Optical Stimulation of Neural Tissue: Current State and Future Challenges

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With thanks to:

• Dr. Peter Konrad, Dr. Chris Kao, Dr. Anita Mahadevan-Jansen, Dr. Mykyta Chermov, Dr. Kurt Schoener, Dr. Mark Mackanos, Jonathan Cayce, Jonathan Malphrus, Austin Duke, Melanie Gault (Vanderbilt University – BME, Neurosurgery)
• Dr. Jonathon Wells, Dr. Matt Keller, Dr. Mark Bendett (Lockheed-Martin Aculight)
• Dr. Hillel Chiel, Dr. Dustin Tyler, Dr. Andrew Rollins, Dr. Michael Jenkins (Case Western Reserve Univ)
• Dr. Claus Peter Richter, Dr. Jay Walsh, Dr. Agnella Izzo-Matic (Northwestern Univ)
• Dr. Anna Roe, Dr. Robert Friedman (Psychology, Vanderbilt Univ)
• Dr. Maarten Frens, Dr. Stefan Louw (Neuroscience, Erasmus University, Rotterdam)

Funding:
- VIO exploratory grant
- DOD - MFEL Program (FA9550-04-1-0045)
- NIH (R01 NS052407, R43 NS051926, R44 NS051926)
- Human Frontiers Science Program (HFSP)
- DOD/DARPA CIPhER Program
- Lockheed-Martin
Neural Stimulation

Since it is known that electrical activity can be measured with optical techniques (DOT, OCT, fluorescence imaging) …..

Is it possible to induce electrical activity with light?

……and why would one want to do this?
The Challenge

• Improving human capabilities through the development of advanced human-machine interfaces

• Electrical stimulation and recording are state-of-the-art and work well (and are being used extensively)
  ➢ Cochlear implants, bionic eye
  ➢ EMG controlled prosthetics, FES, FINE electrodes, etc.

• Can we do better?
Background

- **Electrical stimulation has been and still is the gold standard in neural activation**\(^1\)
  - Applied constant current through metal or ionic electrodes results in AP
  - Inherent and fundamental limitations
    - lack of spatial precision in stimulation (size of electrodes, electric field)
    - electrical stimulation artifact preventing recording from adjacent stimulation
    - Need for physical contact between the nerve and electrodes (storage of charge → inflammation, necrosis)
    - MR compatibility?

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Hypothesis

• **Pulsed laser light can be used for contact-free, damage-free, artifact-free stimulation of discrete populations of neural fibers.**

• **Objectives of this research:**
  - To evaluate and assess the safety and efficacy of optical stimulation in a comparison with electrical stimulation
  - Develop a stand-alone, portable, inexpensive, optical stimulator
  - Translation to clinical applications
  - Push capabilities beyond current state-of-the-art
What is optical stimulation?

- Optical nerve stimulation = induction of an evoked potential (EP/AP) in response to a transient targeted deposition of optical energy.

- What it is NOT:
  - LLLT (low light level therapy)
  - Genetic engineering of light-activatable ion channels in neural cells (‘optogenetics’)
  - Light activation of caged compounds
Spatially selective stimulation in rat sciatic nerve
Spatial selectivity & no stimulation artifact

a. Electrical Stimulator
   - Quadriceps Fascicle
   - Foot fascicle
   - Rat Sciatic Nerve

b. Fiber Coupled Laser
   - Quadriceps Fascicle
   - Hamstring Fascicle
   - Rat Sciatic Nerve

Infrared Nerve Stimulation

- Laser Parameters
- Functional Mapping
- CIPhER: all optical neural interface
- Auditory Nerve / Cochlea / Vestibular System
- Cardiac Pacing
- PNS
- CNS
- Device Development
- Multiplexing/Miniaturization
- Efficacy & Safety Testing
- Implants
- Mechanisms
  - Physical
  - Physiological

VANDERBILT UNIVERSITY School of Engineering
Biomedical Optics Vanderbilt
A brief primer on Laser-Tissue Interaction

Optical properties

Light distribution

Absorption

Rate of heat generation

Thermal properties

Light

Heat conduction

Thermo-mechanical effects/pressures

Photochemical processes

Therapy

Fluorescence

Raman Reflectance

Diagnosis
Laser output characteristics (1)

- **Monochromatic ($\lambda$)**
  
  $E_{\text{photon}} = h \nu = \frac{hc}{\lambda}$

- **Collimated (parallel light rays)**

- **Coherent (waves in phase)**

- **Polarized (E-field orientation)**

- **Can be coupled into fiber optics**
Laser output characteristics (2)

