Optical Stimulation of Neural Tissue: Current State and Future Challenges

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Neural Stimulation

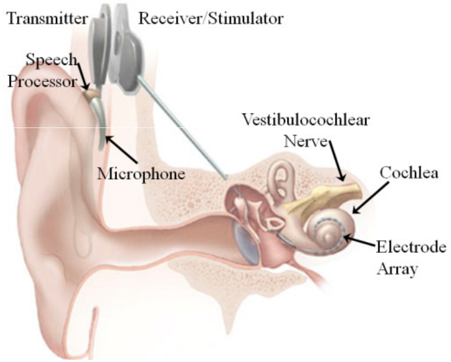
Since it is known that electrical activity can be measured with optical techniques (DOT, OCT, fluorescence imaging) ……

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



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- 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
    - o lack of spatial precision in stimulation (size of electrodes, electric field)
    - o electrical stimulation artifact preventing recording from adjacent stimulation
    - o Need for physical contact between the nerve and electrodes (storage of charge → inflammation, necrosis)
    - o MR compatibility?

1. Fritsch, G. and E. Hitzig, *Archiv Anatomie, Physiologie, und Wissenschaftlische Medicin* **37**, 300-32 (1870).

Hypothesis

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

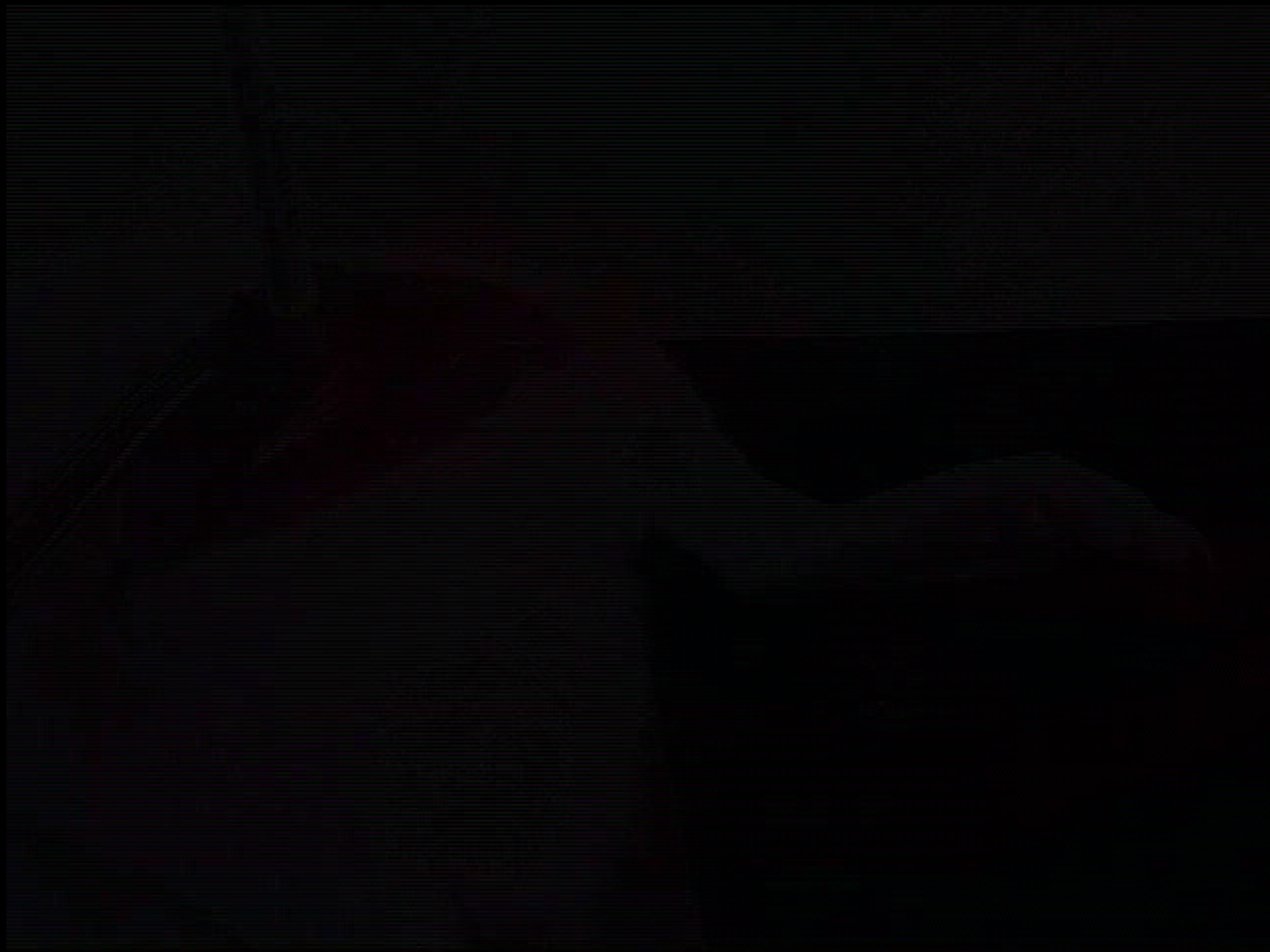
- **Objectives of this research:**
  - To evaluate and assess the safety and efficacy of optical stimulation in a comparison with electrical stimulation
  - Develop a stand-alone, portable, inexpensive, optical stimulator
  - Translation to clinical applications
  - Push capabilities beyond current state-of-the-art

What is optical stimulation?

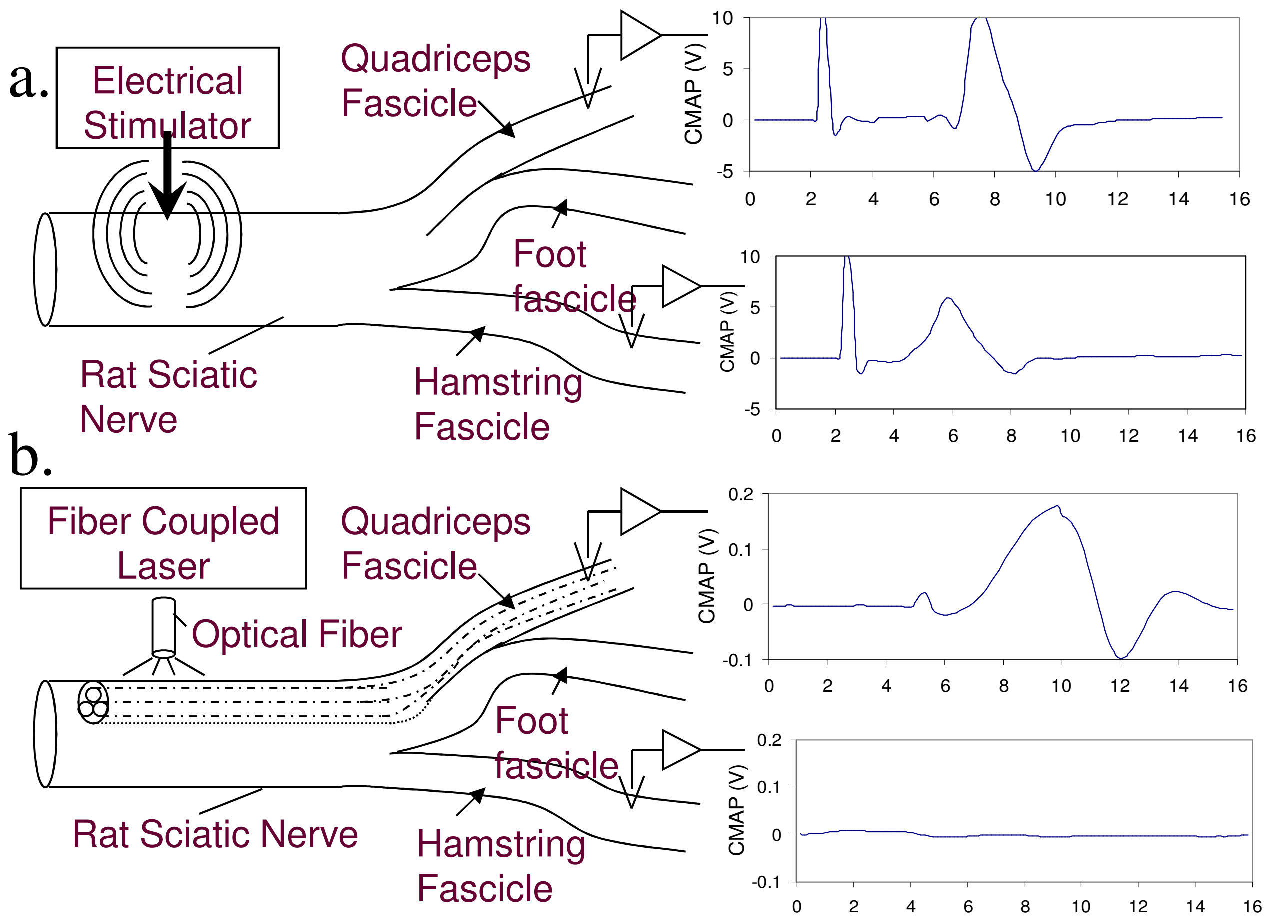
- Optical nerve stimulation = induction of an evoked potential (EP/AP) in response to a transient targeted deposition of optical energy.

