Technologies to Interface with the Brain for Recording and Stimulation

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“As humans, we can identify galaxies light years away and we can study particles smaller than an atom, but we still haven’t unlocked the mystery of the 3 lbs of matter that sits between our ears.”

Barack Obama
What’s in that 3 lbs?

10^{11} neurons
~20 \, \mu m \, \phi

Churchland & Sejnowski 1988
Neurons are not the only story

<table>
<thead>
<tr>
<th>Scale</th>
<th>Section</th>
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</thead>
<tbody>
<tr>
<td>1 m</td>
<td>CNS</td>
</tr>
<tr>
<td>10 cm</td>
<td>Systems</td>
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<tr>
<td>1 cm</td>
<td>Maps</td>
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<tr>
<td>1 mm</td>
<td>Networks</td>
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<tr>
<td>100 µm</td>
<td>Neurons</td>
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<td>1 Å</td>
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50% neurons
50% support cells

Allen & Barres 2009
Information transmitted at synapses

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- $10^{11}$ neurons
- $\sim 20 \mu m$ ø
- $10^{14}$ connections
- $10^3$ synapses/neuron
- $\sim 20$-40 nm wide
Transmission happens in different ways

Chemical Synapse
~20-40 nm wide

Electrical Synapse
~3-4 nm wide

10^2 neurotransmitters
Inhibitory or excitatory
0.1-200 Hz event “firing” rate

Pereda 2014
Action potential: fundamental unit of activity

1. **Resting Potential**
   - $\text{Na}^+ / \text{K}^+$ pump

2. **Depolarization**
   - Voltage-gated $\text{Na}^+$ channel

3. **Repolarization**
   - Voltage-gated $\text{K}^+$ channel

4. **Resting Potential**
   - $\text{Na}^+ / \text{K}^+$ pump

**Diagram:**
- **Threshold:** -55 mV
- **Membrane potential:**
  - $\text{Na}^+$ in
  - $\text{K}^+$ out
  - Time (ms): 1 to 5
Interaction with the brain

- Action potentials typically from chemical inputs at synapses
- Action potentials also from imposed electric field
- Therefore, we can **record** or **stimulate** activity in the brain
- Use (bidirectional) interface technology between device and tissue
  - Interface can be invasive or non-invasive
  - Invasive can be surface or penetrating
  - Greater resolution using penetrating invasive interfaces
  - Most well developed interfaces are electrical
Ancient electrotherapy and “nerve interfaces”

Torpedo fish/electric ray

Nile Catfish

Good for:
- Headaches
- Pain
- Gout...
Galvani and “animal electricity”
Advances in neuromodulation

1840
- First report human cortical simulation

1940s
- Intraoperative stimulation to identify structures

1960s
- High frequency stimulation of ventrolateral thalamus diminishes tremors

1970s
- Stimulation to treat chronic pain and epilepsy

1990s
- Implantable pacemakers + brain electrodes result in deep brain stimulation technology

*Several therapies exist for electrically excitable tissue*
Advances in recording

Galvanometer 1828

When current from the nerve passes through the many turns of wire, the magnetic needle moves.

Rheotome 1868

"negative Schwankung"

Verkhratsky et al. 2006
Advances in recording interfaces

Doubling time every ~7 years

Stevenson & Kording 2011
Where and what we can record

- EEG = electroencephalogram
- ECoG = electrocorticography
- LFP = local field potential
- EAP = extracellular action potential

**Obien et al. 2014**

**A**

- EEG (5-300 µV, <100 Hz)
- ECoG (0.01-5 mV, <200 Hz)
- Implant LFP (<1 mV, <200 Hz)

**B**

- Extracellular LFP+EAP
- EAP (5-500 µV, 0.1-7 kHz)

**Multi Unit**

**Single Unit**
High quality chronic recordings remain elusive

- Cortical recording probes typically last *months* and in rare cases years regardless of species or hardware
  - Hardware related failure modes
  - Tissue related failure modes
- *Prevents realization of chronic large-scale recordings and clinical translation*
It’s all about the device-tissue interface

Rivnay et al. 2017

Wellman et al. 2017
State of the art invasive, penetrating electrical interfaces

Nicolelis et al. 2003
Rousche et al. 1999
Wise et al. 2008
Xu et al. 2002
Normann et al. 1998

Microwire
Utah
Michigan
Interfaces lack long-term reliability

- Attenuation of recordings over time
- Retraction of neural processes from recording sites
- Due to: insertion trauma, immune response, mechanical mismatch between tissue and probes

Biran et al. 2005; Rivnay et al. 2017
Mechanical mismatch of materials

**W:** ~200 GPa  
**Si:** ~150 GPa  
**Polyimide:** ~5 GPa  
**Parylene:** ~3 GPa  
**Silicone:** ~1 MPa

\( E \)  
100 GPa  
1 GPa  
1 MPa  
1 kPa

**Bone:** ~10 GPa  
**Dura:** ~1 MPa  
**Spinal cord & brain:** 100 Pa – 10 kPa
Softer probes reduce inflammation and foreign body response.