- **Continuous Wave (CW) lasers**
  - Power (P (W))

- **Pulsed lasers**
  - Pulse energy ($Q_{\text{pulse}}$ (mJ))
  - Pulse duration ($\tau_p$)
  - Pulse repetition rate (RR)
Pulsed lasers

• Power

  ➢ Peak power: \( P_{\text{peak}} = \frac{Q_{\text{pulse}}}{\tau_p} \)
  
  ➢ Average power: \( P_{\text{average}} = Q_{\text{pulse}} \times RR \)

• Example: Ho:YAG laser:

  ➢ Pulse duration (\( \tau_p \)) = 100 \( \mu \)s
  ➢ Pulse repetition rate (RR) = 5 Hz
  ➢ \( Q_{\text{pulse}} = 100 \text{ mJ} \)

\[
\begin{align*}
  P_{\text{peak}} &= \frac{100 \text{ mJ}}{100 \text{ } \mu\text{s}} = 1 \text{ kW} \\
  P_{\text{avg}} &= 100 \text{ mJ} \times 5 \text{ Hz} = 0.5 \text{ W}
\end{align*}
\]
CW Lasers

- Can be used in ‘pulsed’ mode (off-on-off-on-off….)
- $P_{peak} = P_{avg}$ if duty cycle (DC) = 100%
- DC = RR * $\tau_p$ (what fraction of the time is laser on?)
- If DC < 100%: $P_{avg} = P_{peak} \times DC$

- Example: Power = 5 W; 1 ms pulse, 100 Hz
  - DC = 100 (Hz) * 1 $10^{-3}$ (s) = 0.1 = 10%
  - True $P_{avg} = 5$ (mJ/p) * 100 (Hz) = 0.5 (W)
‘Intensity’

- **Pulsed**
  - Radiant Exposure, \(H\) (J/cm\(^2\))
  - \(H = \frac{Q_{\text{pulse}}}{\text{Area}}\)

- **CW**
  - Irradiance, \(E\) (W/cm\(^2\))
  - \(E = \frac{\text{Power}}{\text{Area}}\)

**What is the area, \(A\)?**

Spotsize fundamentally determined by:

1) Diffraction limit: \(d \approx \frac{\lambda}{2 \ NA} \approx \frac{\lambda}{2}\)

2) Fiber size

**Gaussian beam**

\[r = \omega_L\]

\[E(r) = \frac{1}{e^2} E(r = 0) = 0.13 \ E(r = 0)\]
Light interaction with tissue

- Reflection
- Refraction
- Absorption
- Scattering
Tissue Optics

- Absorption (if $E_{\text{photon}} \sim v_{\text{resonance}}$)
- Optical energy $\rightarrow$ thermal or chemical energy
- Beer’s law: $E(z) = E_0 e^{-c \xi(\lambda)z} = E_0 e^{-\mu_a(\lambda)z}$
- $\lambda$-dependent absorption coefficient, $\mu_a$ (cm$^{-1}$)
- ‘Penetration depth’:
  $\delta = \frac{1}{\mu_a}$
  $E(z) = \frac{1}{e} E_0 \approx 0.37 E_0$
Effect of absorption
Tissue Optics

- Scattering (if $E_{\text{photon}} \neq \nu_{\text{resonance}}$)
- Re-radiating dipole (no energy transfer)
- Scattering coefficient, $\mu_s (\text{cm}^{-1})$
- Scales with $\sim \lambda^{-0.4 \text{ to } 0.8}$
- In which direction?
  - $\text{avg cos } \Theta = g$ (anisotropy factor)
- Reduced scattering coefficient:
  - $\mu_s' = (1-g) \mu_s$
- Effective attenuation coefficient:
  - $\mu_{\text{eff}} = \sqrt{3\mu_a(\mu_a + \mu_s')}$
  - $\delta_{\text{eff}} = \frac{1}{\mu_{\text{eff}}}$
Effect of scattering

Water with intralipid

Increasing $\mu_s$

Laser light
How much light gets to some point \((r,z)\) in tissue?