- 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

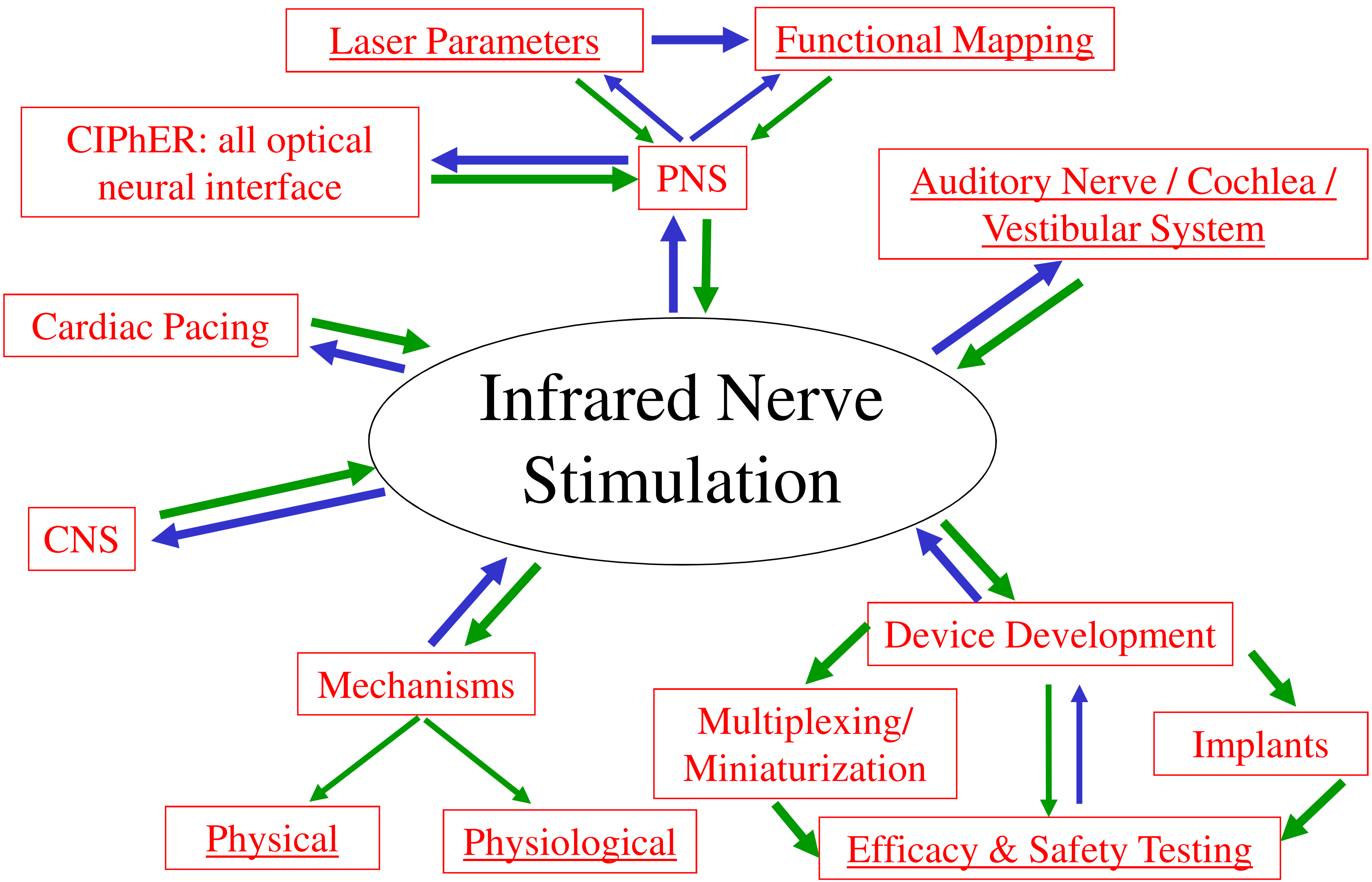
Spatially selective stimulation in rat sciatic nerve



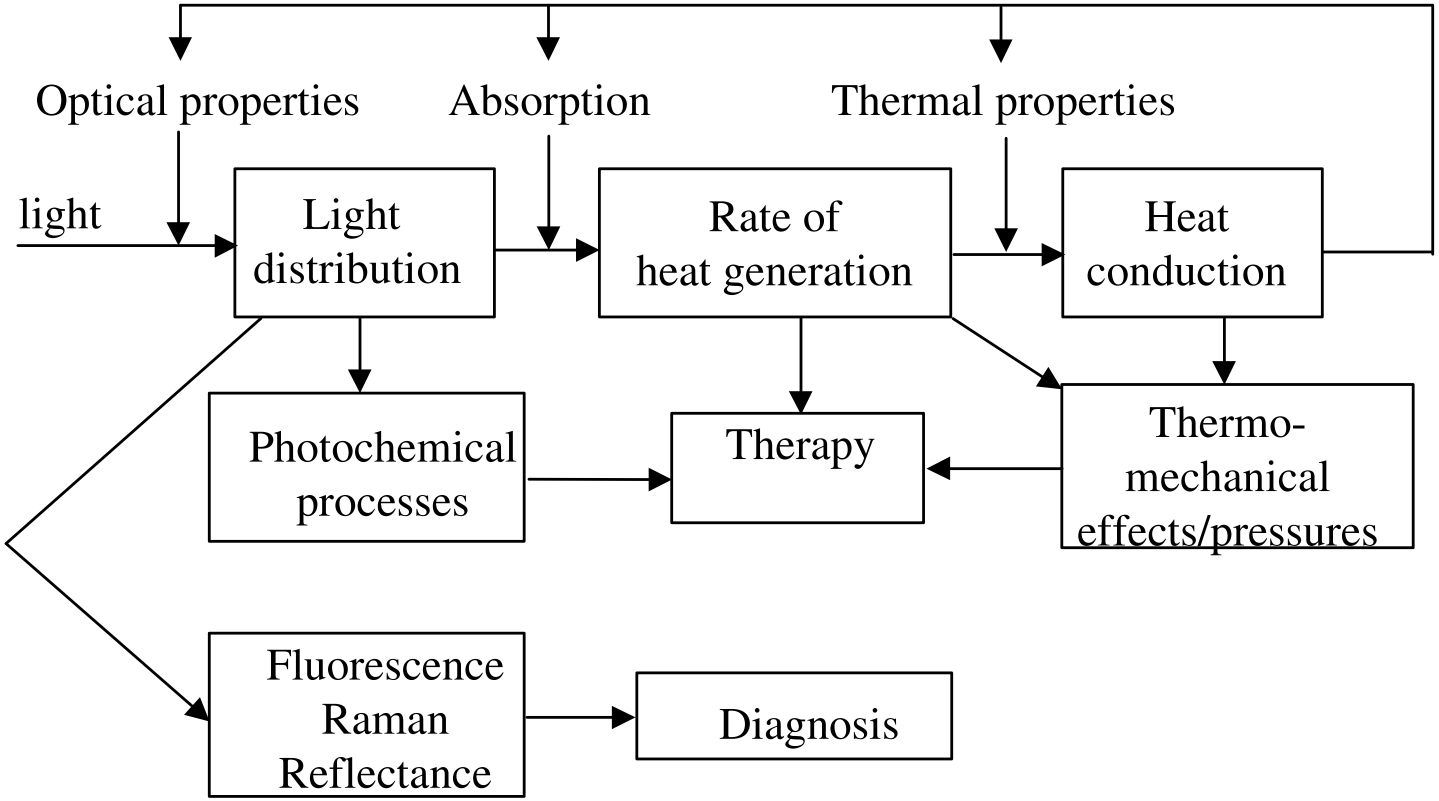
Spatial selectivity & no stimulation artifact



Wells JD, Konrad PE, Kao CC, Jansen ED, Mahadevan-Jansen A – J Neurosci Methods **163**(2): 326-37 (2007)

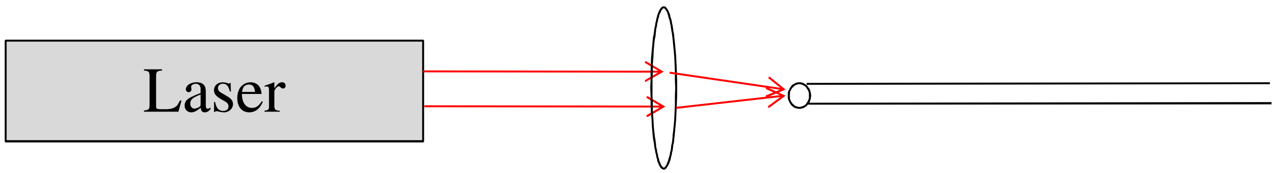

Laser Parameters
Functional Mapping
CIPhER: all optical neural interface
PNS
Auditory Nerve / Cochlea / Vestibular System
Cardiac Pacing
Infrared Nerve Stimulation
CNS
Mechanisms
Device Development
Multiplexing/ Miniaturization
Implants
Physical
Physiological
Efficacy & Safety Testing

A brief primer on Laser-Tissue Interaction



Laser output characteristics (1)

- Monochromatic (λ)
  - $E_{photon} = h\,v = \dfrac{h\,c}{\lambda}$
- 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_{pulse} (mJ))
  - Pulse duration (τ_p)
  - Pulse repetition rate (RR)

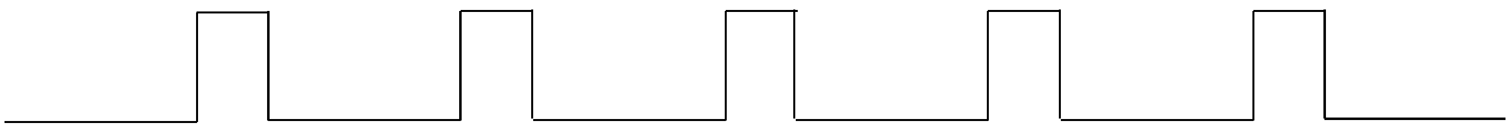
Pulsed lasers

- Power
  - Peak power: $P_{peak} = \frac{Q_{pulse}}{\tau_p}$
  - Average power: $P_{average} = Q_{pulse} * RR$

- Example: Ho:YAG laser:
  - Pulse duration (τ_p) = 100 μs
  - Pulse repetition rate (RR) = 5 Hz
  - Q_{pulse} = 100 mJ

$P_{peak} = \frac{100\ mJ}{100\ \mu s} = 1\ \text{kW}$

$P_{avg} = 100\ mJ * 5\ \text{Hz} = 0.5\ \text{W}$



CW Lasers

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

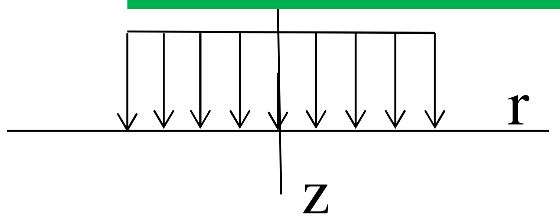
- Example: Power = 5 W; 1 ms pulse, 100 Hz
  - DC = 100 (Hz) * 1 10^{-3} (s) = 0.1 = 10%
  - True P_{avg} = 5 (mJ/p) * 100 (Hz) = 0.5 (W)

'Intensity'

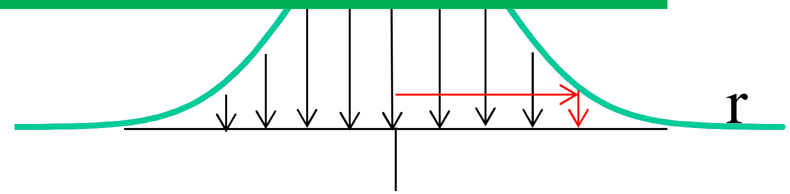
- Pulsed
  - Radiant Exposure, H (J/cm^2)
  - $H = Q_{pulse}$ / Area
- CW
  - Irradiance, E (W/cm^2)
  - E = Power / Area

What is the area, A?

