Using Intelligent Materials to Enable Wireless Brain-Machine Interface

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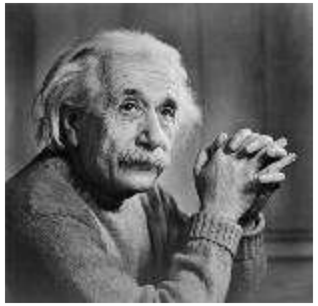
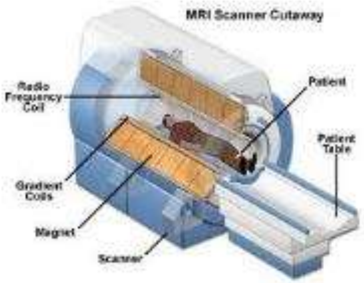
Outline

- Significance: Brain-like Computing and Finding Cure to Currently Untreatable Brain Diseases
- Intelligent Materials
- Applications
- Conclusions and Impacts

Advanced Materials Will Pave The Way to The Future





- ➢Today, we are lucky to live through a special time of a new wave of paradigm shifts in science and technology. Engineering is the driving force of this technology revolution. The next generation of engineers will lead the society to advances which are unimaginable today…

- ➢Crossing disciplinary boundaries: Engineers can break current disciplinary barriers to revolutionize most impactful application areas such as medicine, energy, information, sustainability and resilience, etc.

- ➢The technology world is becoming more multidisciplinary and interdisciplinary. We need engineers trained to excel in this new world!

Motivation: Brain-Like Computing is the Future

Problem Significance

➢The current CMOS technology cannot longer maintain the Moore's Law, Quantum Computing (QC) might be a promising alternative for some niche applications, e.g., encryption, however, its capability to replace an entire computer remains an open question.

Solution: Brain-Like Computing

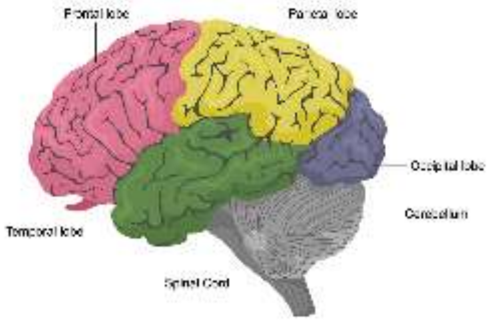
➢Brain-Like Computing (BLC) is a viable alternative.
➢Unlike Quantum Computing, BLC is already widely used and works at room temperature …
➢There are open engineering questions that need to be answered for implementing the new hardware.
➢Paves a way to bionic future.

Impact

➢BLC is vital to implement computationally powerful neuro-biological architectures present in the nervous system and thus create superior artificial intelligence (AI) systems
➢Reciprocally, BLC will improve our fundamental understanding of the brain and thus enable many disruptive medical applications
➢Connecting The Brain to AI will elevate the mankind to the next level of development

Supercomputer (USA or China),
Cost: ~$500mln
Energy consumption:
a power plant (~7 MW)

The human brain is still more superior in every respect…,
Uses only 20 W of power…



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Mysteries of the Brain

- To date, we still don't know how the brain works (computing architecture of the brain), because it is challenging to establish contacts to over 80bln neurons !? The engineering which underlies the communication between neurons, i.e., spatial and temporal dependencies of electric currents and thermal management, is an open question.

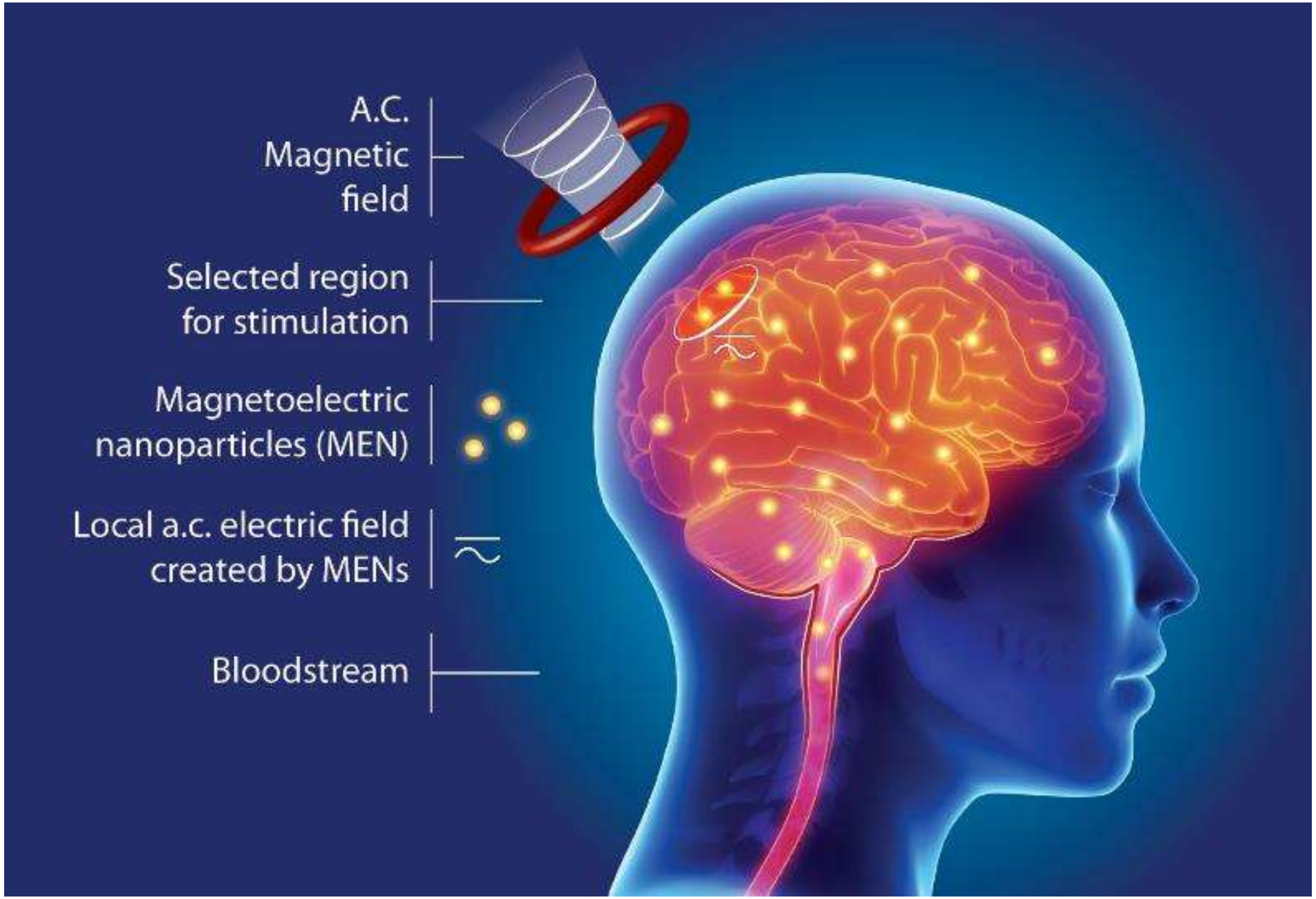
We know the brain follows a very different computing architecture compared to modern computers (metrics from I. Schuller**)**

- Thermal management: Temperature variation in the brain is < 2^0C compared of >50^0C in CMOS chip
- Fan-out is 10^5 compared to 3-4 in CMOS chip
- Power is ~20 W compared to 7 MW in CMOS
- Noise is stochastic resonance compared to …
- Error Rate is ~75% compared to ~0% in CMOS
- Unit size: ~10 microns compared to 10 nanometers in CMOS
- Operational voltage: ~ 0.01 V compared to 1 V in CMOS
- Speed: ~1 msec compared to <1 nsec
- Dimensionality/Geometry: 2D (likely >> 3D) compared to 2D (or 2.5D) in CMOS

Hypothesis: Directly learning from the brain by building high-precision wireless brain-machine interface (BMI) might help shed light on understanding the brain's computing architecture.

By enabling BMI, we achieve two big goals. (1) We solve the open question of the brain computing architecture. (2) We also learn how to cure currently untreatable brain-related diseases.
By connecting the human brain to AI, elevate the homo sapiens to the next level …

Our Solution: Intelligent Materials To Create Wireless High-resolution Brain-Machine Interface



- Today, we know more about black holes in space compared to what we know about our own brain…
- The reason we know so little about the brain is the fact that it is difficult to access neurons wirelessly. The electric circuitry of the network of about 80 bln neurons strongly interferes with remote electric fields, thus requiring physical electrodes (implants).
- Optogenetics is promising, however, it is limited by the poor penetration of the UV light through the skull and the need for genetic modification of the brain tissue.
- Neuralink and other research companies/centers rely on using wired implants to write/read information in/from individual neurons
- DARPA N3 Program

*K. Yue, R. Guduru, J. Hong, P. Liang, M. Nair, and S. Khizroev, “Magneto-electric nanoparticles for non-invasive brain stimulation,” *PLoS* 7(9), e44040 (2012)
**R. Guduru, P. Liang, J. Hong, A. Rodzinski, A. Hadjikhani, J. Horstmer, E. Levister, and S. Khizroev, “Magnetoelectric “spin” on stimulating the brain,” *Nanomedicine (London)* 10 (13), 2051-2061 (2015)

Intelligent Materials: MagnetoElectric NanoParticles (MENPs)*

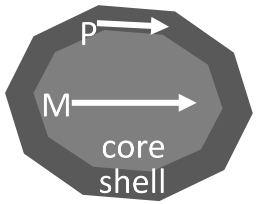
- Using intelligent materials allows to combine strengths of multiple fields while mitigating their drawbacks!
- Intelligent materials change their certain intrinsic properties depending on specific molecular-level variations in the microenvironment.
- Intelligent materials allow a two-way way connection to individual cells: (i) detect and (ii) control.