- If \(\mu_a \gg \mu_s'\): Beer’s law & beam profile
- If \(\mu_a \leq \mu_s'\): Modeling
  - Monte Carlo
  - Kubelka-Munk
  - Diffusion Approximation
  - Adding-Doubling

- Optical properties depend on wavelength, \(\lambda\)
  - Over \(~8\) orders of magnitude in effective penetration depth
Scattering and Absorption

Chicken breast (left) and liver (right) illuminated by red (top image) and green (bottom image) laser light via a fiber. Note the effect of the color of the light and the higher blood content in the liver on the light distribution.
Heat Source and Temperature Rise

- **Pulsed:**
  \[ W(r, t) \ (J/cm^3) = \mu_a(r, z) \ (1/cm) \times H(r, z) \ (J/cm^2) \]

- **CW:**
  \[ S(r, z) \ (W/cm^3) = \mu_a(r, z) \ (1/cm) \times E(r, z) \ (W/cm^2) \]
  or \[ \mu_a \ (r, z) \ (1/cm) \times \phi(r, z) \ (W/cm^2) \]
  \[ W(r, z) \ (J/cm^3) = S(r, z) \ (W/cm^3) \times \tau_{\text{pulse}} \ (s) \]

- \[ \Delta T(r, z) = \frac{W(r, z)}{\rho c} \] (impulse response)
Peripheral Nerve Geometry & desired penetration depth

Nerve diameter  1-2 mm
Outer sheath      ~ 150 um
Fascicles         50-400 um

Need penetration depth of 250-500 um (for peripheral nerves)

We need penetration depth of 250-500 µm (for peripheral nerves)
Translational Research

Free Electron Laser

IRCM laser development / Dual use
## LMA Capella R-1850 Infrared Neuro-Stimulator

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of operation</td>
<td>Pulsed</td>
</tr>
<tr>
<td>Polarization</td>
<td>Non-Polarized</td>
</tr>
<tr>
<td>Emission wavelength</td>
<td>1.85- 1.88 µm</td>
</tr>
<tr>
<td>Bandwidth (FWHM)</td>
<td>&lt;20 nm</td>
</tr>
<tr>
<td>Fiber Diameter</td>
<td>100-600 µm core</td>
</tr>
<tr>
<td>Fiber Coupling</td>
<td>SMA</td>
</tr>
<tr>
<td>Pulse duration (FWHM)</td>
<td>10 µs to 100ms</td>
</tr>
<tr>
<td>Rep rate</td>
<td>0.4 – 1000 Hz</td>
</tr>
<tr>
<td>Pulse energy</td>
<td>&lt; 5 mJ (@ 1ms)</td>
</tr>
<tr>
<td>Power requirements</td>
<td>115 or 220 V AC</td>
</tr>
<tr>
<td>Dimensions (Power Sup.)</td>
<td>12.5” x 13.25” x 4.75”</td>
</tr>
<tr>
<td>Weight</td>
<td>11.5 lbs</td>
</tr>
<tr>
<td>Cooling</td>
<td>Air Cooled</td>
</tr>
</tbody>
</table>
Damage versus Stimulation Thresholds

Near-term light-based implant development

• Battery → Photons demonstrated

• Next steps
  ➢ Single channel light-based stimulator
    o Miniaturize
    o Implant delivered for chronic safety studies

  ➢ Three channel light-based stimulator (cochlear implant)
    o Multiple channels
    o Wireless controls
    o Light delivery development
    o Long-term primate safety and efficacy studies with optimized parameters

  ➢ VCSEL array development in parallel
    o Wavelength: 1850nm ± 10nm
    o Peak power of 10mW
    o Array size: 10 x 10
    o Array spacing: Approximately 100μm
    o Drive electronics on chip

---

10 channels
6 x 50 x 84 mm
47 grams

4 x 12 x 12 mm
1 mm x 1 mm
Towards an optical neural interface:

• Develop multichannel INS probe
  – Co-aligned configuration with nerve
  – Multiplexed (4→8→ ….channels)
  – Parameter optimization
  – In vitro / in vivo testing:
    – Feasibility / efficacy
    – Tissue damage assessment

• Integrate in nerve cuff & fully optical neural interface
Stimulation with a cuff
Can we hear light???
Optical Stimulation of the auditory nerve
High Repetition Rate – single nerve recording

Neuron3 (20June06) - 200 Hz

Neuron3 (20June06) - 300 Hz

Electrode recordings
Rate: 190 pps

Electrode recordings
Rate: 220 pps

Laser trigger

Time [ms]
Extended Optical Stimulation

400Hz, 15 mJ/cm²
Conclusions – Cochlear stimulation

• Cochlear stimulation is feasible
  ➢ Threshold much lower than motor nerve stim
  ➢ High rep rate stimulation is feasible without damaging tissue
  ➢ Spatial precision comparable with acoustic stimulation

• Challenges
  ➢ Wavelength optimization
  ➢ Miniaturization
  ➢ Multiplexing
  ➢ Delivery interface
Combined electrical and optical stimulation
Damage versus Stimulation Thresholds

Can the optical stimulation threshold be lowered?