Spotsize fundamentally determined by:
1) Diffraction limit: $d \approx \lambda / 2\ NA \approx \lambda / 2$
2) Fiber size



Uniform beam

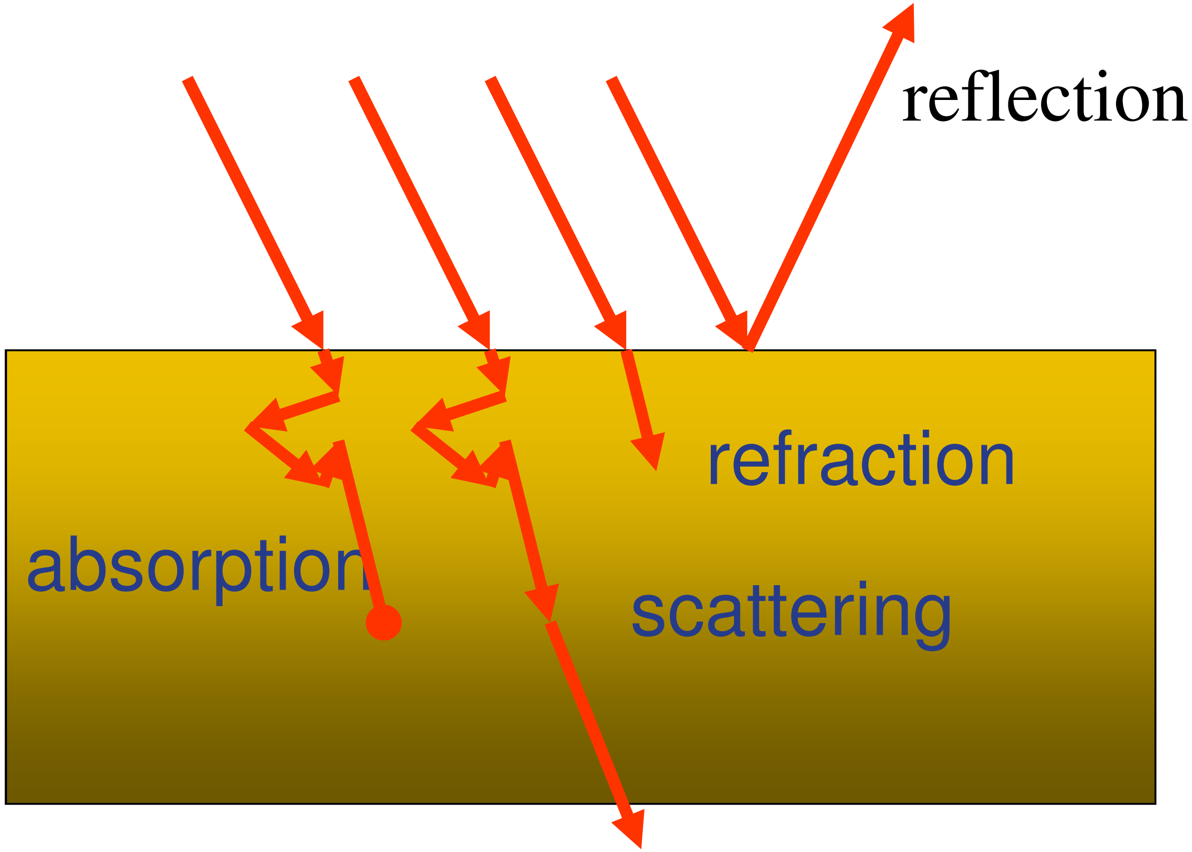


Gaussian beam

$r = \omega_L$

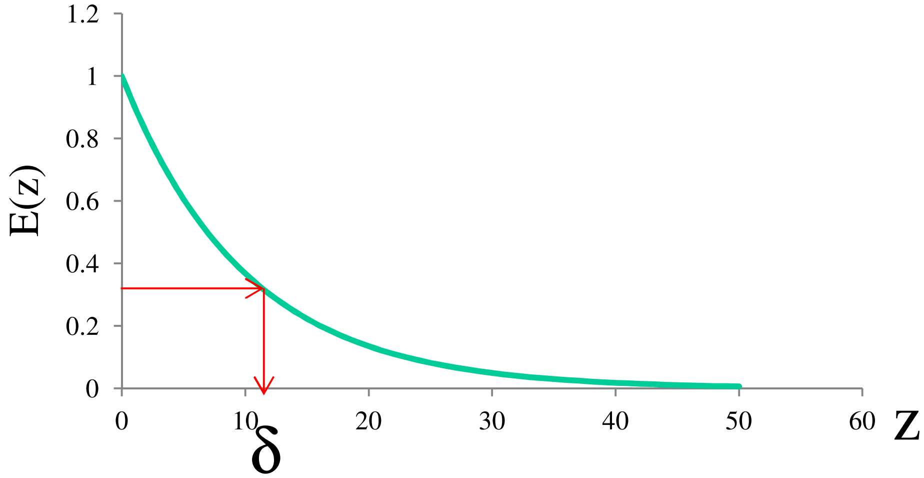
$$E(r) = \frac{1}{e^2} E(r=0) = 0.13\, E(r=0)$$

Light interaction with tissue

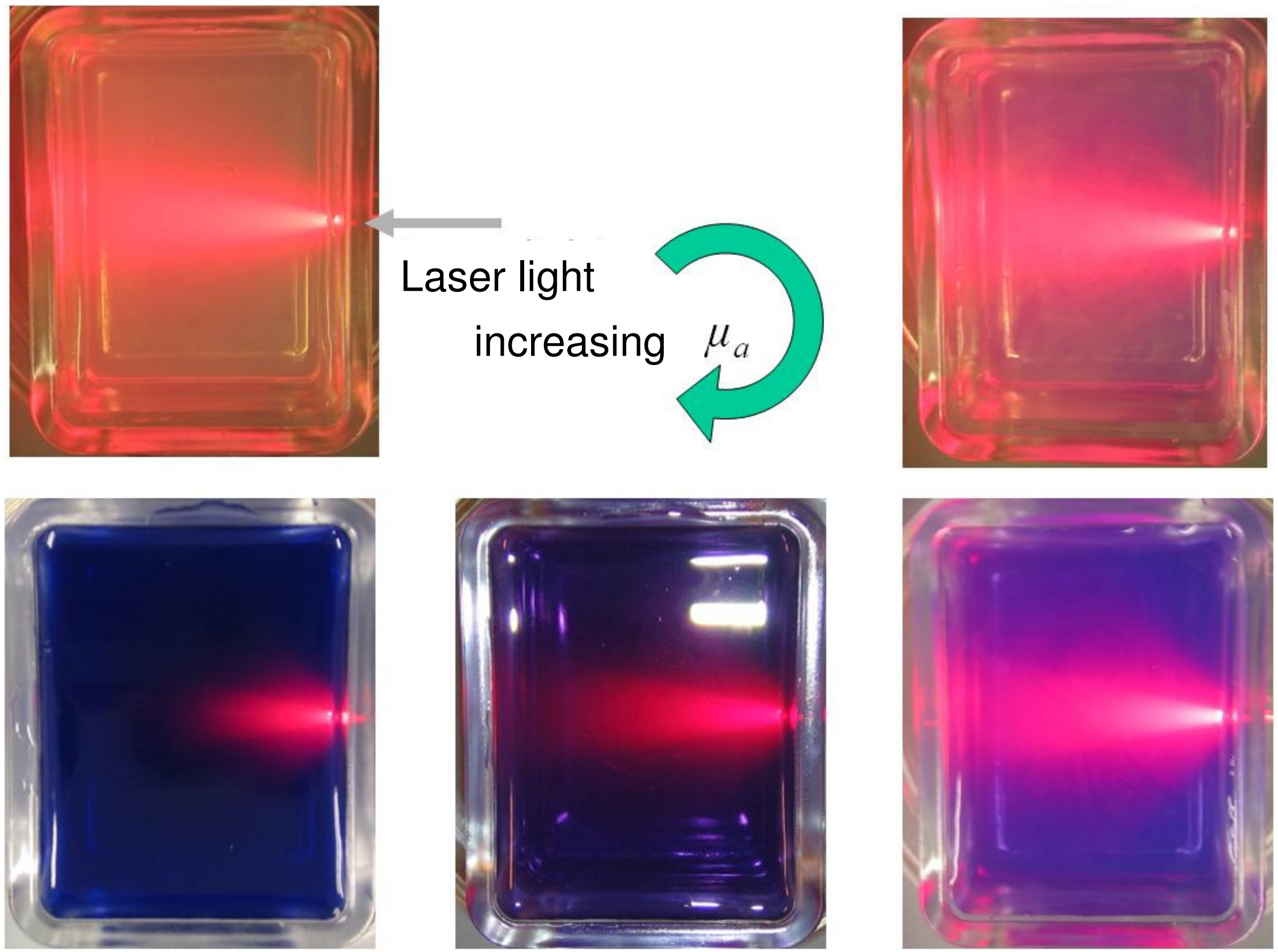


Tissue Optics

- Absorption (if $E_{photon} \sim \upsilon_{resonance}$)
- Optical energy → thermal or chemical energy
- Beer's law: $E(z) = E_0\, e^{-c\,\xi(\lambda) z} = E_0\, e^{-\mu_a(\lambda) z}$
- λ-dependent absorption coefficient, μ_a (cm^{-1})
- 'Penetration depth':
  - $\delta = \frac{1}{\mu_a}$
  - $E(z) = \frac{1}{e} E_0 \approx 0.37\, E_0$