Note: Unlike any other nanoparticles, MENPs display a non-zero magnetoelectric (ME) effect. Owing to the ME effect, MENPs allow to connect intrinsic electric fields to remotely controllable magnetic fields. Thus, the ME effect can be used for both wireless “writing” (stimulation/nano-electroporation) and “reading” (recording/detection) intrinsic electric fields from single neurons or other cells, e.g., cancer cells, thus controlling and reflecting intrinsic cellular characteristics:

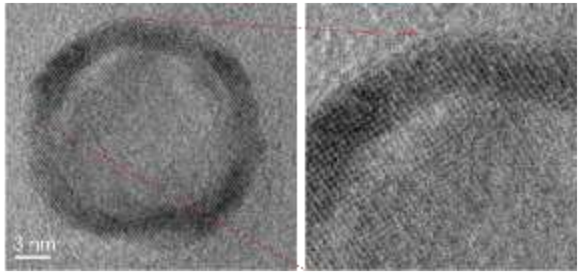
Writing: $P_i = -dG/dE_i = -\alpha_{ii}H_i$

Reading: $M_i = -dG/dH_i = \alpha_{ii}E_i$,

Illustration of Coreshell Magnetoelectric Nanoparticles (MENPs)
(P and M show directions of electric polarization and magnetization)



Transmission Electron Microscopy (TEM) Image of Perfect Crystal Lattice Matched Coreshell MENP ($CoFe_2O_4$-$BaTiO_3$) with a record high ME coefficient (of over 1 V/cm/Oe). (The record high ME is due to the perfect lattice match [2]) (By Ping Wang)



Expertise required:

- Intelligent materials operate based on the principles of quantum physics
  They allow to intrinsically connect to the brain and the rest of the body at the molecular level wirelessly, i.e. without using invasive electrodes
- The need to enable wireless connection at the molecular level calls for expertise in electromagnetism, quantum physics, advanced materials and thermodynamics
- Cross-disciplinary research is vital: ECE experts should work with other engineers, biologists, chemists and physicists

Next-generation **N**on-surgical **N**eurotechnology (**N3**) Program

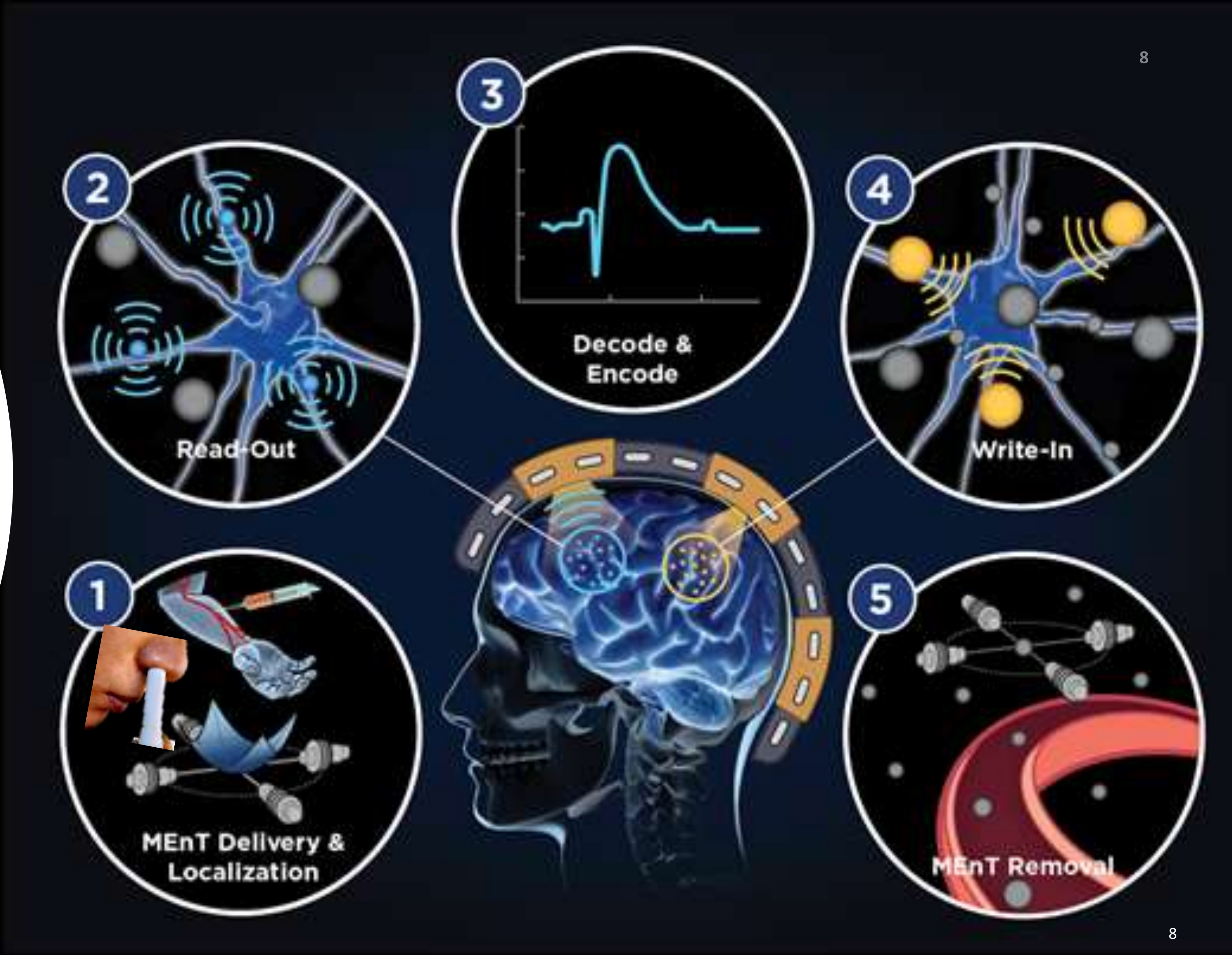
Multi-channel, deep brain, high spatial resolution (1mm3) read-write BCI

Vision:

Machine enhance human

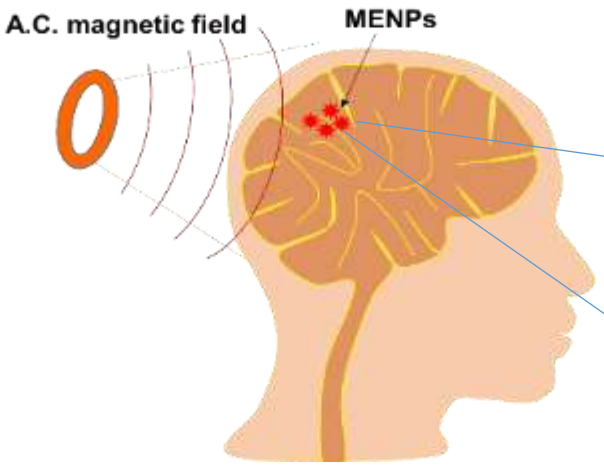
Integration of human intelligence and AI

*the illustration by Battelle (P. Ganzer)

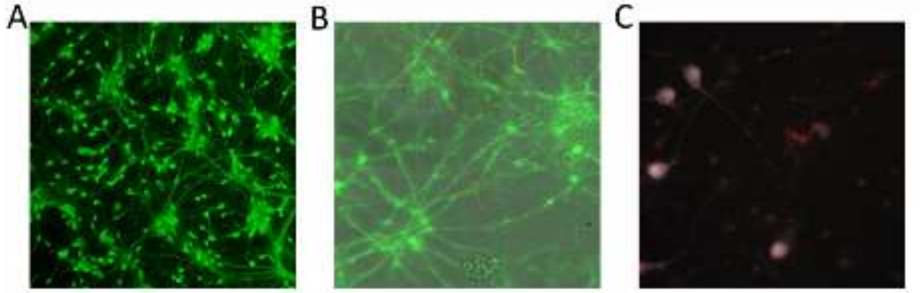


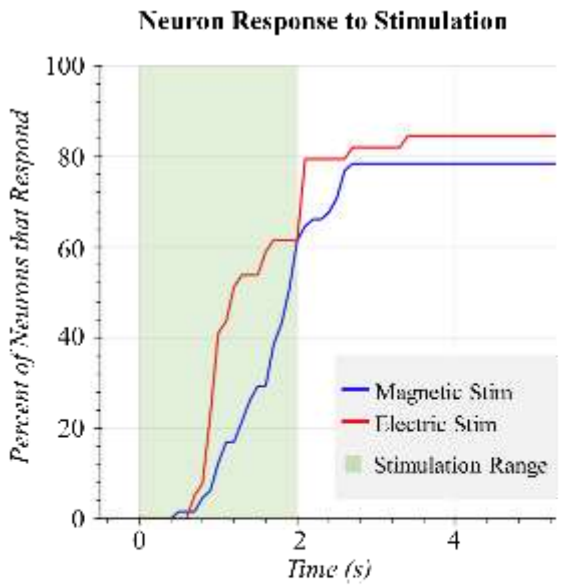
Wireless Writing Into Neurons With MENPs*

Highly Dispersed High-density Solution of MENPs, administrated either through intranasal (IN) inhalation or intravenous (IV) injection
(by Elric Zhang and Isadora Smith)



Fluorescence images: (a) W/O and (b) With MENPs, (c) Neuron Stimulation With MENPs.





