuRE

MEASSuRE is a complete solution for researchers to independently and concurrently stretch cells/tissue mechanically (Mechanics Module), image them optically (Imaging Module), and record/stimulate electrophysiological activity (Electrophysiology Module).

Mechanics Module	Imaging Module	Electrophysiology Module
· radial, linear · custom strain fields · one fast impulse stretch or cyclical stretch · up to 50% strain · up to 75/s strain rate · any stretch pattern · high reproducibility	· before, during and after stretching · up to 2,000 frames per second at 2MP resolution · custom software to independently measure the tissue strain	· electrodes stretch with the cells/tissue · recording/stimulation before, during, and after stretching · comparison of cell health and function pre and post stretch · soft MEAs on elastomeric substrates · standard rigid MEAs are also available

To best meet the needs of researchers, there are three models of MEASSuRE available for different applications.

1.1 The Models of MEASSuRE

1.1.1 MEASSuRE-Mini

1. **Mechanics Module:**
   strain rate up to 1/s, strain up to 20%
   can be used in an incubator
2. **Imaging Module:**
   frame rate: 150fps
3. **Electrophysiology Module:**
   2×60 channels

Applications: Physiological Stretch

- *Tissue engineering, regenerative medicine*
- *Organ-on-a-Chip, pre-clinical drug development*
- *Mechanobiology*

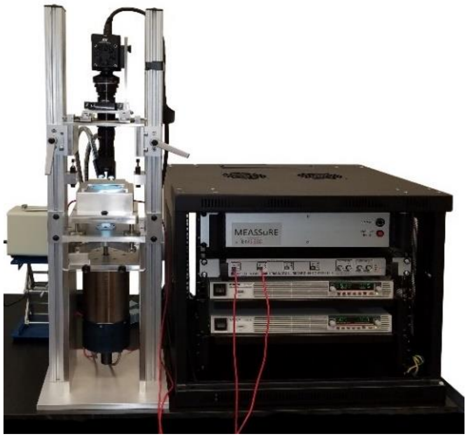
1.1.2 MEASSuRE-Premium

1. **Mechanics Module:**
   strain rate up to 50/s, strain up to 50%
2. **Imaging Module:**
   frame rate: 2,000 fps
3. **Electrophysiology Module:**
   2×60 channels

Applications: Pathological Stretch

- *Traumatic brain injury (TBI), repeated concussions*
- *Spinal cord injury (SCI)*
- *Neurodegenerative diseases*
- *Muscle injuries*

1.1.3 MEASSuRE-X



1. **Mechanics Module:**
   strain rate up to 75/s, strain up to 50%
2. **Imaging Module:**
   frame rate: 2,000 fps
3. **Electrophysiology Module:**
   2×60 channels

Applications: Pathological Stretch

- *Traumatic brain injury (TBI), repeated concussions*
- *Spinal cord injury (SCI)*
- *Neurodegenerative diseases*
- *Muscle injuries*

1.2 How is MEASSuRE used?

Mechanics

apply mechanical stretch & mimic ***biomechanics*** *of cells in the body*

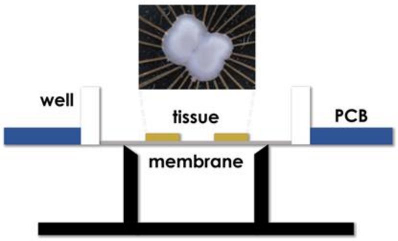
Imaging

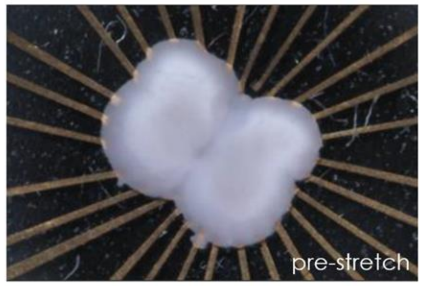
visualize cells during stretch & precisely ***quantify*** *the cell strain*