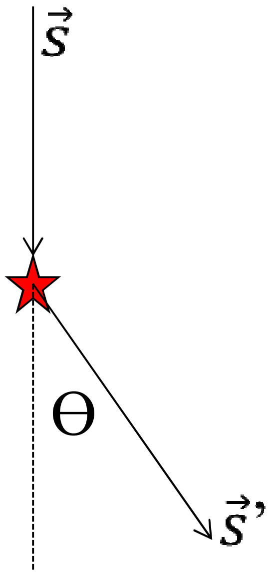


Effect of absorption



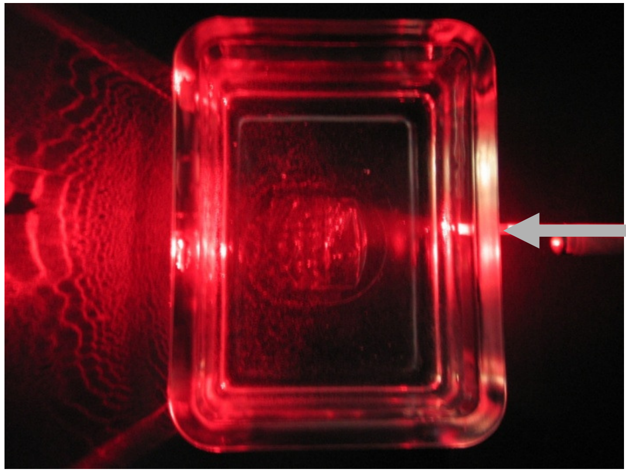
Tissue Optics

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



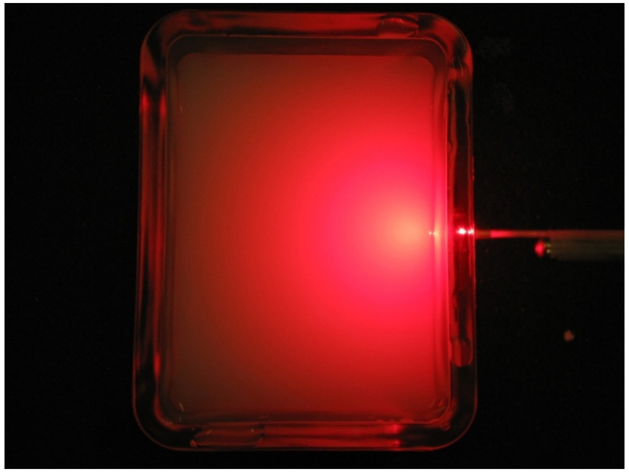
Effect of scattering

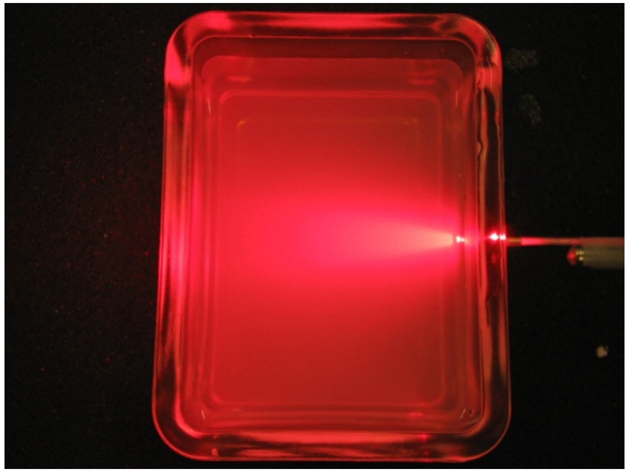
Water with intralipid

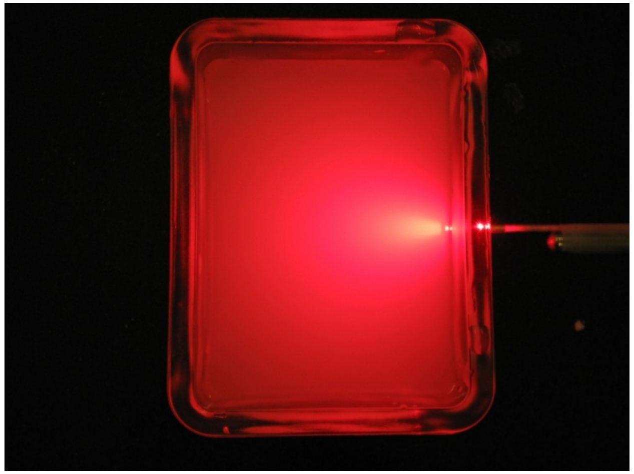


Laser light

Increasing μ_s

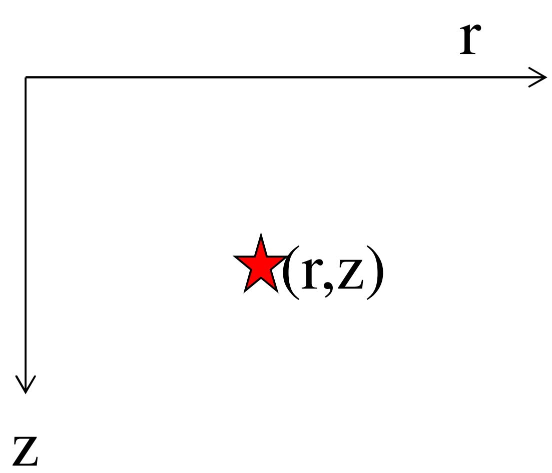






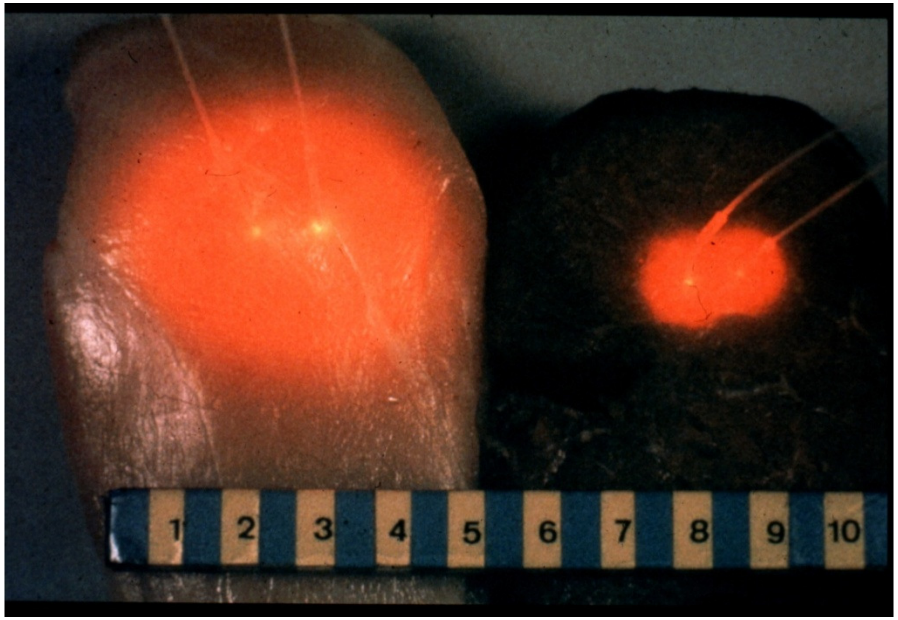
How much light gets to some point (r,z) in tissue?

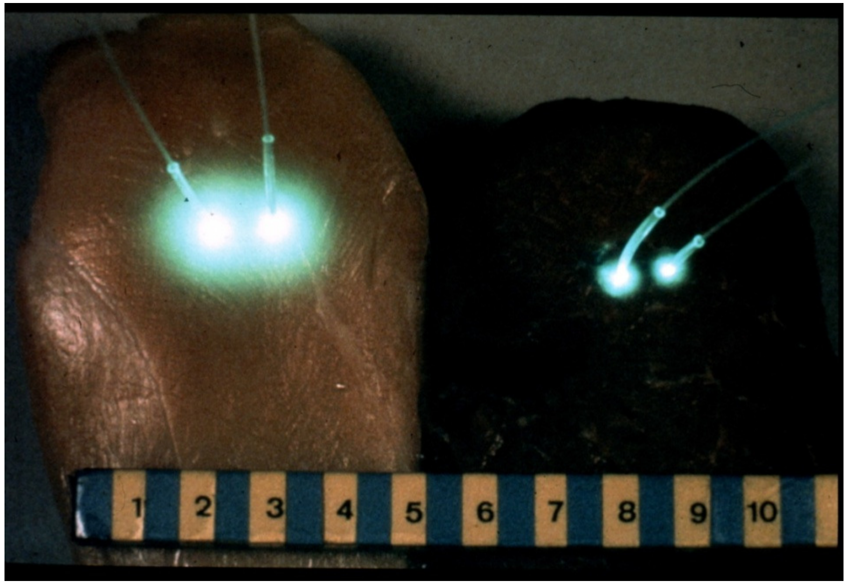
- If $\mu_a >> \mu_s$': Beer's law & beam profile
- If $\mu_a \leq \mu_s$': Modeling
  - Monte Carlo
  - Kubelka-Munk
  - Diffusion Approximation
  - Adding-Doubling



- Optical properties depend on wavelength, λ
  - 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.