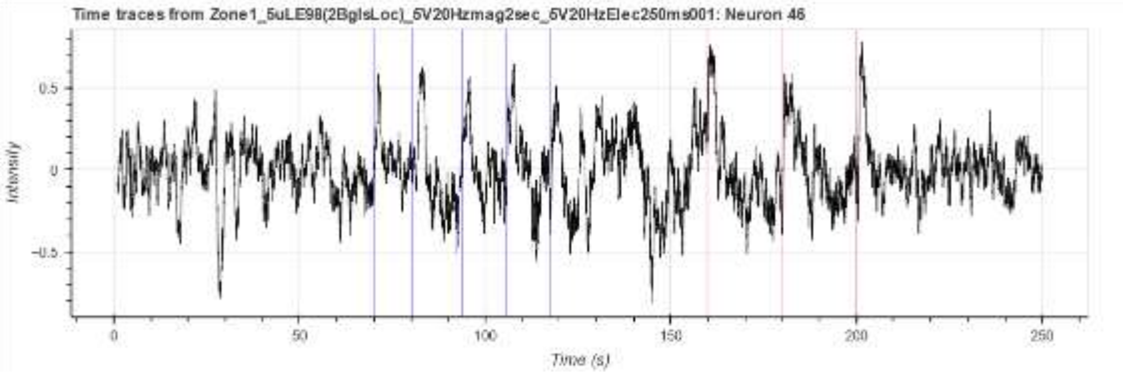
Note: Wireless stimulation with MENPs is equivalent to wired electric stimulation*.

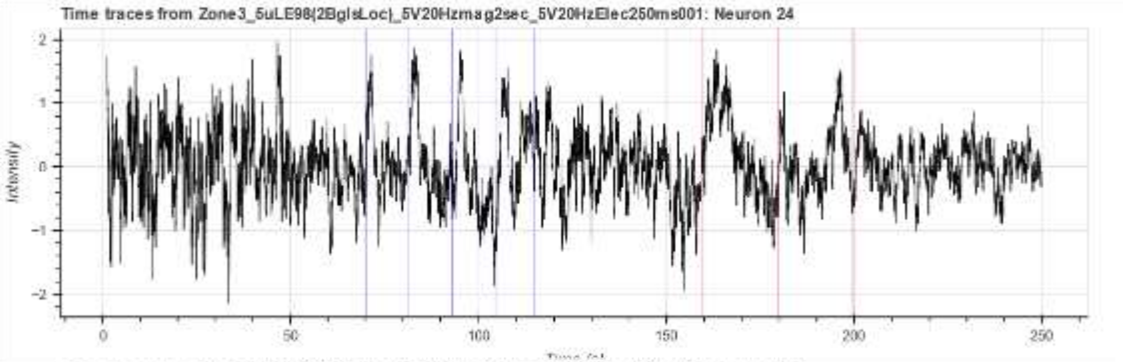
*E. Zhang et al, "Magnetic-field-synchronized wireless modulation of neural activity by magnetoelectric nanoparticles," *Brain Stimulation* **15** (6): 1451-1462 (2022)

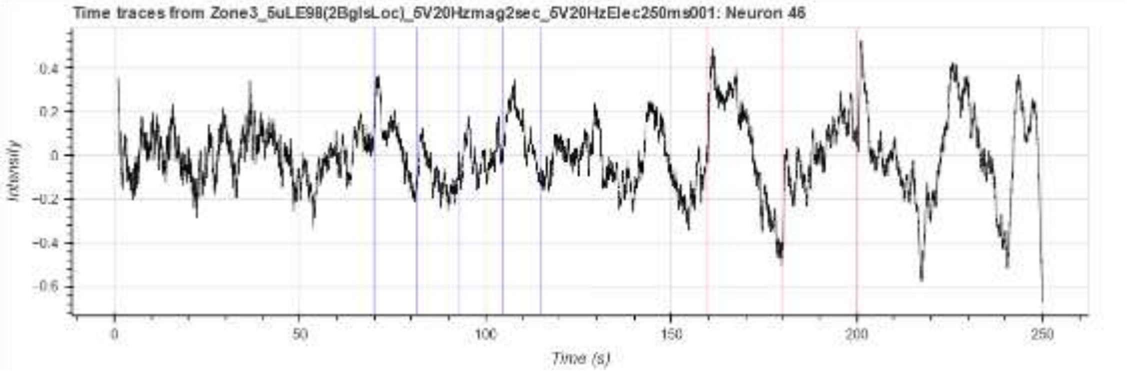
Calcium Imaging Time Traces and Spike Triggered Averages (Analysis by Elric Zhang)

Wireless Magnetic Stim (blue lines)

Electrode Electric Stim (red lines)

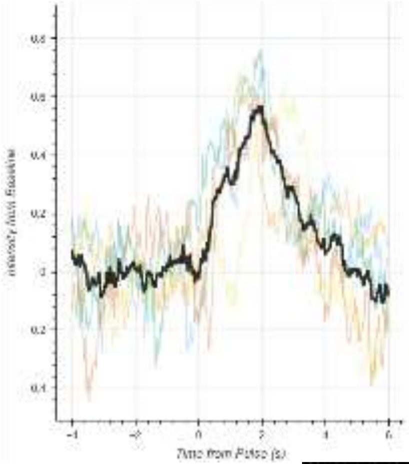




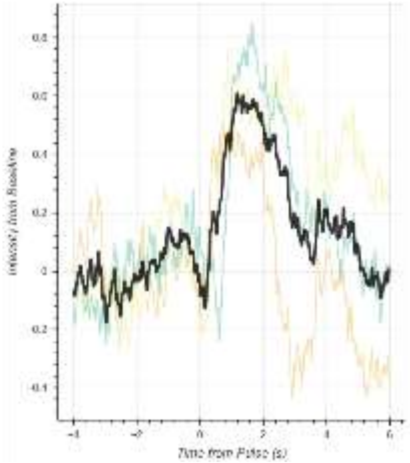


Note: We send five magnetic pulses followed by three control electric pulses. The neuronal response is identical. We are using hippocampal neural cell cultures

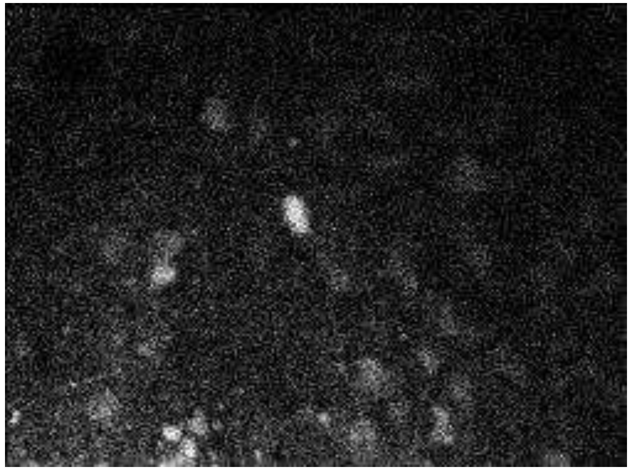
Magnetic Pulse Triggered Average Signal for Example Neuron