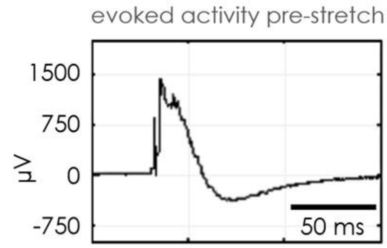
Electrophysiology

assess ***tissue health*** *before, during, & after stretch*

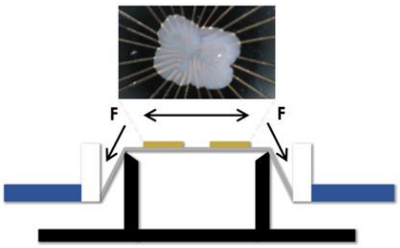
Before Stretch

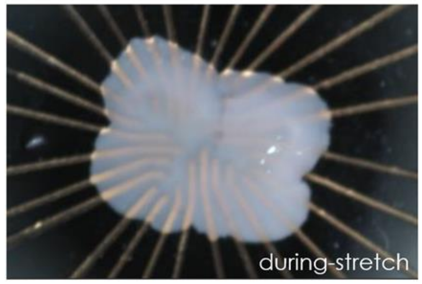




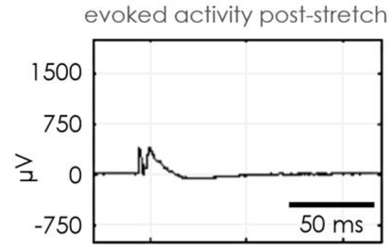


During Stretch





organotype spinal cord slice
courtesy of Bonnie Firestein, PhD & Rutgers University



hippocampal tissue slice
courtesy of Barclay Morrison, PhD & Columbia University

Features

- *mechanical, electrical, & optical interface with cell cultures*
  - *independent & concurrent*
  - *direct comparison of cell health & function pre- & post-stretch*
  - *repeated and cyclic stretches*
  - *visualization of cells during stretch*
  - *software enabled measurement of cell strain*
- *high strain (50%) & strain rates (75/s)*
- *any strain pattern can be programed using macros*
- *various strain profiles (radial, linear, custom)*
- *closed-loop feedback control for highly reproducible strain profiles*
- *affordable compared to competition*

Applications

- *functional drug screening (neuroprotective)*
- *neurotrauma research (TBI, SCI, concussion)*
- *drug development*
- *tissue engineering / regenerative medicine*
- *organ-on-a-chip models*
- *mechanobiology*

Benefits

- *better predict clinical outcomes*
  - *eliminate drug candidates early*
- *reduce failure rate in clinical trials*
- *save time, money & research animals*

2. Individual Modules of MEASSuRE

Each module of MEASSuRE is available as a stand-alone unit that can be purchased and operated separately. Individually purchase modules can be combined to the full MEASSuRE system due to the modular nature of MEASSuRE.

2.1 Electrophysiology Module

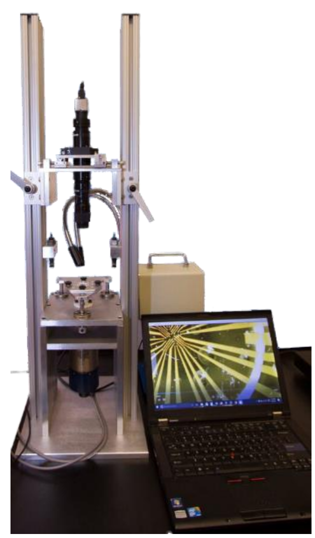
- *120-channel controller*
- *60-channel recording and stimulation (can be upgraded to 120 channels)*
- *Compatible with stretchable and rigid MEAs*
- *Significantly lower cost compared to the competition from MultiChannel Systems, MED64, or Axion Biosystems*
- *This module is the same the same in all models of MEASSuRE*

2.2 Mechanics Module

- *3 cell stretcher models available for different applications: neurodegenerative diseases, neurotrauma, tissue engineering, drug screening*
- *Variable strain rates*
- *Various strain profiles available (radial, linear, custom)*
- *Customizable*
- *Use in an incubator*
- *Imaging and Electrophysiology Modules can be added*
- *Different modules available depending on application; see Mechanics Module of MEASSuRE*