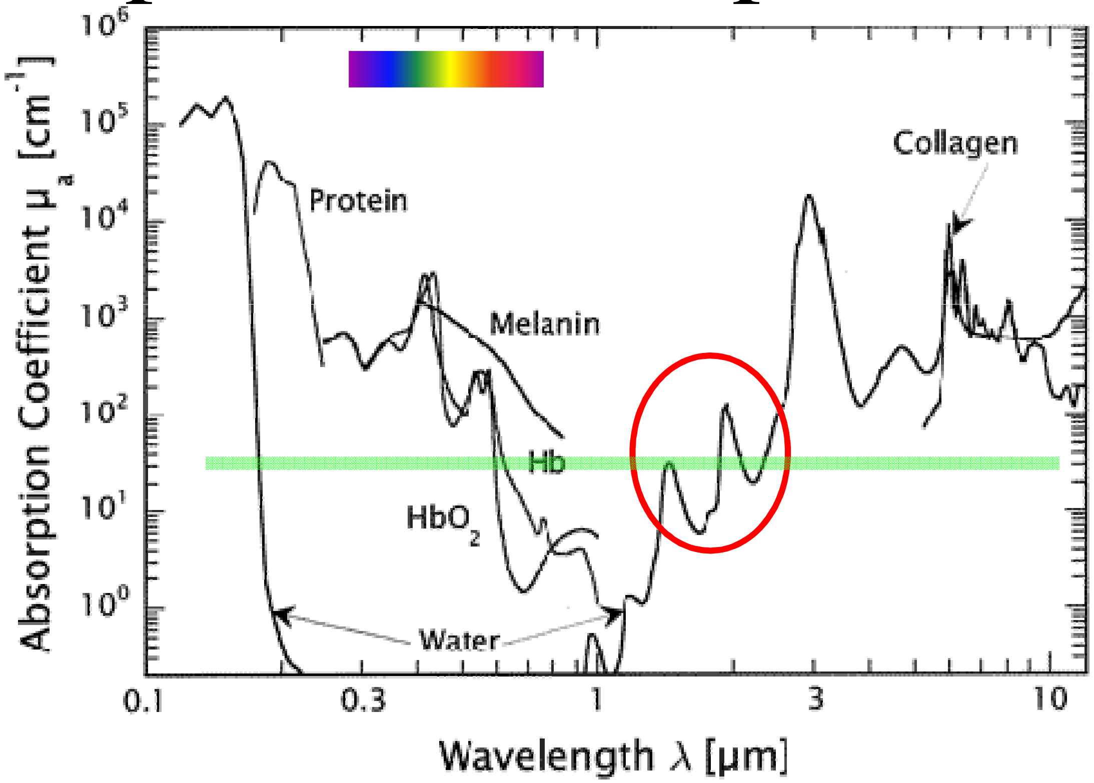
Heat Source and Temperature Rise

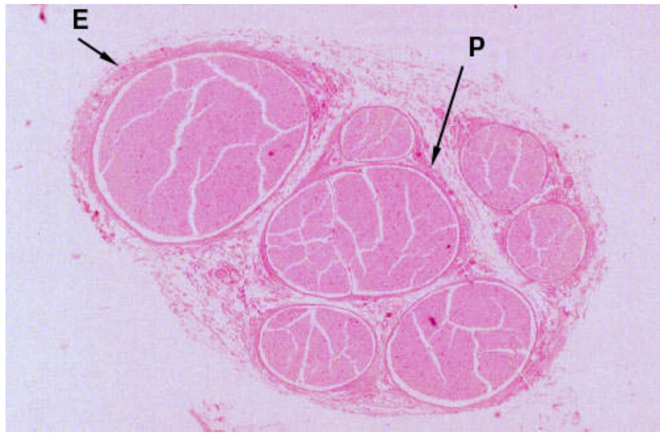
- Pulsed:
  - W (r,t) (J/cm^3) = μ_a(r,z) ($1/cm$) * H(r,z) (J/cm^2)
- CW:
  - S (r,z) (W/cm^3) = μ_a(r,z) ($1/cm$) * E(r,z) (W/cm^2)

    (or μ_a (r,z) ($1/cm$) * φ(r,z) (W/cm^2)
  - W (r,z) (J/cm^3) = S(r,z) (W/cm^3) * τ_{pulse} (s)

- $\Delta T(r,z) = \frac{W(r,z)}{\rho c}$ (impulse response)

Peripheral Nerve Geometry & desired penetration depth





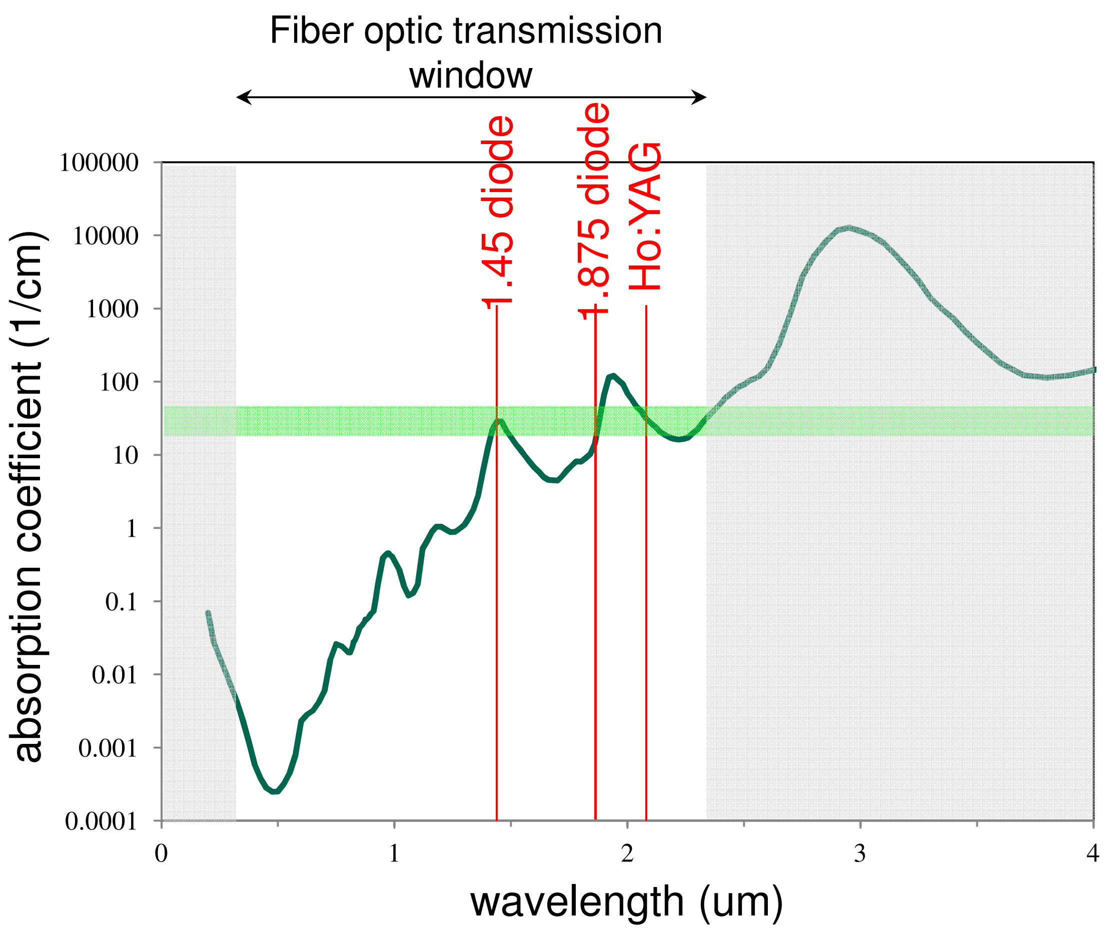
Nerve diameter	1-2 mm
Outer sheath	~ 150 um
Fascicles	50-400 um

$$\delta = 1/\mu_a$$

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

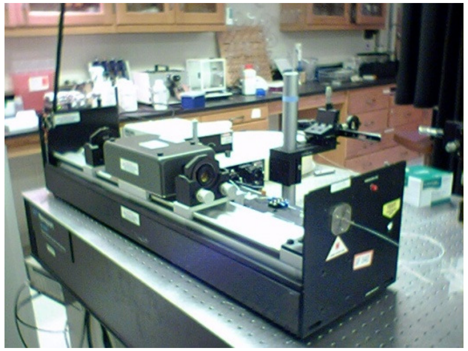
Wells, et al, Optics Letters, **30**(5): 504-507 (2005)
Wells, et al, J. Biomed Optics, **10**(6):064003 (2005)

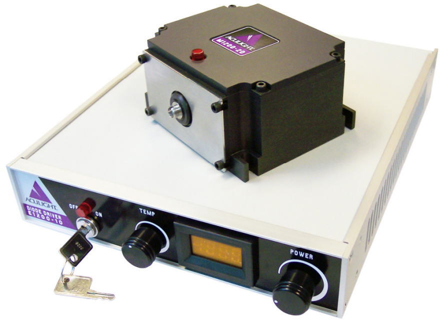
We need penetration depth of 250-500 um (for peripheral nerves)



Translational Research

Free Electron Laser



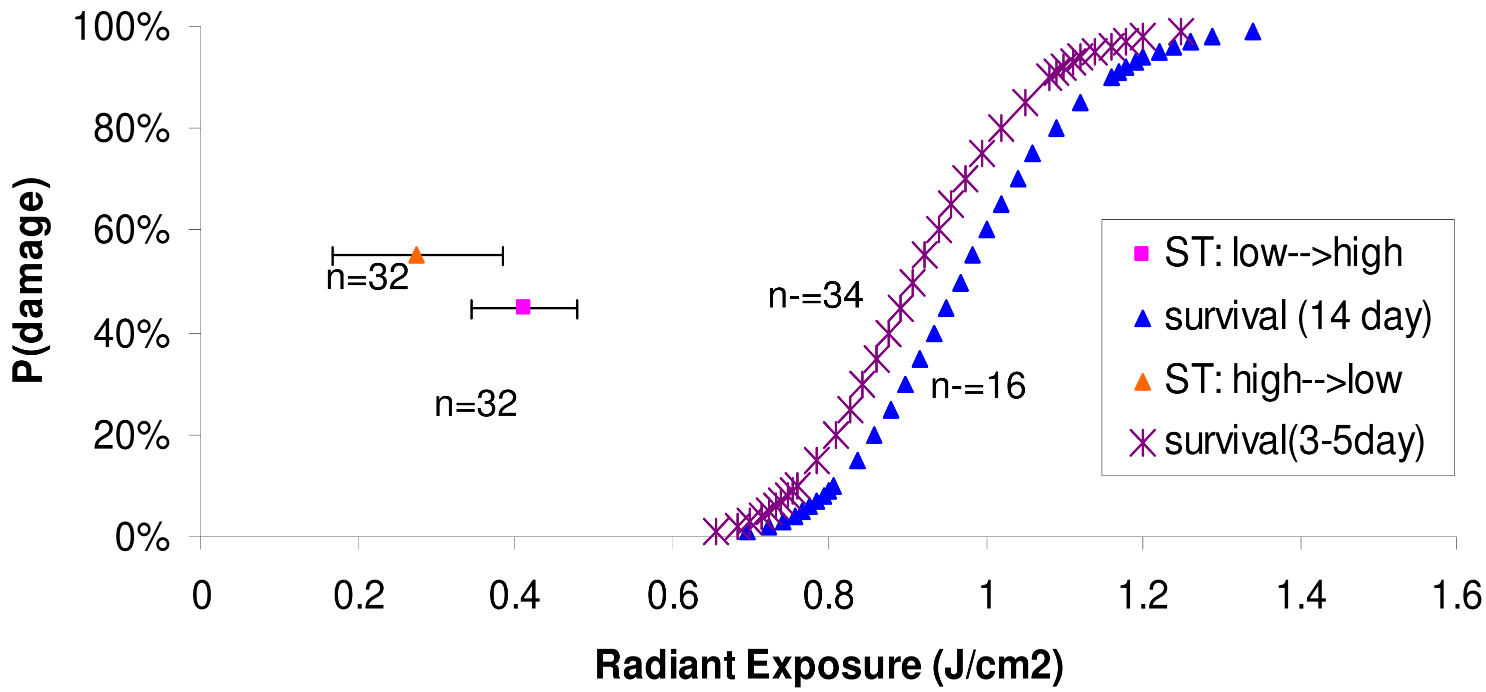


IRCM laser development / Dual use

LMA Capella R-1850
Infrared Neuro-Stimulator

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

Damage versus Stimulation Thresholds



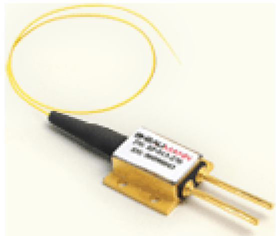
Wells JD et al. – Lasers in Surgery and Medicine (39(6): 513-26 (2007))