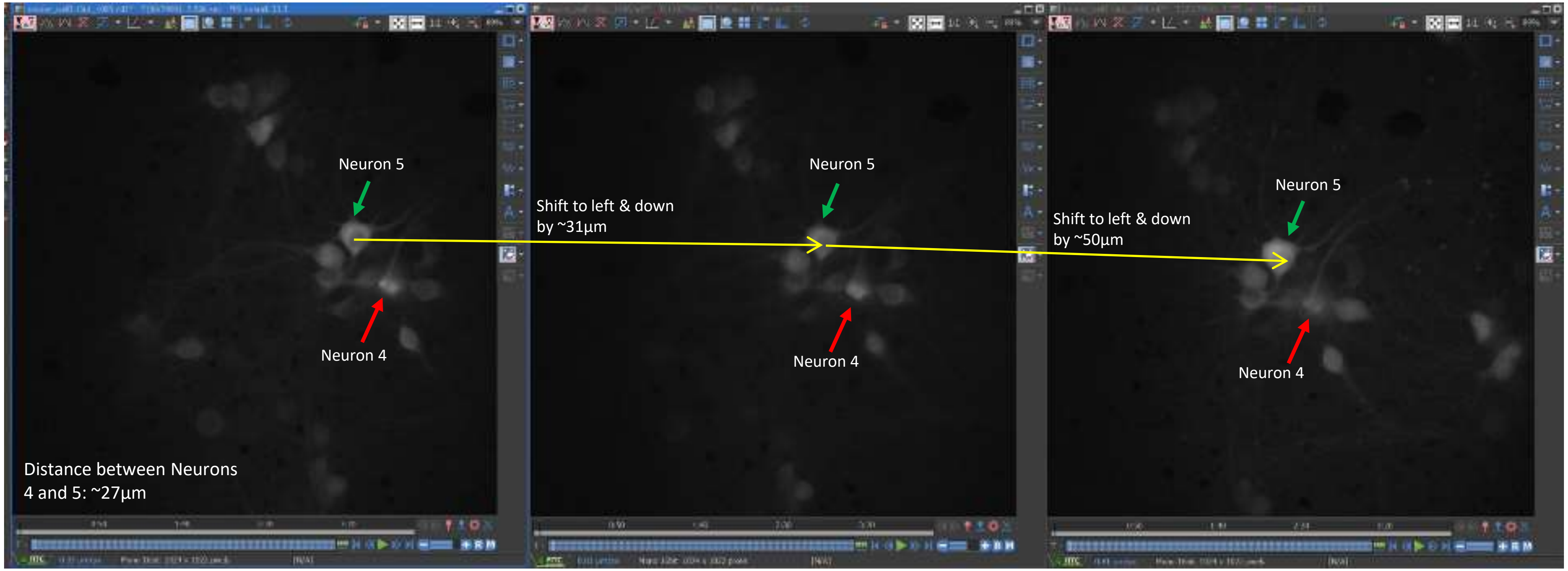
Electric Pulse Triggered Average Signal for Example Neuron



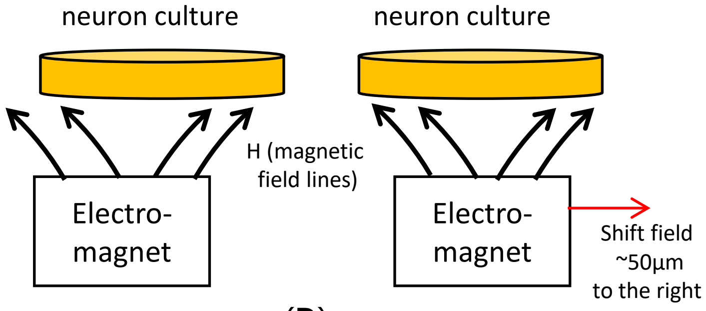
Video taken from the brain of a mouse with MENPs; firing is synchronized with application of magnetic fields



Task 6 – Writing Spatial Resolution Via Magnetic Field Gradient



(**A**) Location 1 (**B**) Location 2 (**C**) Location 3



(**D**)

Fig. 6. Preliminary experiments demonstrate that by shifting a non-uniform 10 pulse/s (pps) pulsed magnetic field by a distance of ~50µm relative to a cell culture dish, the change in the magnetic field distribution on the same set of neurons in a GCaMP6 expressing cortex culture will stimulate different neurons. **A.** Field Location 1 of the non-uniform pulsed magnetic field relative to the culture. **B.** Field Location 2, which is shifted ~31µm from field location 1, and **C.** Field Location 3, which is shifted ~50µm from field location 2, ~80µm from field location 1. Most of the same cells are in all three FOVs, which are 330µm x 330µm and the resolution is 0.33µm/pixel. **D.** Illustration of the shifting of the stimulating pulsed magnetic field. Plots of Ca++ intensity of neurons 4 (red) and 5 (green) in the two FOVs are shown in **Fig. 5** on next slide.

Task 6 – Raw Data Showing Differential Neural Stimulation Via Magnetic Field Gradient Control

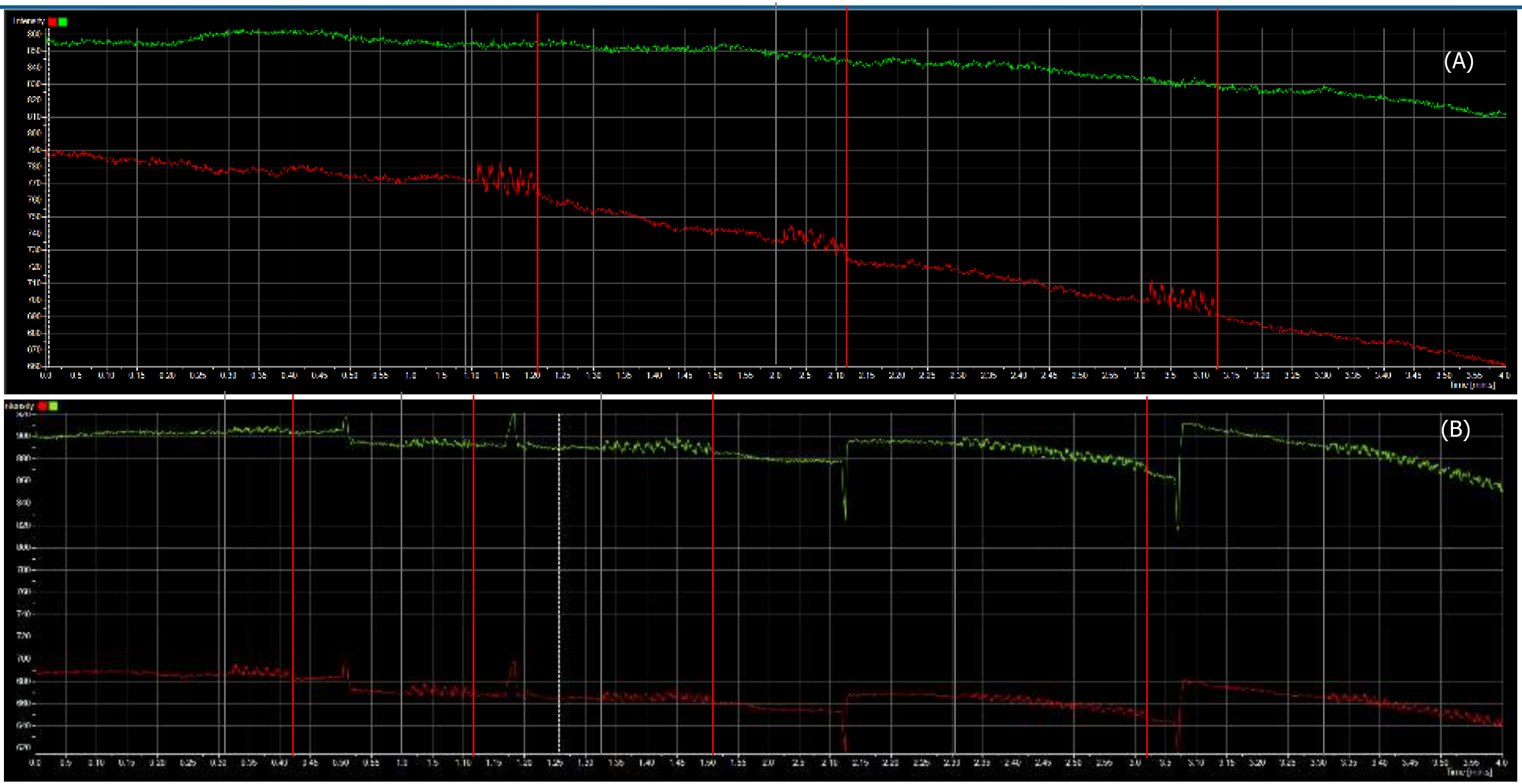


Fig. 7 A. Plots of Ca++ intensity of neurons 4 (red) and 5 (green) in field location 1 as shown in **Fig. 6A** (previous slide). **B.** Plots of Ca++ intensity of neurons 4 (red) and 5 (green) in field location 3 as shown in **Fig. 4C**. The field generating (**B**) is shifted by ~80µm from field generating (**A**), thus neurons 4 and 5 in (**B**) are under different magnetic field gradient than neurons 4 and 5 in (**A**). (**A**) shows that neuron 5 had no detectable response in location 1 but had significant response when shifted to location 3 as shown in the plots in (**B**). Conversely, neuron 4's response decreased when the field is shifted to location 3. Red and green vertical lines indicate the approximate on and off times of magnetic stimulation. The 4 large spikes in (**B**) are manual adjustment to counter defocus drift in the microscope.