2.3 Mechanics & Imaging Module

- *3 cell stretcher models available with variable strain rates and strain profiles available (radial, linear, custom)*
- *Optical imaging of live cells during stretching motion*
- *High frame rate and resolution*
- *Customizable*
- *Fluorescent imaging possible*
- *Electrophysiology Module can be added to complete the MEASSuRE system*



2.3.1 Imaging upgrades

The current imaging module consists of a **high-speed camera**, *a* **1× adapter**, *a* **Zoom 6000 lens**, *a* **2× lens attachment**, *and an* **LED fiber optic illuminator with dual gooseneck lights** – *sufficient for running experiments with tissue slices. Experiments with dissociated cells, however, may need to consider higher resolution imaging with the following hardware and light source upgrades to the current module.*

Standard | **Upgrades**

1× adjustable standard adapter

- **No magnification**
- *Standard length*

2× adjustable short adapter

- **2× magnification**
- *Shorter adapter to compensate for larger objective*

Zoom 6000 lens

- **Cannot be coupled with an objective**
- *4.5× magnification*
- *12mm fine focus*

UltraZoom 6000 lens

- **Can be coupled with an objective**
- *4.5× magnification*
- *12mm fine focus*

2× lens attachment

- *2× magnification*
- *Increases magnification*
- *Decreases field of view*

10× Motic objective

- *10× magnification range*
- *Increases magnification*
- *Decreases working distance*

LED Fiber Optic Illuminator with Dual Gooseneck Lights

- **LED-50W**
- *Gooseneck light*
- *Illuminates sMEA from the side*

LED Fiber Optic Illuminator with Ring Light

- **LED-80W**
- *Small ring light attachment*
- *Illuminates sMEA from above*

3. Consumables

3.1 Stretchable microelectrode arrays (sMEAs) for in vitro applications

Rigid microelectrode arrays (MEAs) for recording and stimulation of extracellular electrophysiological activity from single cells and tissue slices (neurons, muscles) are standard tools in many laboratories for decades. Soft and stretchable microelectrode arrays (sMEAs) have recently been invented. A major benefit of sMEAs is that they provide a soft and dynamic mechanical environment for the cells, which is more physiologically relevant than rigid glass MEAs or merely flexible MEAs. This means that results obtained with sMEAs better predict the behavior of cells in vivo.

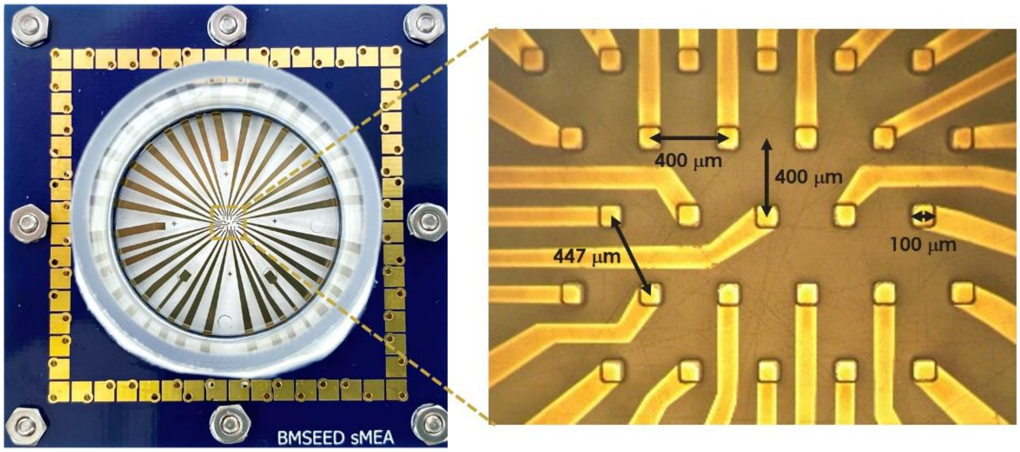
sMEAs are used in the same way as traditional rigid or flexible MEAs for recording and stimulation of extracellular electrophysiological activity in tissue slice or dissociated cell cultures. Electrophysiological measurements with sMEAs can be accomplished with the data acquisition system from BMSEED (see above) as well as from Multichannel Systems.