Near-term light-based implant development

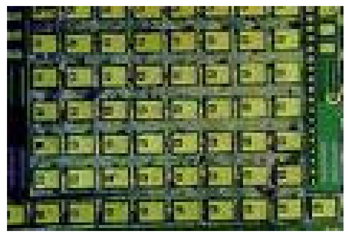
10 channels
6 x 50 x 84 mm
47 grams

- 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



4 x 12 x 12 mm

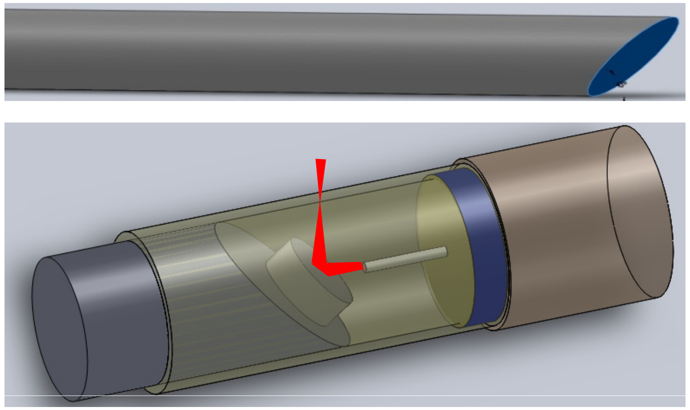


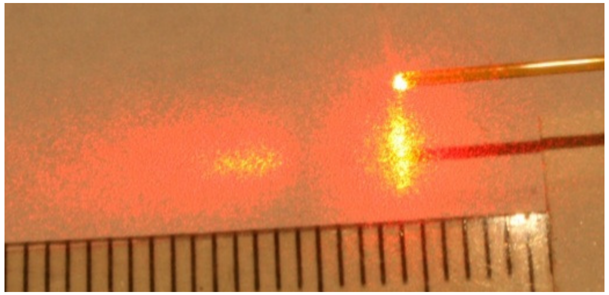
1 mm x 1 mm

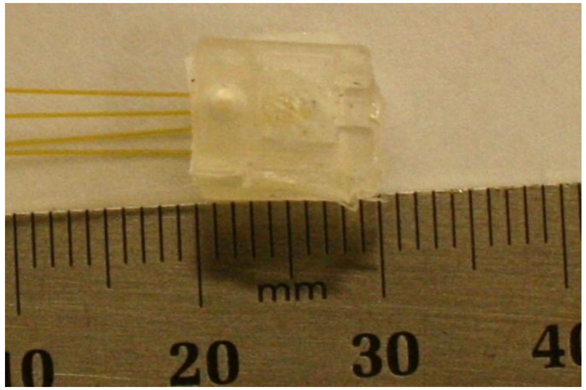
Towards an optical neural interface:

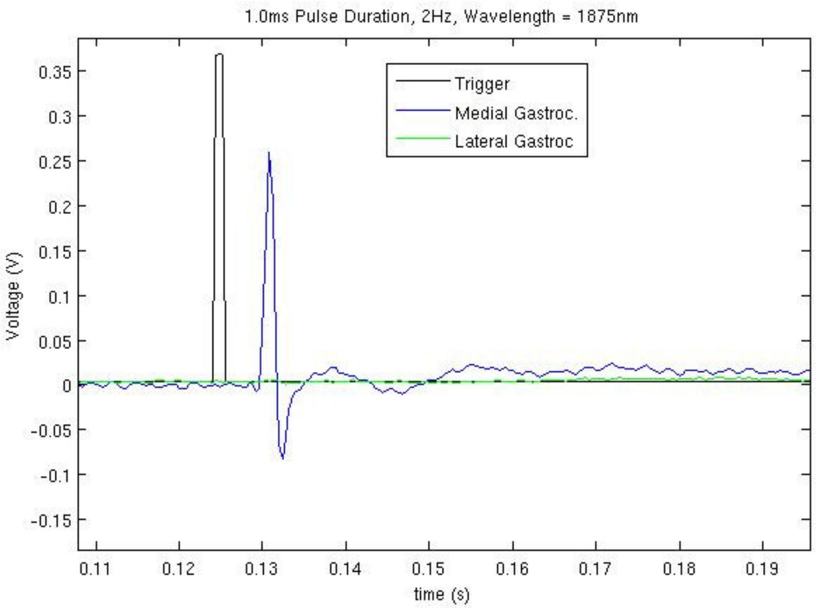
- Develop multichannel INS probe
  - Co-aligned configuration with nerve
  - Multiplexed (4→8→ ….channels)
  - Parameter optimization
  - In vitro / in vivo testing:
    - Feasibility / efficacy
    - Tissue damage assessment
- Integrate in nerve cuff & fully optical neural interface