Writing: Disruption of Spontaneous Activities

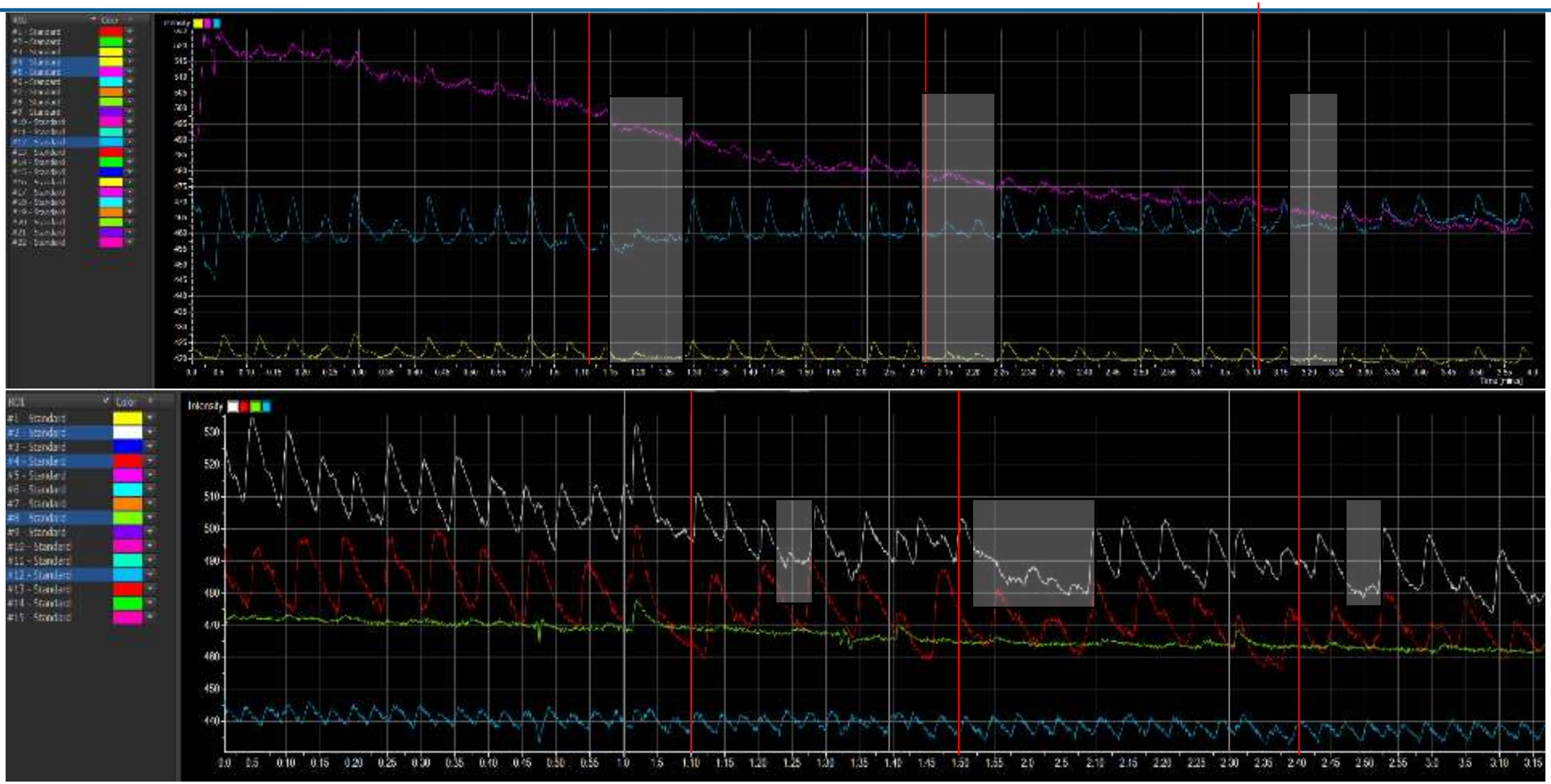


Fig. 9. Experiments showing disruption of spontaneous neural activity using magnetic stimulation (top) and using electrode stimulation in hippocampus cultures. **Top**: Magnetic stimulation. lots of measurement of Ca++ intensity of neurons 4 (yellow), 5 (purple) and 12 (blue). Note the disruption/suppression of neural firing in the three traces in the shaded box after each magnetic stimulation. **Bottom**: Electrode stimulation: Plots of measurement of Ca++ intensity of neurons 2 (white), 4 (red), 8 (green) and 12 (blue). Note the disruption/suppression of neural firing in the white trace in the shaded box after each electrode stimulation. The bottom plot also shows that in our experiment conditions, even with strong electrical stimulation using electrodes, not every electrical stimulation generates a consistent response, and some neurons shows no detectable response.

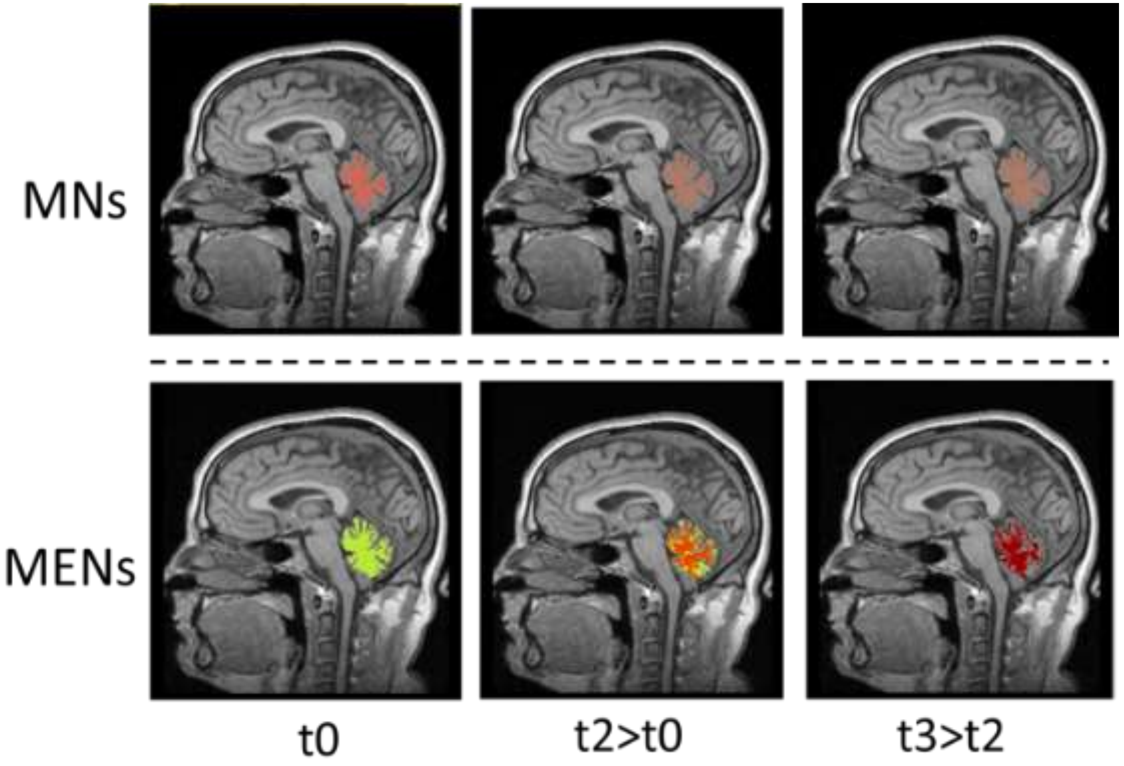
Reading Information Back From the Brain

MPI versus MRI

(by Rakesh Guduru)

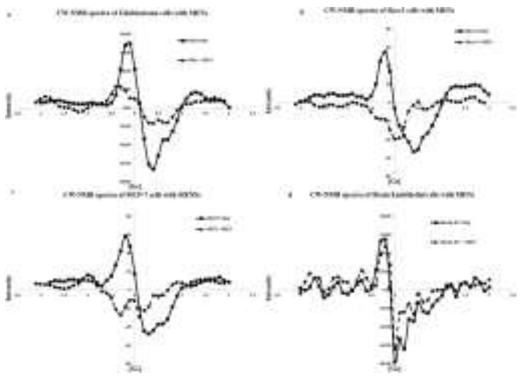
$$S = M \times \frac{Sin\,(FA)(1 - exp(1 - \frac{TR}{T1}))}{1 - Cos\,(FA)\,exp(1 - \frac{TR}{T1})} \times exp$$

With MRI and regular magnetic nanoparticles, the signal depends only on the particle concentration. It is different with MENPs...



Functionalized Imaging (with MPI) by MEnTs

NMR Signals of Different Cell Lines**



Note: New physics allows to detect cancer cells due to their signature electric field profiles

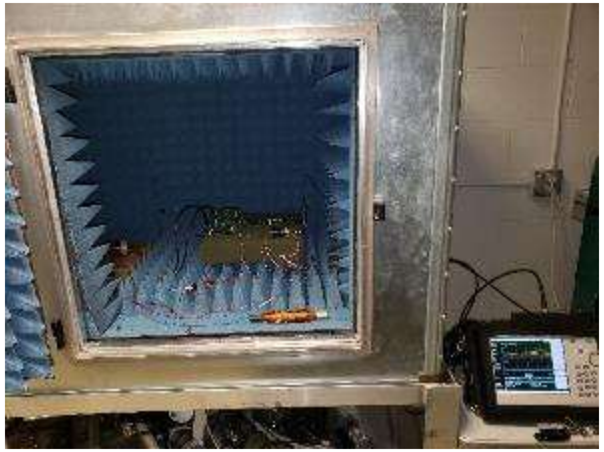
*R. Guduru, P. Liang, M. Yousef, J. Horstmyer, and S. Khizroev, "Electric field mapping of the brain with magnetoelectric nanoparticles," *Bioelectronic Medicine* 4 (10): s42234-018-0012-9 (2018)

A. Nagesetti, A. Rodzinski, E. Stimphil, T. Stewart, C. Khanal, P. Wang, R. Guduru, P. Liang, I. Agoulnik, J. Horstmyer, and S. Khizroev, "Multiferroic coreshell NMR sensitive nanoprobes for cancer cell detection," *Scientific Reports* **7, 1610 (2017)

Task 6 – Test Bed to Wirelessly Read Back

A.