Hypothesis:
Combining subthreshold electrical stimulation with optical stimulation lowers the optical stimulation threshold while maintaining the benefits of high spatial selectivity of optical stimulation.
If possible, such an approach....

- Would increase safety margin
- Allow higher repetition rate stimulation
- Facilitate multiplexing (arrays)
- Reduce power requirements on laser end
  - Facilitate implantable devices
- May facilitate acceptance in electrical stimulation community
Controlling Hybrid Stimulation
Comparative Physiology Approach

Duke et al., J Neural Eng, In Review
Optical threshold as function of Electrical Stimulation

Duke et al., J Biomed Optics 14, 060501 (2009)
Characterization of hybrid stimulation in Aplysia

Role of:
- Spatial overlap
- Temporal overlap
- Drift in threshold

Optimize n-dimensional parameter space

Duke et al., J Neural Eng, in review (2011)
Optical Inhibition

- A novel enabling tool in neuroscience
- Clinical utility to ‘silence’ (over)active neurons?
  - Parkinson’s, Epilepsy, ET, etc.

Duke et al., J Neural Eng, in review (2011)
Conclusion

• Electrical ‘priming’ of system lowers optical stimulation threshold
  ➢ But modalities do not appear to follow simple linear superposition
  ➢ Why? Should they?
  ➢ What does this tell us about mechanism?

• Spatial precision is maintained

• Development of integrated probe under way
  ➢ Optimize spatial and temporal superposition
Translation to Human: Dorsal Rhizotomy

- Perfect procedure for clinical trial
  - Safety Study
  - Efficacy Study

- Employ Ho:YAG
  - 2.12 µm, 2 Hz, 0.2 - 1.5 J/cm², 20 pulses, 600 micron fiber probe
  - 7 cases to date
Results:

Electrical Stimulation:
Activation of all left side muscles and contralateral crosstalk

Optical Stimulation: 0.2 J/cm², λ =2.12 µm, 600 µm fiber, 2 Hz, 20 pulses
Left side Stim- Right Hamstring activation
Conclusions:

• Optical stimulation presents a simple yet novel approach to contact-free, damage-free, artifact-free, spatially specific *in vivo* neural activation

• Pulsed infrared light is used to evoke physiologically valid action potentials in neural tissues (PNS and CNS, motor and sensory)

• Optimal stimulation wavelengths must be matched to tissue morphology
Opportunities and challenges

• Towards human applications (FDA/IDE)
• An optical pacemaker
• Moving to spinal cord, cortex, cerebellum
• Neurobiological mechanism
• Better recording methods
• Devices: miniaturization, multiplexing, interfaces
• Chronic studies
• Training people in neurophotonics
• …..
Acknowledgments

• Dr. Peter Konrad, Dr. Chris Kao, Dr. Anita Mahadevan-Jansen, Jonathan Cayce, Jonathan Malphrus, Austin Duke (Vanderbilt University - BME)
• Dr. Sharon L. Thomsen
• Dr. Tom Milner, Dr. Bo Chen, Dr. Jihoon Kim (UT Austin)
• Dr. Claus Peter Richter, Dr. Jay Walsh, Dr. Agnella Izzo-Matic (Northwestern University)
• Jim Webb, Dr. Jonathon Wells, Dr. Mark Bendett (Lockheed-Martin Aculight)
• Dr. Anna Roe, Dr. Robert Friedman (VU Psychology)
• Dr. Hillel Chiel, Dr. Andrew Rollins, Dr. Michael Jenkins (Case Western Reserve Univ)
• W.M. Keck Foundation Free Electron Laser Center staff

Funding:
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Translation to Human: Dorsal Rhizotomy
Mechanisms

By now you’re probably wondering….. how does INS work?
Mechanisms: Summary

• Physical basis of optical stimulation
  ➢ electric field effect – highly unlikely
  ➢ photochemical effect – would expect a wavelength dependence (other than water absorption)
  ➢ photomechanical effect – no pressure waves, unlikely role for thermal expansion
  ➢ photothermal effect – appears to be the driving mechanism (dT/dz or dT/dt)

• Biological mechanism: undetermined at this point
  ➢ dT/dz dependence of state of Na⁺ channels
  ➢ T-dependent ion channels (TRPV-1)
  ➢ Thermally induced change in membrane capacitance