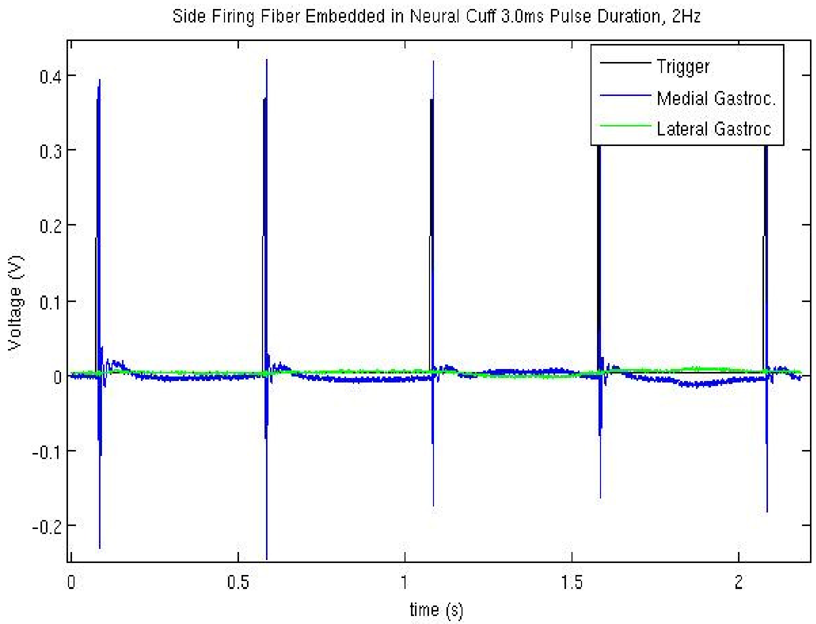
Stimulation with a cuff





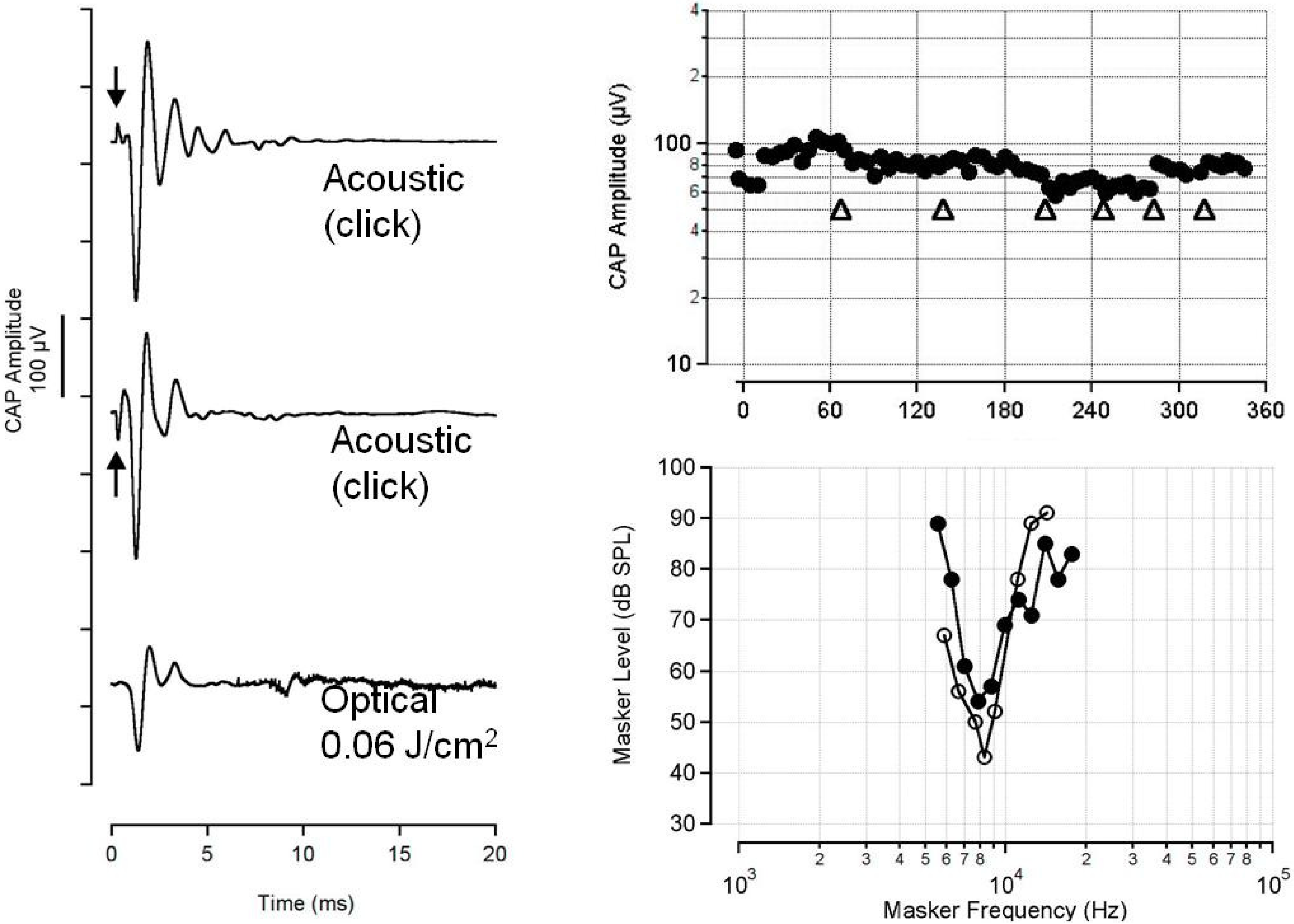




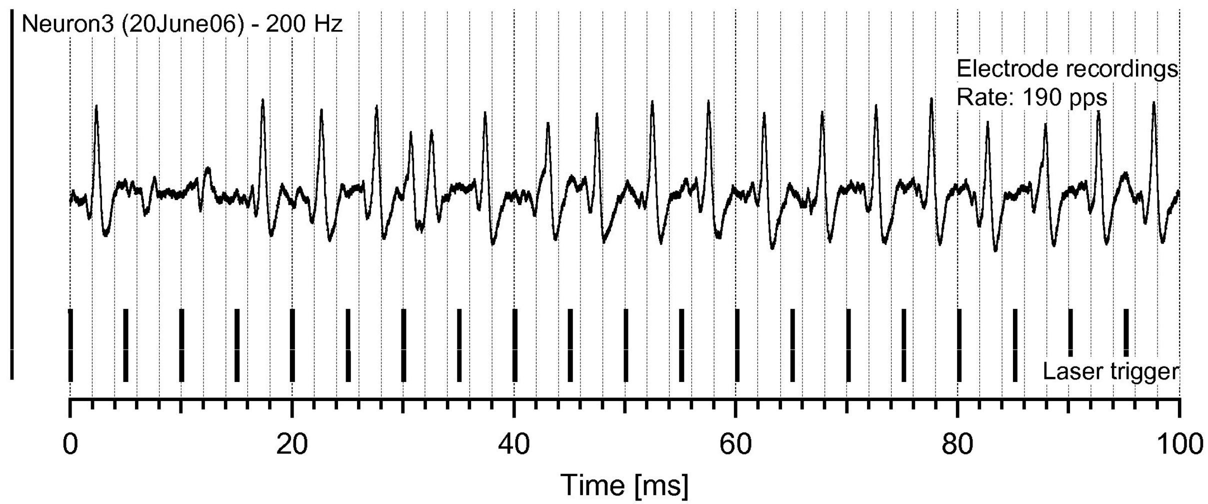


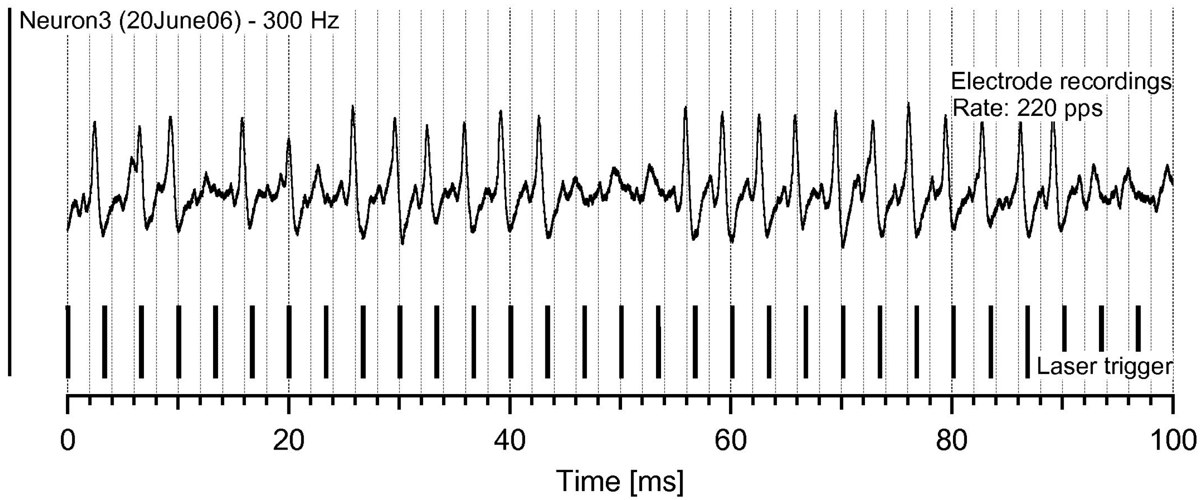
Can we hear light???

Optical Stimulation of the auditory nerve

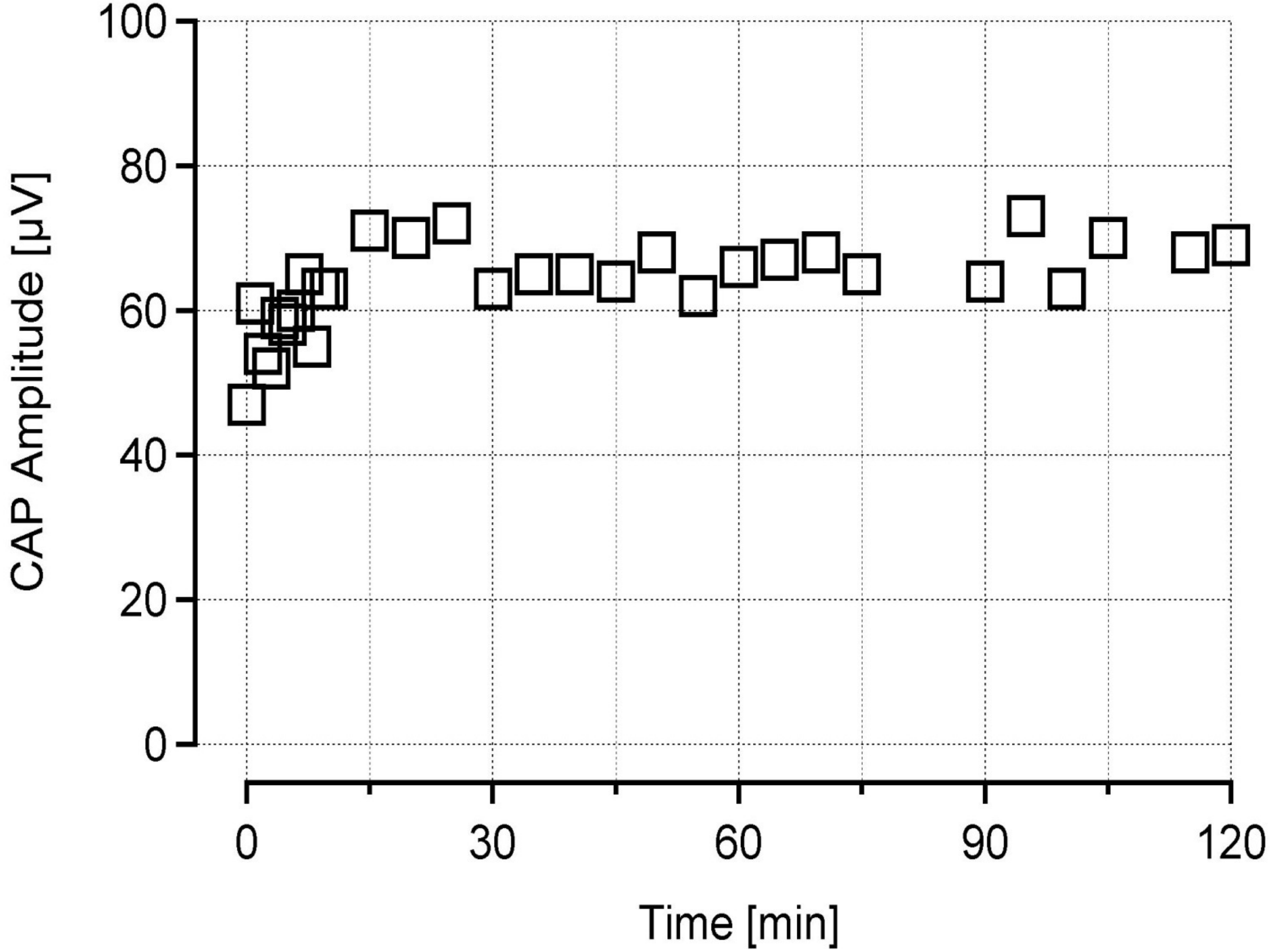


High Repetition Rate – single nerve recording





Extended Optical Stimulation



400Hz, 15 mJ/cm^2

Courtesy of Dr. Claus-Peter Richter

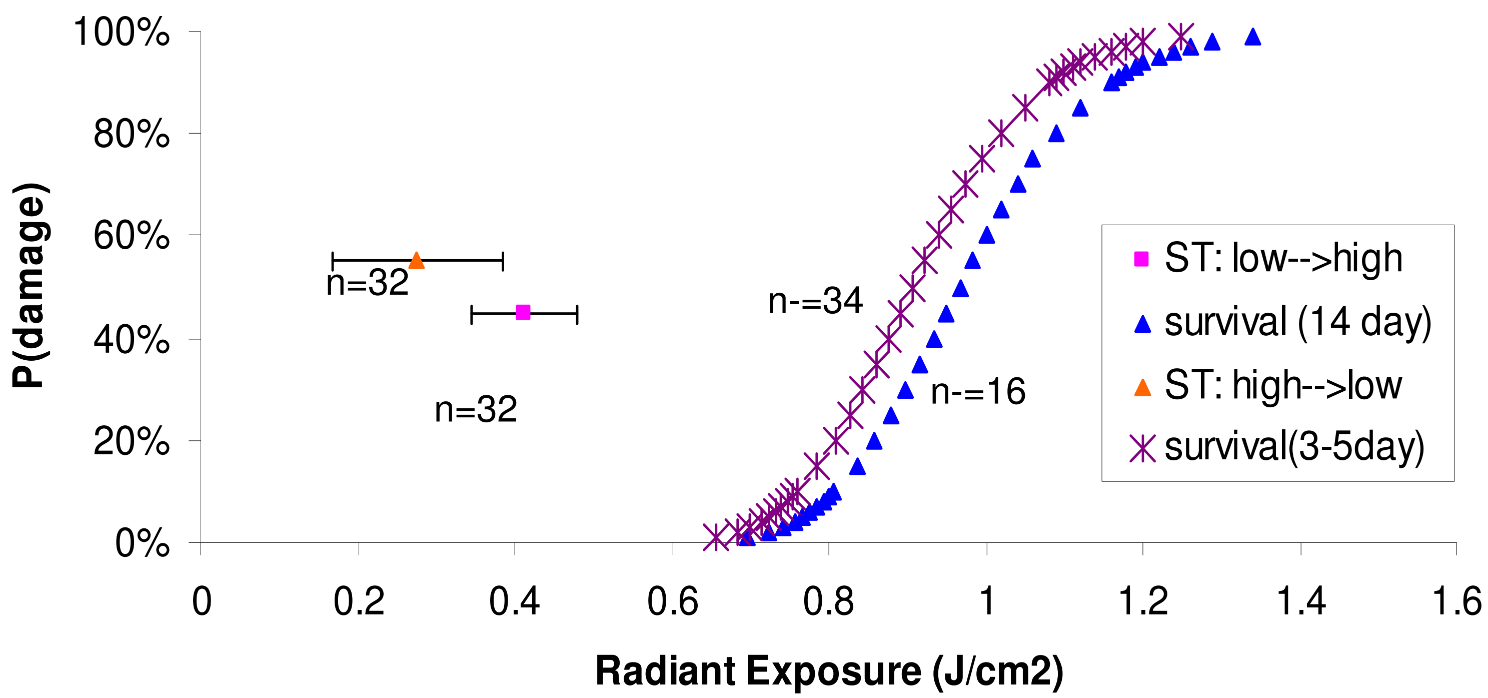
Conclusions – Cochlear stimulation

- 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



Wells JD et al. – Lasers in Surgery and Medicine (39(6): 513-26 (2007))

Can the optical stimulation threshold be lowered?