Lacour et al. 2016

Nguyen et al. 2014
Many mechanisms of failure

- Corrosion
- Coating failure
- Delamination
- Blood-brain barrier breach
- Micromotion
- Disruption of glial networks
- Formation of glial scar
- Neuronal death

Chen et al. 2016
Brain is a highly vascular organ
15% cardiac output goes to brain
In mouse, mean distance from center of neuron to nearest vasculature 15 μm

Fotuhi *et al.* 2009
Making stiff electronics soft

Substrate/Form factor

- **a** Flexible substrates
- **b** Wavy, serpentine shapes
- **c** Composite fibres and carbon electrodes

Electrode material

- **d** Conductive polymers
- **e** Microcomposites
- **f** Nanocomposites

Chen *et al.* 2016
Hippocampus Cross-section

Penetrating Hippocampal Probes

64 electrode deep brain polymer probe array

• Goal: simultaneous recording from multiple hippocampus regions
• Involved in memory formation
• Most advanced polymer array

Xu, Weltman et al. in revision
• Parylene C and Pt
• 20-30 µm thick, 5.5 mm long, 140 µm wide
• 30 µm Ø electrodes
• Two groups of four electrodes per probe target CA1 and CA3
• Linear array
  – 8 electrodes per probe
  – 8 probes per array
  – 64 total recording sites
Soft probes tend to buckle

\[ F_{\text{buckling}} = \frac{\pi^2 E w t^3}{5.88 L^2} \]

Jeon et al. 2014
Surgical insertion of soft probes

Insertion Shuttle

Biodegradable Coating

Felix et al. 2013

Wu et al. 2013
Deep brain placement strategy

Exposed probes penetrate brain → Brace reaches brain surface → Brace dissolved in saline → Remainder of bare probe inserted

PEG = polyethylene glycol

Xu, Weltman et al. in revision
Acute hippocampal recordings

- Acute recordings from CA1 and CA3
- Complex spikes
  - Burst of 2-6 with decreasing amplitude
  - \( \leq 6 \text{ ms} \) durations

Xu, Weltman *et al.* in revision
Increasing channel counts

Nicolelis et al. 2003

Lehew & Nicolelis 2008

Wise et al. 2008

Barrese et al. 2016
Combining microelectronics with polymer probes

Flexible Neural Probe Array for Large-Scale Recording

Major Goals

Design & Fabrication of High-density Parylene Probes

ASIC Die Integration for On-Device Multiplexing

ASIC = application-specific integrated circuit

64 electrodes $\times$ 8 probes $\times$ 8 rows = $4096$ recording sites

Xu, Weltman et al. in revision
Scholten & Meng 2016
Optical recording and stimulation

**Recording**

- **A** Incident illumination
- **B** Voltage-sensitive dye
- **C** Voltage-sensitive receptor
- **D** Conformational change of emissive chromophores

**Stimulation**

- **UV light**
- **Optogenetics**

**Rivnay et al. 2017**
Electrochemistry and microfluidics

Chapman et al. 2017
Joining forces – hybrid interfaces

Mature electrode arrays outfitted with optical fibres

Integrated optoelectronic approaches

Multifunctional neural probes

Chen et al. 2016
Alternative nanomaterial methods

Optical nanomaterials
- **a** Optoelectronic transitions
  
Mechanoresponsible nanomaterials
- **d** Micro- and nanobubbles
  
- **e** Piezoelectronic materials
  
Magnetic nanomaterials
- **g** MNP clustering
  
- **h** MNP translation or rotation
  
- **i** MNP heating

Chen et al. 2016
From the outside

<table>
<thead>
<tr>
<th>Method</th>
<th>Penetration depth (m)</th>
<th>Spatial resolution (m)</th>
<th>Temporal precision (s)</th>
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<tbody>
<tr>
<td>Light</td>
<td>$10^{-6}$</td>
<td>$10^{-3}$</td>
<td>$10^{-3}$</td>
</tr>
<tr>
<td>Light (cranial window)</td>
<td>$10^{-4}$</td>
<td>$10^{-2}$</td>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>$10^{-2}$</td>
<td>$10^{-3}$</td>
<td>$10^{-1}$</td>
</tr>
<tr>
<td>Ultrasound (cranial window)</td>
<td>$10^{0}$</td>
<td>$10^{3}$</td>
<td>$10^{0}$</td>
</tr>
<tr>
<td>Magnetic fields</td>
<td>$10^{6}$</td>
<td>$10^{3}$</td>
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Chen et al. 2016
Grand challenges in neural interfaces

- Many complex problems for reliable interface technology to nerves
  - Many incremental approaches attempted
  - Incomplete knowledge of root causes of tissue response
  - Variable tissue response
  - No good animal surrogates for testing designs
  - No standards – lack of definitive guidance for the engineer/designer

- Engineering challenges for high density recordings
  - Achieving physiologically relevant scale
  - Materials, manufacturing, integration, and packaging

- Advanced interfaces in their infancy
  - Precise and even cell-type specific
  - Other modalities beyond electrical
  - Hybrid, multi-modal interfaces: electrical, optical, electrochemical, fluidic, magnetic, ultrasound

- Regulation, fundraising, and translation
There are no easy answers – complexity of interface engineering

Wellman et al. 2017
Grand challenges in neural interfaces

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Final comments

- Neurological disorders 7% of global disease burden
- Many of these may benefit from treatments involving neural interfaces

- **However**, many fundamental issues remain unsolved

- We need to fully share *both failures and success* as a community in order for us to break through these obstacles
- Will require close, large scale collaboration between engineers, scientists, clinicians, and patients, as well as, academia and industry
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