Spatial selectivity is maintained

**CMAP from gastrocnemius (target)**

**CMAP from biceps femoris**

Combined optical and electrical stimulation in nerve
Thermal response

Optical Stimulation: Strength-response curve

Range of Laser Energy resulting in normal physiologic response

Damaged physiologic response

Threshold response to Electrical Stimulation

Threshold response to Optical Stimulation

y = 0.1809x + 0.008  
R² = 0.992
Electrical Stimulation

- Spiral ganglion cells
- Apex
- Base
- Electrode contacts
Optical Stimulation

Spiral ganglion cells

Apex

Base

Optical Sources
Optical Pacing of the Embryonic Heart

New Scientist.Home
|Tech |Health | News

Laser sets quail embryos' hearts racing
18:00 15 August 2010 by Jeff Hecht

innovations report
A heart beats to a different drummer
16.08.2010
Researchers pace embryonic heart with laser

Laser mends broken heart

Laser-tissue Interactions

Irradiance [W/cm²]

- Plasma-induced ablation
- Photodisruption
- Photoablation
- Thermal interaction
- Photochemical interaction

Exposure time [s]

- 1,000 J/cm²
- 1 J/cm²

Hormesis
Mechanisms: Hypotheses

- Electric field effect?
- Photochemical
  - Alteration in the state of the ion channels?
  - Targeting specific neuro-transmitters?
- Photothermal
  - Transient membrane permeability?
  - Alteration of transmembrane proteins?
  - T or ΔT (dT/dx or dT/dt)?
- Photomechanical
  - Light induced stress waves (TE or recoil?)
Electric field effect

• Theoretical calculations do not predict voltage increase sufficient to produce current needed to drive action potential
  ➢ $S_{\text{threshold}} = \frac{1}{2} c \varepsilon_o E_{\text{max}}^2$
  ➢ $E_{\text{max}} = 0.155 \text{ V/mm}^2 \rightarrow 0.05 \text{ mA/mm}^2$ (surface)
  ➢ Field oscillations at $\sim 10^{14}$ Hz

• Excite with Alexandrite laser ($\lambda = 760 \text{ nm}$, 350 $\mu$s)
  ➢ Fiber delivered (600 $\mu$m spotsize)

• Observations:
  ➢ No stimulation for $E_p < 200 \text{ mJ}$ (70.7 J/cm$^2$)

• Conclusion: electric field effect is not the mechanism for optical stimulation
Do axons have unique optical properties?

FTIR

![Graph showing relative magnitude vs. wavelength (µm) for different substances: Axon, Sucrose, Pellet, Water. The graph displays distinct peaks at different wavelengths for each substance.](image)
Photochemical effect

- Photon energy in IR too low for direct photochemistry (< 0.1 eV), intensity insufficient for multiphoton effects
- Would expect wavelength dependence other than simply following the water absorption curve – not observed

- Conclusion: photochemical effect is not the mechanism for optical stimulation
Thermal response

Ho:YAG
600 µm fiber
0.4 J/cm²

$T_{\text{max}} = 35.9 \, ^\circ\text{C}$
$\Delta T_{\text{max}} = 8.9 \, ^\circ\text{C}$
$\Delta T_{\text{average}} = 3.6 \, ^\circ\text{C}$
Confinement Zones

- Stress confinement
- Thermal confinement

Diagram showing penetration depth vs. pulse duration for different laser materials:
- Nd:YAG (Q-switched)
- Ho:YAG (Q-switched)
- XeCl
- ArF
- Er:YAG

Equation:
\[ \tau = \frac{\delta^2}{4\kappa} \]

- Pulsed duration \[ \tau \delta \approx \end{aligned} \]

Markers:
- Green circle: 5 µs
- Purple circle: 250 µs
- Orange circle: 1 ms
- Blue circle: 5 ms

Graph scales:
- X-axis: Pulse duration [µs]
- Y-axis: Penetration depth [mm]
<table>
<thead>
<tr>
<th>Current Nerve Stimulator Areas of Activity</th>
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<tr>
<td>Vestibular infrared nerve stimulation</td>
</tr>
<tr>
<td>CNS stimulation</td>
</tr>
<tr>
<td>Eye pain sensor</td>
</tr>
<tr>
<td>Cochlear scanner</td>
</tr>
<tr>
<td>Vestibular nerve stimulation</td>
</tr>
<tr>
<td>Sweat gland neuropathy study</td>
</tr>
<tr>
<td>Central and renal nerve</td>
</tr>
<tr>
<td>Cavernous nerve</td>
</tr>
<tr>
<td>Whisker nerves</td>
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<tr>
<td>CNS and PNS</td>
</tr>
<tr>
<td>Cochlear INS</td>
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<tr>
<td>Facial nerve monitor</td>
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<tr>
<td>Facial nerve</td>
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<tr>
<td>Cardiac stimulation</td>
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<td>Aplysia studies</td>
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