B.



C.

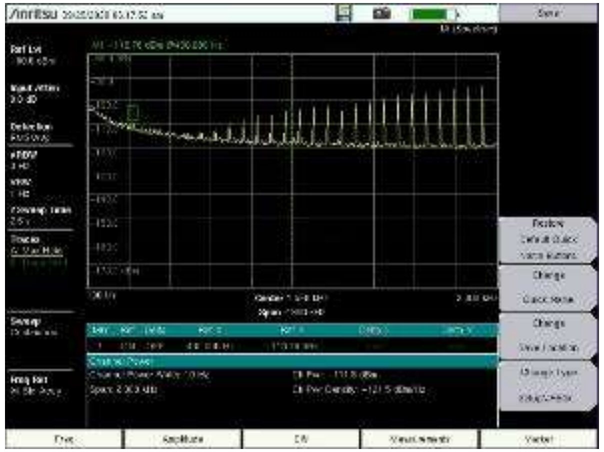


Fig. 10. Loop antenna based magnetometry test bed (Battelle). A & B. Pictures of the shielded chamber test bed (loop antenna around ferrite rod, magnetometry circuitry, and spectrum analyzer [outside of chamber in **B**] shown). Recent progress includes integration of the magnetometry electronics and extensive testing of the new interface. 60Hz interference from the AC line has been mitigated via a 10uF blocking cap on the input. The test setup in **A & B also** includes a 38 turn excitation coil connected to a function generator and the sensor and accompanying instrumentation amplifier / gain stage. **C.** Spectrum analyzer data. The response of the sensor was recorded on the spectrum analyzer in 100Hz steps from 300Hz to 2.9Khz with the source set to -20dBm. The current through the excitation coil was measured at each frequency so the theoretical magnetic field could be calculated. Results are promising and the instrumentation is close to finalized.

Expected plan is to use this newest bed in concert with neuronal cell cultures grown on multi-electrode array plates. Cell culture testing to start today (9/27/20).

Task 6 – Wirelessly Reading Back: Time-Frequency Analysis

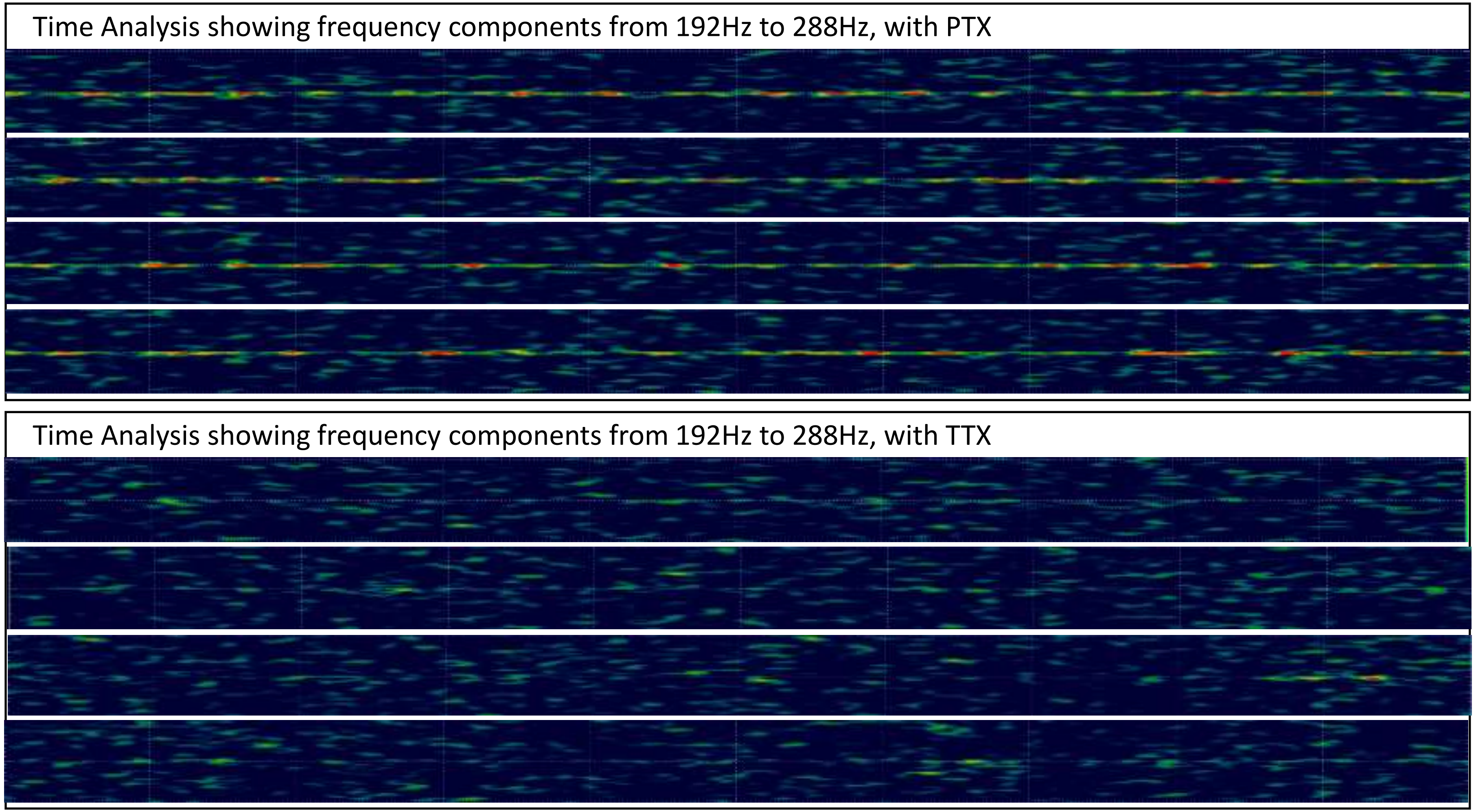
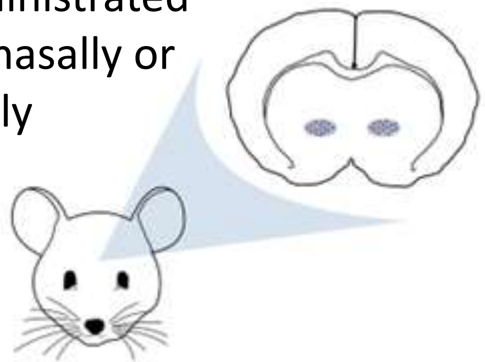


Fig. 3. Examples of 4 recordings before adding TTX (top panel) and after adding TTX (bottom panel), analyzed using a sliding window with a 10ms second resolution to resolve the onset of the detected signals to a time resolution of 10 ms (recording duration = ~17 seconds each). **Top**: Before TTX, showing the detection of the frequency shift to 237.7 Hz activity due to spontaneous neuron firing. **Bottom**: After TTX, showing the signal at 237.7Hz significantly diminishes (some signal remains due to the harmonic 240Hz due to powerline noise). Setup to record Ca++ ground truth signal is currently not available due to COVID.

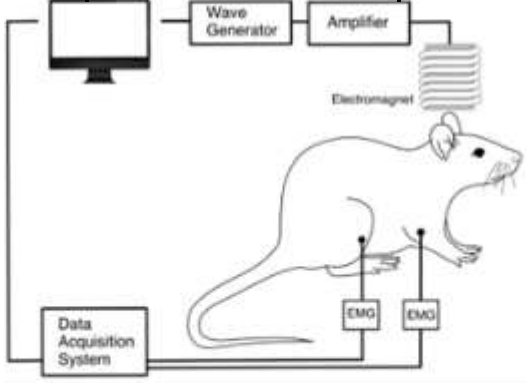
In Vivo Experiments:

Rodents: in collaboration with Dr. Noga's group at the Miami Project to Cure Paralysis

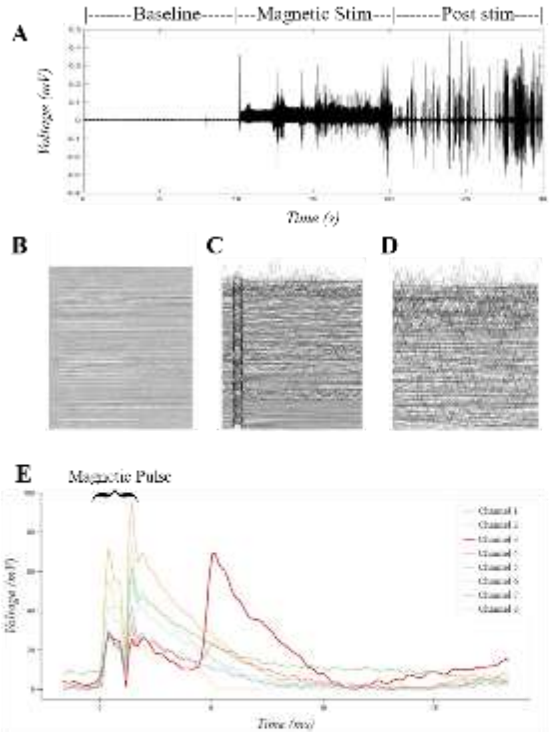
MENPs administrated either intranasally or intravenously