Nomenclature for MEAs:

32/34/60	p	s/g	MEA/SW	-	100	-	400	-	2/4iR
number of recording electrodes	*pocket*	*s: stretchable g: glass*	*MEA: micro-electrode array SW: stretchwell*		*electrode diameter*		*electrode spacing (center-to-center)*		*number of internal reference electrodes*

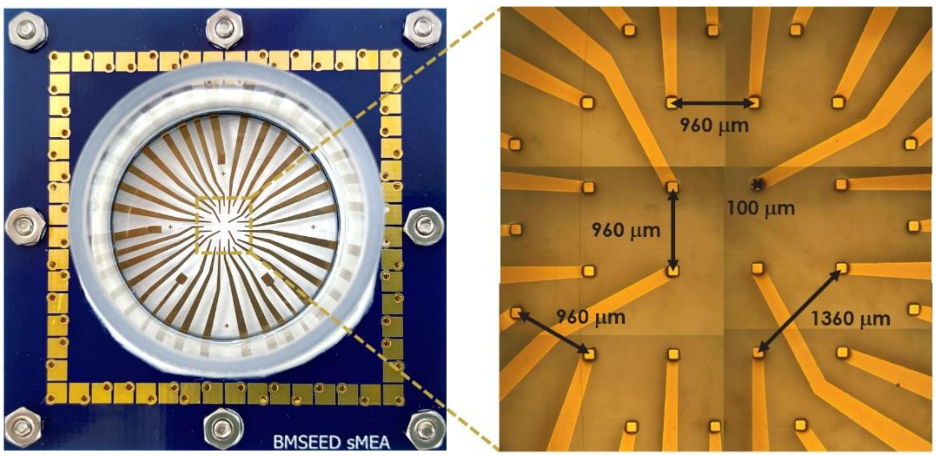
3.1.a Model: 32sMEA-100-400-4iR (Gen 4e)

- **32 electrodes: 28 microelectrodes + 4 internal reference electrodes**
- *internal reference electrodes compatible with Multi Channel Systems amplifier*
- *electrode material: gold*
- *area covered by recording electrodes: 2.32 mm × 1.72 mm*
- *100 µm diameter recording sites*
- *400 µm distance between recording sites in the same row*
- *447 µm distance between recording sites in different rows*
- *plastic ring*
- *recording & stimulation*
- *soft and elastically stretchable (silicone substrate)*
- *compatible with MultiChannel Systems data acquisition system*



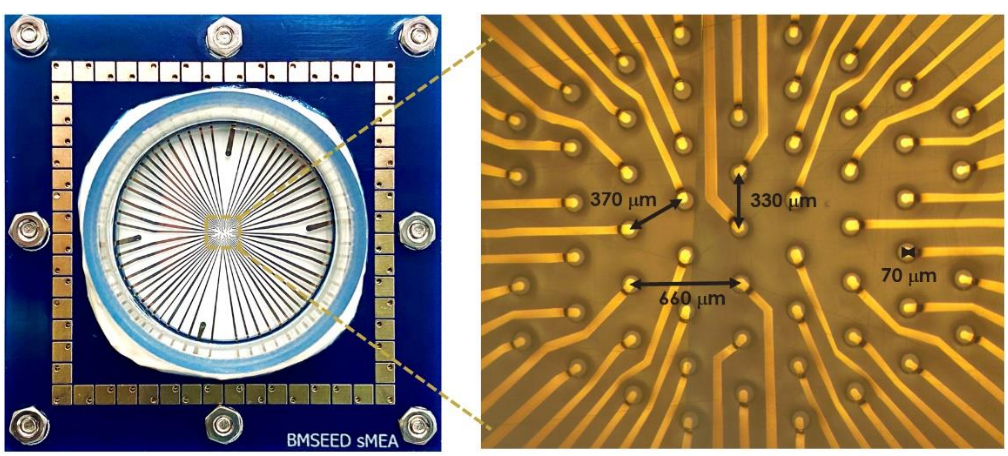
3.1.b Model: 32sMEA-100-960-4iR (Gen 4f)