Experimental Setup

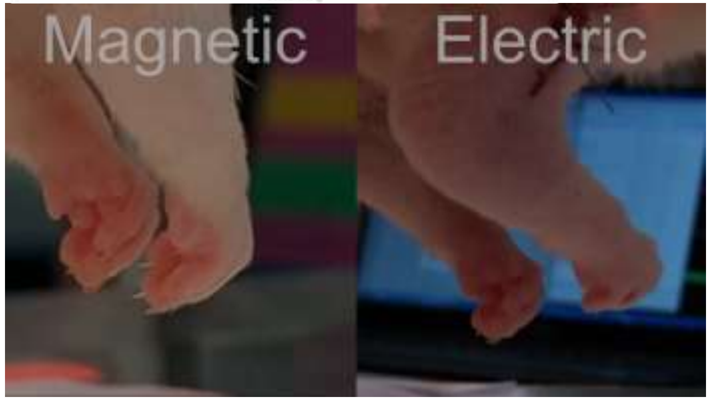


Field-synchronized EMG response (MENPs localized in the CnF region)



Typical EEG Signals from CnF (Very Similar to Wireless MENPs' signals)

Wireless Control of Fine Movements: Left and right whiskers, arms, fingers, exhale, chew, body jerk



Conclusions:

- Wirelessly controlled response through MENPs was similar to the traditional electrode-based response.
- In the case of cuneiform nucleus (CnF) stimulation, motor conduction velocity in rat ≈ 30 m/s, expected response time from CnF is 3 – 4 ms (coincides with experiments)
- We could wirelessly control 8 different observation types (body movements) including movements of left and right arms, fingers, whiskers, large exhale, chew, and body jerk.

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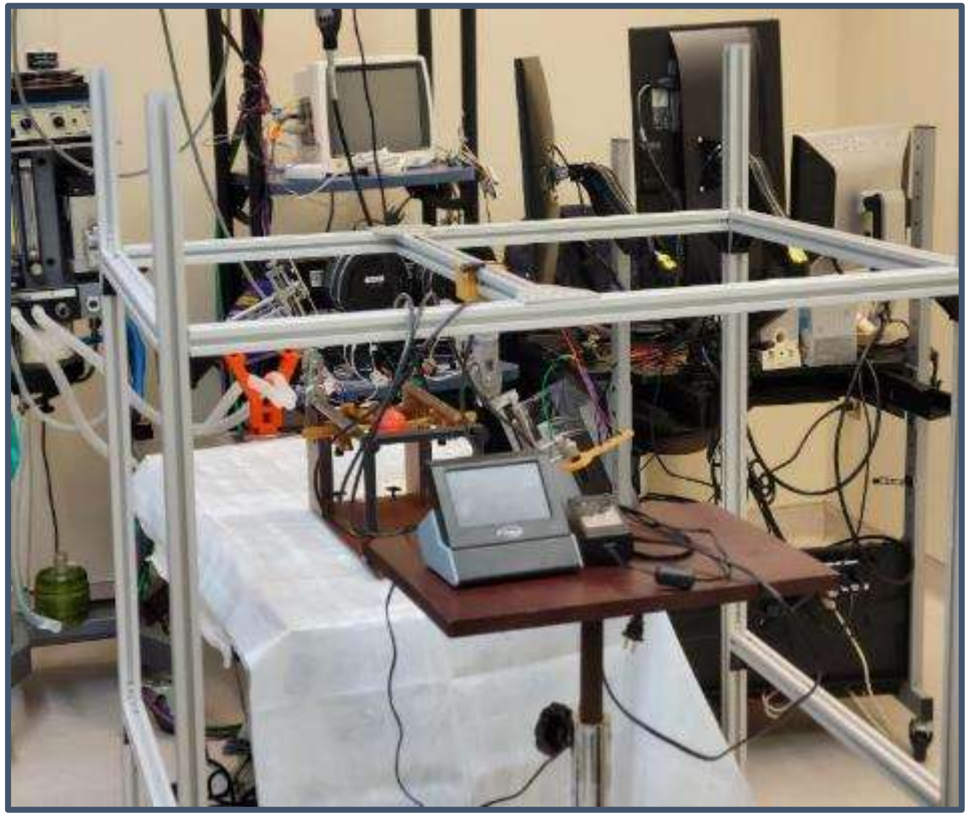
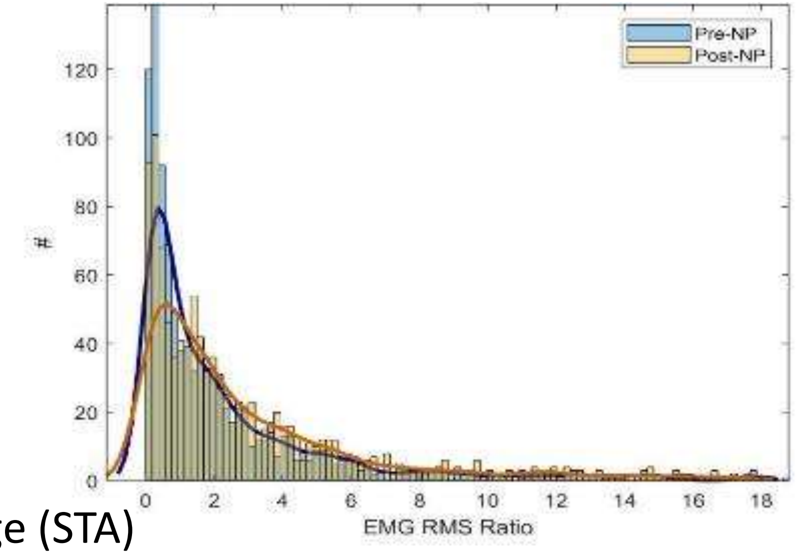
In Vivo Experiments:
Non-human Primates (NHPs): in collaboration with Dr. Weber's group at Carnegie Mellon University

NHP Experimental Setup

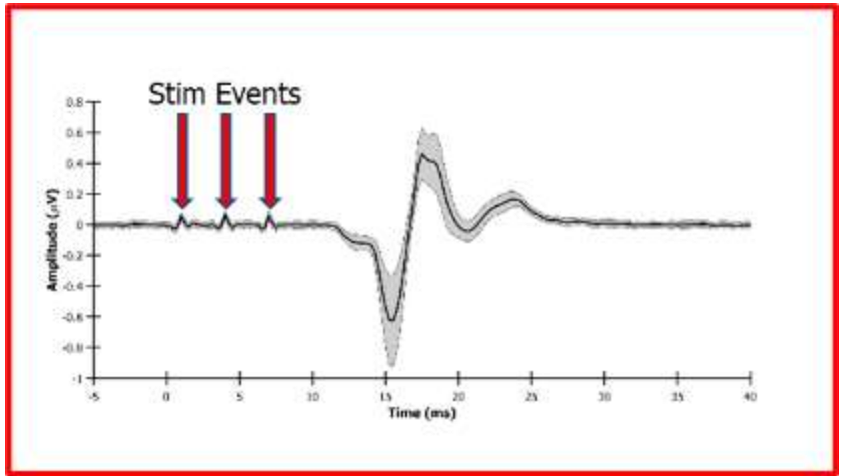


NHP EMG RMS Ratio Pre/Post MENPs

(2-sample test: statistical difference between Pre/Post MENPs response, $p<0.001$)



Stimulus Triggered Average (STA)
(across trials on a sample channel)

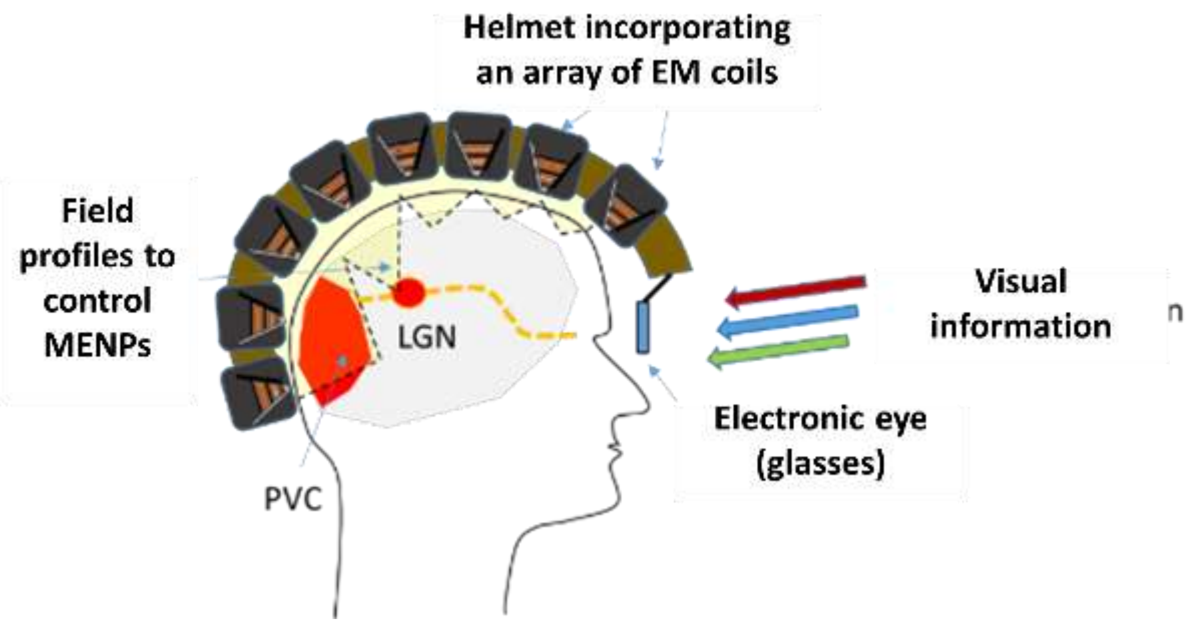


<u>The main aim</u> of this experiment was to show that we could use MENPs to wirelessly induce high-resolution local stimulation synchronized with magnetic field application.