- **32 electrodes: 28 microelectrodes + 4 internal reference electrodes**
- *internal reference electrodes compatible with Multi Channel Systems amplifier*
- *electrode material: gold*
- *area covered by recording electrodes: 5.0 mm × 5.0 mm*
- *100 µm diameter recording sites*
- *960 µm distance between adjacent recording sites*
- *plastic ring*
- *recording & stimulation*
- *soft and elastically stretchable (silicone substrate)*
- *compatible with MultiChannel Systems data acquisition system*



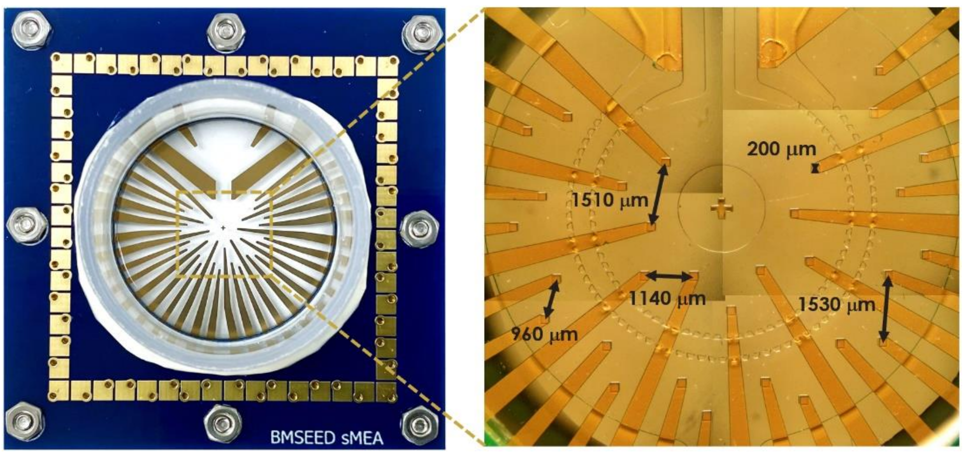
3.1.c Model: 60sMEA-70-330-4iR (Gen 6a)

- **60 electrodes: 56 microelectrodes + 4 internal reference electrodes**
- *electrode material: gold*
- *70 µm diameter recording sites*
- *330 µm distance between recording sites in the same column*
- *370 µm distance between recording sites in different columns*
- *plastic ring*
- *recording & stimulation*
- *soft and elastically stretchable (silicone substrate)*
- *compatible with MultiChannel Systems data acquisition system*



3.1.d Model: **34sMEA-200-960-4iR (Gen 7a)**

- **60 electrodes: 56 microelectrodes + 4 internal reference electrodes**
- *electrode material: gold*
- *200 µm diameter recording sites*
- *960 µm distance between recording sites in the center section*
- *1140 µm distance between recording sites in the outer section*
- *plastic ring*
- *recording & stimulation*
- *soft and elastically stretchable (silicone substrate)*
- *compatible with MultiChannel Systems data acquisition system*



3.2 0SW-0-0-0iR (Stretchwell, SW)

Stretchwells do not contain any electrodes, but are exactly the same as sMEAs in all other aspects. The purpose of stretchwells is twofold.

First, stretchwells are used to optimize cell seeding protocols for sMEAs. Stretchwells are significantly cheaper than sMEAs but require the same cell seeding protocol. Using stretchwells for cell seeding protocol optimization therefore saves money.

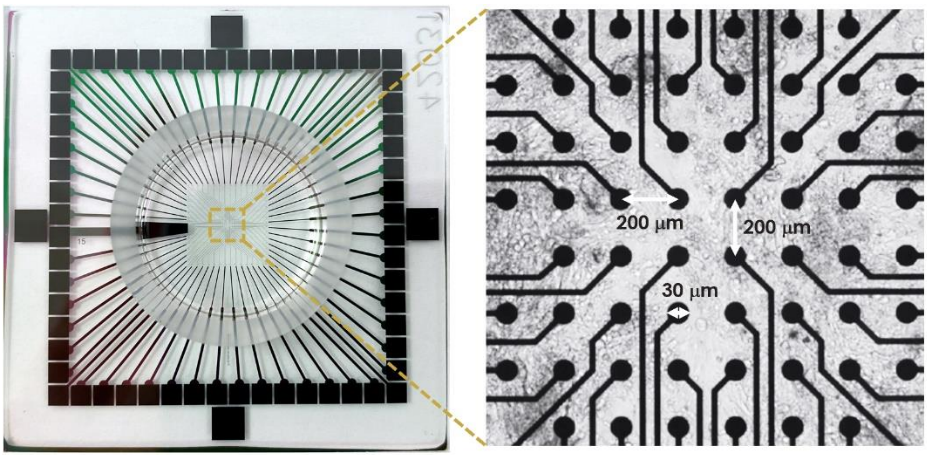
Second, stretchwells are used with the Mechanics Module if recording electrophysiological activity is not intended for the experiment either because the cells are not electrophysiologically active or because other aspects are investigated. Again, this saves money because stretchwells are cheaper.

3.3 Rigid microelectrode arrays (MEAs) for in vitro applications

Rigid glass MEAs for electrophysiological measurements are also available from BMSEED. The glass MEA model shown below is generally available in stock. However, MEAs with different layout are available upon request.

Model: 60gMEA-30-200-1iR (glass MEA)

- **60 electrodes: 59 microelectrodes + 1 internal reference electrode**
- *electrode material Ti/TiN*
- *30 μm diameter recording sites*
- *200 μm distance between recording sites*
- *glass ring*
- *recording & stimulation*
- *rigid, hard, and not stretchable glass substrate*
- *compatible with MultiChannel Systems data acquisition system*



3.4 Stretchable microelectrodes for in vivo applications

BMSEED offers soft and stretchable microelectrodes for acute and chronic implantations in vivo. The softness of the electrodes reduces the probability to cause damage of the tissue and the stretchability of the electrodes provides electromechanical durability during surgery and the implantation period.

3.4.1 Brain interfaces

Our brain interfaces are intended for epidural or subdural implantation intracranially to record local field potentials from the surface of the brain (electrocorticography, ECoG).

Benefits of BMSEED's brain interfaces:

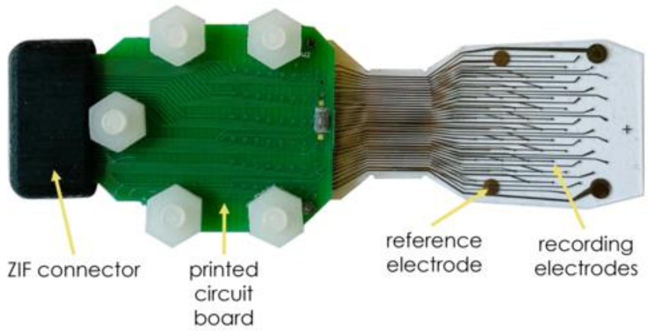
- *High electrode density for high resolution recording*
- *Large cortical area coverage*
- *Small electrode diameter for recording from specific cortical columns*
- *Thin substrates of 0.3mm or less compared to 2-5mm for conventional ECoG arrays*
  - *Avoid increasing intracranial pressure*
  - *Avoid vascular depression*
  - *Follow the curvature of the brain*
- *Thin film technology for reduced bending stiffness*

Model: 32ECoG-300-2000-2iR

- **32 electrodes: 30 microelectrodes + 2 reference electrodes**
- *electrode material: gold*
- *300 μm diameter recording sites*
- *2,500 μm distance between recording sites in the same row*
- *2,000 μm distance between recording sites in different rows*
- *23 mm × 20 mm cortical coverage*
- *ZIF clip or Omnetics connector interface*