Ongoing Collaborations with Other Groups at UM

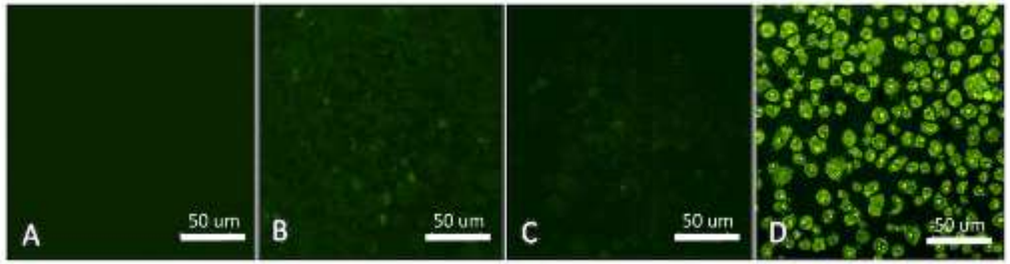
- Miami Project to Cure Paralysis (collaboration with B. Noga): Neurodegenerative diseases/disorders (Parkinson's, Autism, Parkinson's, MS, Essential Tremor, etc.)
- Bascom Palmer Eye Institute (collaboration with V. Porciatti): Eyesight restoration or "Seeing Without Eyes", a collaboration with Bascom Palmer Eye Institute
- Sylvester Comprehensive Cancer Center (collaboration with W. El-Rifai): Currently untreatable or poorly treatable cancers, e.g., glioblastomas, pancreatic cancers, gastric cancers, etc.

"Seeing Without Eyes"



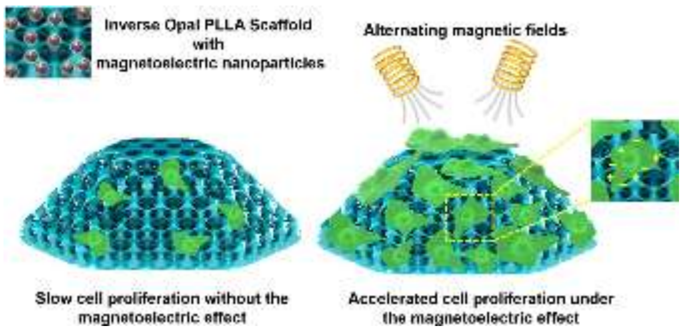
Molecular Level Cell Repair

Confocal microscopy imaging of the high-specificity uptake of Flutax-2 by multi-drug resistant (MDR) cell line MES-SA/DX5 for four different drug-delivery-system combinations:
(a) no drug,
(b) free Flutax-2 (drug uptake per mg of protein: <0.3%),
(c) MENPs loaded with Flutax-2 with no field (<0.2%), and
(d) MENPs loaded with Flutax-2 in a 30 Oe d.c. field (>6%).
The scale bar is approximately 50 um.

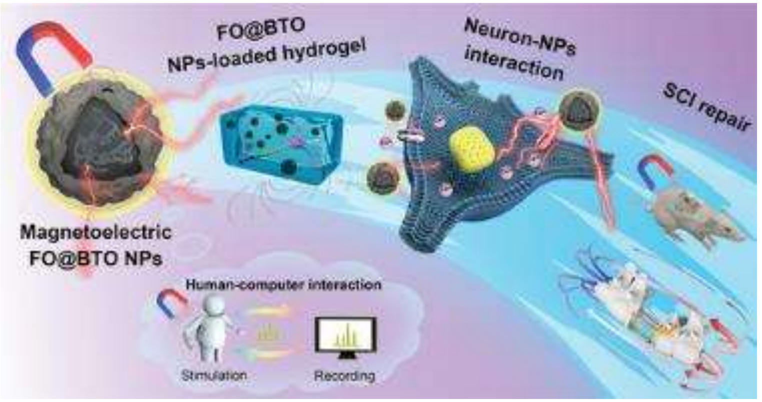


This Research Initiative Has Spread Across the Globe

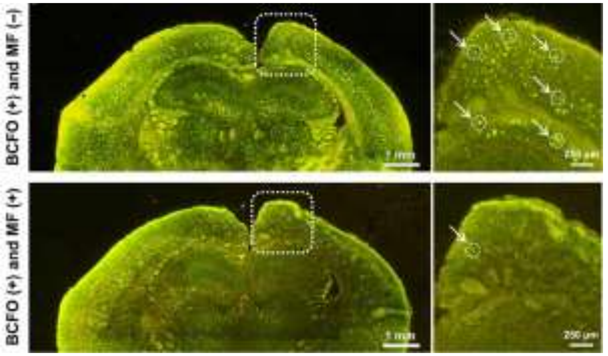
Multi-scale Robotics at ETH-Zurich, Switzerland
(regulate cellular functions for tissue engineering (human-derived osteoblast cells)



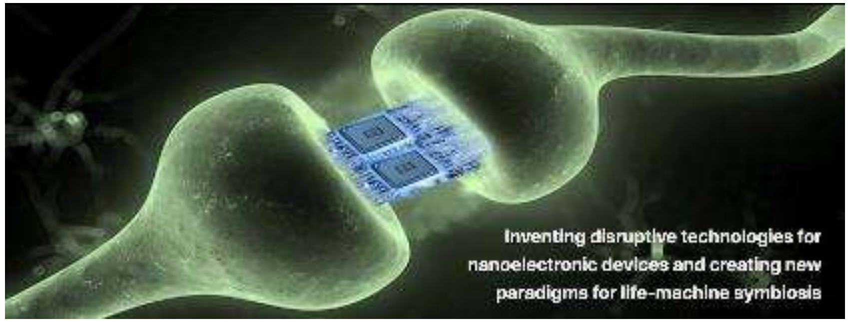
Sichuan University, China
(nerve regeneration)



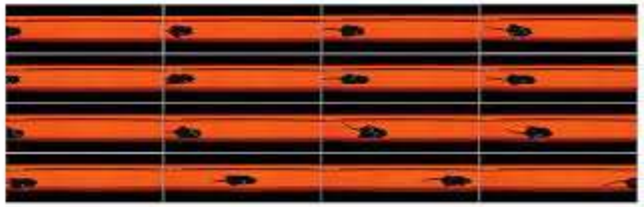
KAIST, South Korea
(Alzheimer’s Disease)



Massachusetts Institute of Technology, USA
(Parkinson’s, Alzheimer’s, …)



Max Planck Institute, Germany
(neural modulation)



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Magnetoelectric Nanoparticles Incorporated Biomimetic Matrix for Wireless Electrical Stimulation and Nerve Regeneration', *Advanced Healthcare Materials* ***10**;* 2100695 (2021)

***Nonresonant powering of injectable nanoelectrodes enables wireless deep brain stimulation in freely moving mice, *Science Advances*, **7** (2019)

Bok, I., et al., In silico assessment of electrophysiological neuronal recordings mediated by magnetoelectric nanoparticles. *Scientific Reports*, 2022. **12**(1)

Conclusions

- This study paves the way for advanced materials to engineer the brain, opens a pathways to unprecedented medical treatments, and enables brain-like computing – a holy grail hardware for artificial intelligence (AI)
- Our future goal is to extend the range of intelligent materials composition and translate our findings into different application areas

Direct Impact Areas:

Medicine > Neurodegenerative diseases, cancer, HIV/AIDS, and others

Next-generation Computing > (there is no better computer than the human brain)

Supercomputer (China),
Cost: ~$500mln
Energy consumption:
a power plant (~7 MW)

Human Brain (USA),
Cost: ~$?
Energy consumption:
Only 20 W

Multidisciplinary Team (Alphabetical Order)

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PhD Student

Akin, Yagmur
PhD Student

Andre, Victoria
PhD Student

Campos, Manuel
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Chen, Shawnus
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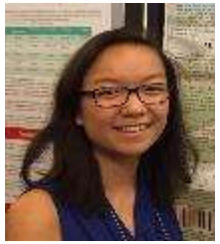

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Toledo, Dennis
PhD Student

Zhang, Elric
PhD Student

Yang, Luke
High-school Research Intern

Lead Collaborator

Liang, Ping
PI, CNMI

Collaborating Labs

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- Ganzer, Patrick, UM
- Jin, Xiaoming, IUPUI
- Noga, Brian, UM
- Pardo, Marta, UM
- Schuller, Ivan, UCSD
- Webber, Douglas, CMU

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