Model: 96ECoG-300-2000-4iR (under development)

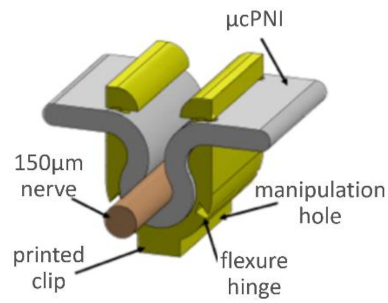
- **96 electrodes: 92 microelectrodes + 4 reference electrodes**
- *electrode material: gold*
- *300 μm diameter recording sites*
- *2,500 μm distance between recording sites in the same row*
- *2,000 μm distance between recording sites in different rows*
- *23 mm × 20 mm cortical coverage*
- *ZIF clip or Omnetics connector interface*



3.4.2 Peripheral nerve interfaces (PNIs)

BMSEED is developing a PNI that combines our stretchable microelectrode technology with a 2-photon 3-D printed microclip for epineural recording and stimulation of peripheral nerves. This microclip PNI (μPNI) provides the following benefits:

- *Interface with nerves as small as 100μm diameter*
- *Small form factor*
- *Increased signal amplitude*
- *No sutures or adhesives required*
- *No damage to the nerve*
- *Six electrodes or more can be placed around the circumference of the nerve for differential signal acquisition*

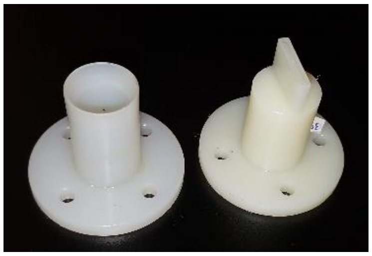


4. Accessories

4.1 Electrophysiology Interface Board (EIB)

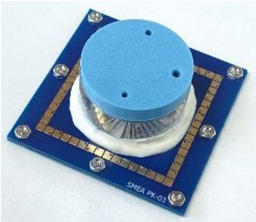
- *Shield sMEA electrophysiology recordings from external noise*
- *Shield Omnetics connectors and Intan headstages from potential media splashing*
- *More secure latching mechanism compared to the standard Plexon board*

4.2 Strain Profile



- *Change the strain profile of the Mechanics Module (as part of MEASSuRE or stand-alone tool) by changing the Teflon or Nylon indenter*
- *The standard strain profiles are radial and uniaxial strain, but custom strain profiles are available upon request*

4.3 sMEA Cap



- *Cover media to maintain sterility and prevent splashing*
- *Several recordings for longitudinal measurements*
- *Protect cells during stretch motion in the Plexon board or EIB*

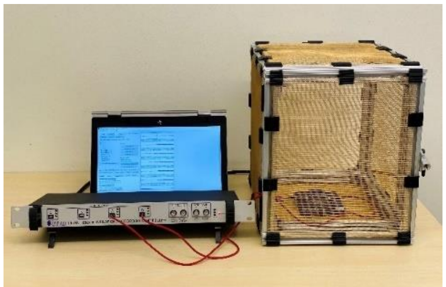
4.4 60 Channel Expansion Kit for Ephys Module

- *Increase the number of simultaneously usable channels from 60 to 120*
- *Perform two 60-channel recordings simultaneously*

4.5 Temperature Controller

- *Control the temperature of your cell culture outside of the incubator between room temperature and 45°C*
- *No physical contact to medium*
- *Low cost*

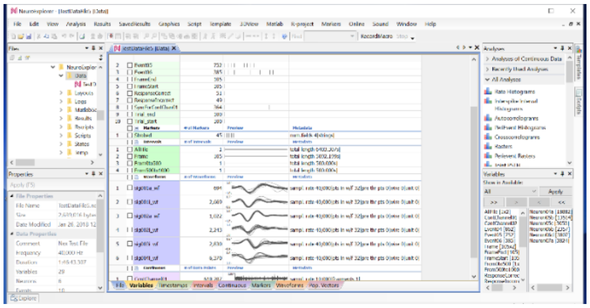
4.6 Faraday Cage



- *Eliminate electromagnetic interferences from the environment (e.g., lamps, computers, electronic equipment) with your experiment by shielding them with a Faraday cage*
- *Convenient and low cost*
- *Several sizes available*

4.7 Data Analysis Software

- *NeuroExplorer software package for data analysis*
- *Analyze continuously recorded signals as well as sequences of timestamps (spike trains, behavioral events) and short signal fragments (spike waveforms)*
- *More than 40 analysis types to explore data*
- *Calculate statistical properties (e.g., confidence limits for histogram and spectra; histogram peak locations and z-scores)*



- *The output files from the Electrophysiology Module can be directly imported in NeuroExplorer without file conversion.*

5. References

5.1 In vitro applications

1. *O. Graudejus, T. Li, J. Cheng, N. Keiper, R.D. Ponce Wong, A.B. Pak, J. Abbas (2017) The effects of bending on the resistance of elastically stretchable metal conductors, and a comparison with stretching.* **Applied Physics Letters**, *110, 221906.*
2. *W. H. Kang, W. Cao, O. Graudejus, T.P. Patel, S. Wagner, D.F. Meaney, B. Morrison III (2015) Alterations in hippocampal network activity after in vitro traumatic brain injury.* **Journal of Neurotrauma**, *32(13):1011-1019.*
3. *O. Graudejus, B. Morrison, C. Goletiani, Z. Yu, S. Wagner (2012) Encapsulating elastically stretchable neural interfaces: yield, resolution, and recording/stimulation of neural activity.* **Advanced Functional Materials**, *22, 640-651.*
4. *S. P. Lacour, S. Benmerah, E. Tarte, J. FitzGerald, J. Serra, S. McMahon, J. Fawcett, O. Graudejus, Z. Yu, B Morrison (2010) Flexible and stretchable micro-electrodes for in vitro and in vivo neural interfaces.* **Medical & Biological Engineering Computation**, *48(10), 945-954 (Special Issue).*
5. *Z. Yu, O. Graudejus, C. Tsay, S. P. Lacour, S. Wagner, B. Morrison (2009) Monitoring hippocampus electrical activity in vitro on an elastically deformable microelectrode array.* **Journal of Neurotrauma**, *26(7), 1135-1145.*
6. *O. Graudejus, Z. Yu, J. Jones, B. Morrison III, S. Wagner (2009) Characterization of an elastically stretchable microelectrode array and its application to neural field potential recordings.* **Journal of the Electrochemical Society**, *156(6) P85-P94.*

5.2 In vivo applications

1. *O. Graudejus, C. Barton, R.D. Ponce Wong, C.C. Rowan, D. Oswalt, B. Greger (2020) A Soft and Stretchable Bilayer Electrode Array with Independent Functional Layers for the Next Generation of Brain Machine Interfaces.* **Journal of Neural Engineering**, *17(5) 056023.*

5.3 General science of our technology

1. *O. Graudejus, T. Li, J. Cheng, N. Keiper, R.D. Ponce Wong, A.B. Pak, J. Abbas (2017) The effects of bending on the resistance of elastically stretchable metal conductors, and a comparison with stretching.* **Applied Physics Letters**, *110, 221906.*
2. *O. Graudejus, Z. Jia, T. Li, S. Wagner (2012) Size dependent rupture strain of elastically stretchable metal conductors.* **Scripta Materialia**, *66, 919-922.*
3. *J. Jones, O. Graudejus, S. Wagner (2011) Elastically stretchable insulation and bi-level metallization and its application in a stretchable RLC circuit.* **Journal of Electronic Materials**, *40(6), 1335-1344.*
4. *O. Graudejus, P. Görrn, S. Wagner (2010) Controlling the morphology of gold films on poly(dimethylsiloxane).* **ACS Applied Materials & Interfaces**, *2(7), 1927-1933.*