Hypothesis:

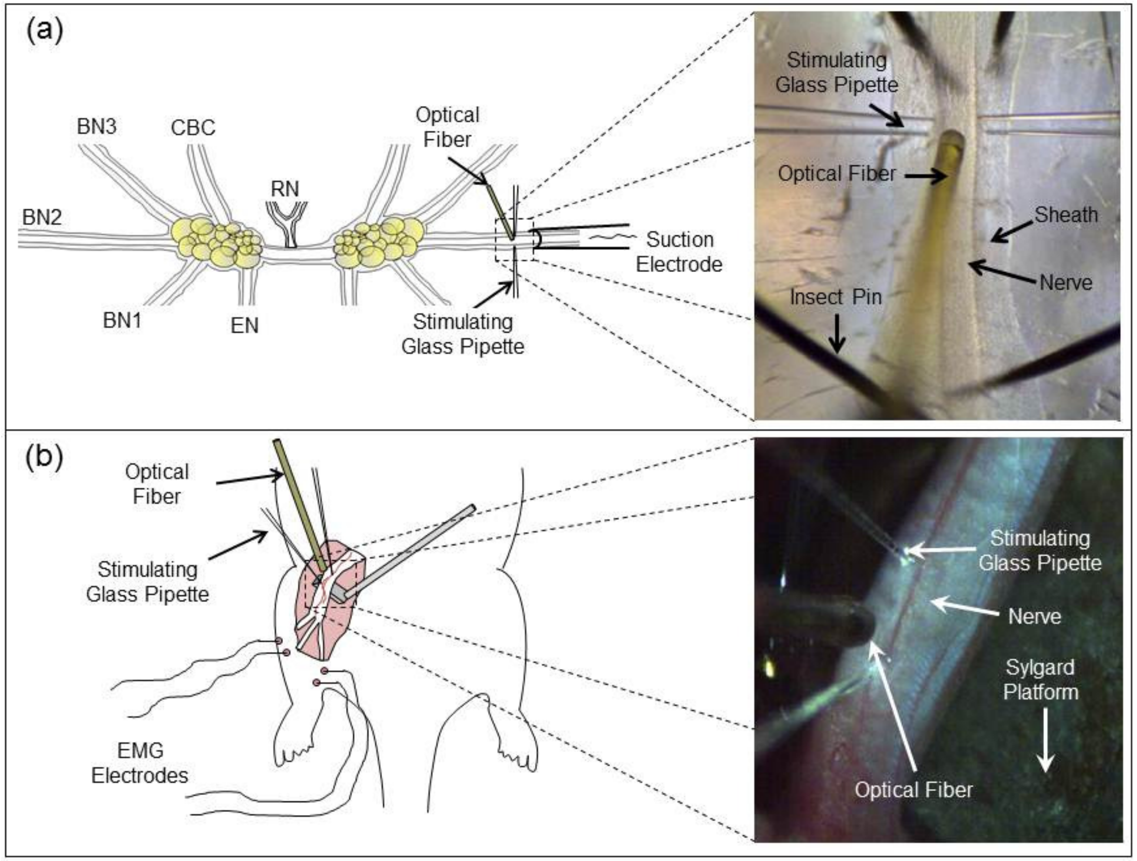
Combining subthreshold electrical stimulation with optical stimulation lowers the optical stimulation threshold while maintaining the benefits of high spatial selectivity of optical stimulation

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

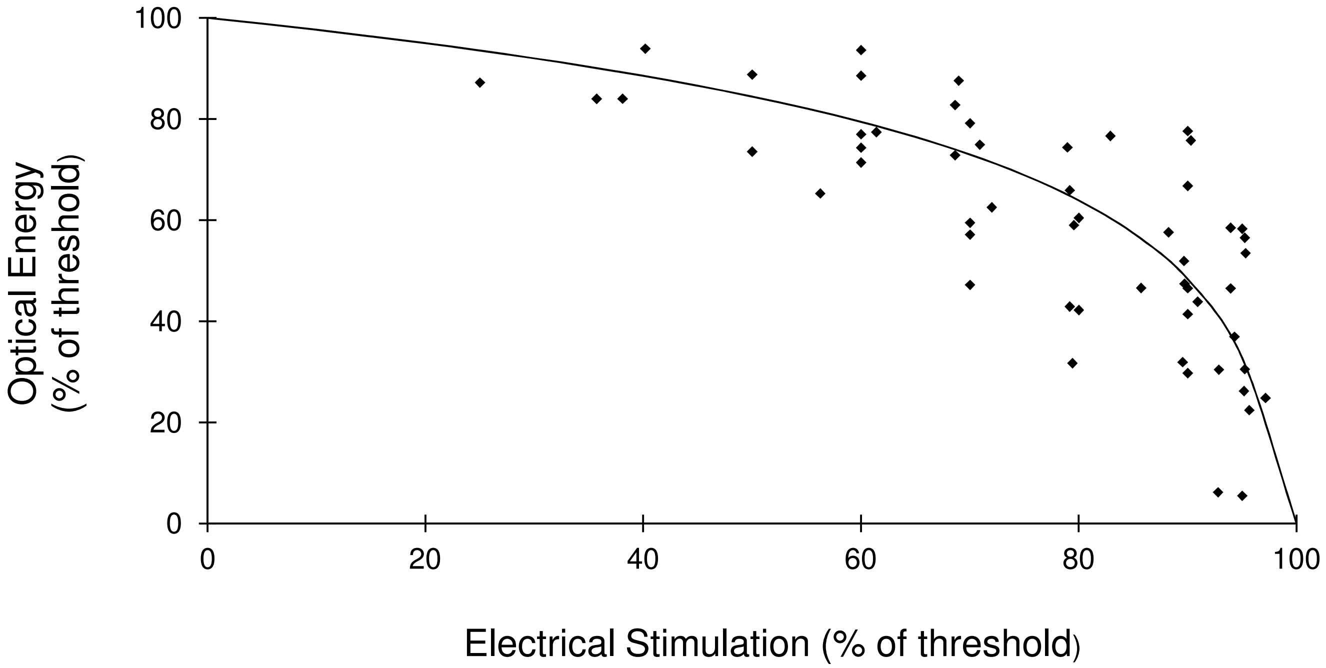
Controlling Hybrid Stimulation

Comparative Physiology Approach



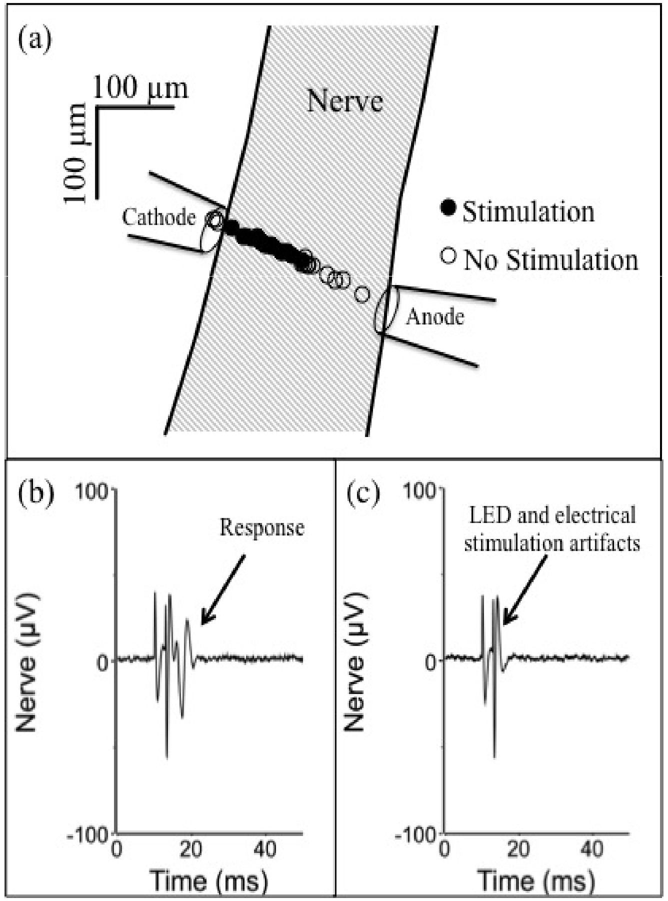
Duke et al., J Neural Eng, *In Review*

Optical threshold as function of Electrical Stimulation



Duke et al., J Biomed Optics 14, 060501 (2009)

Characterization of hybrid stimulation in Aplysia



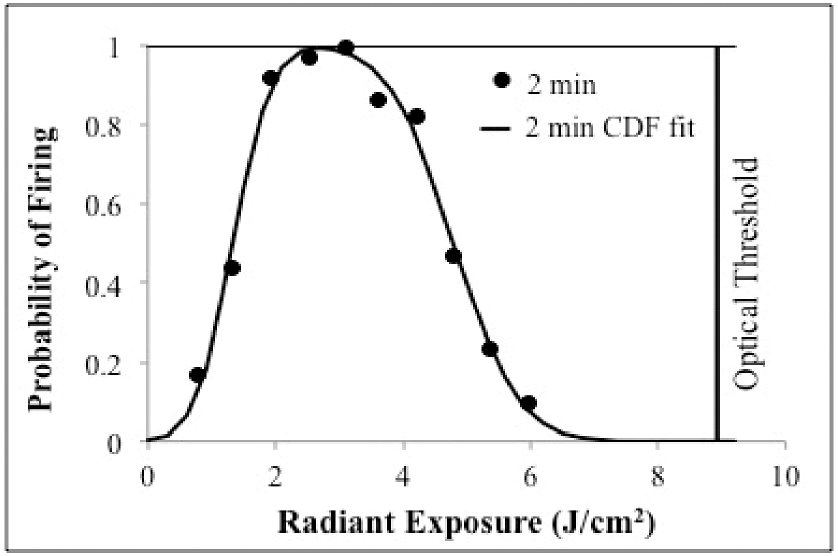
Role of:

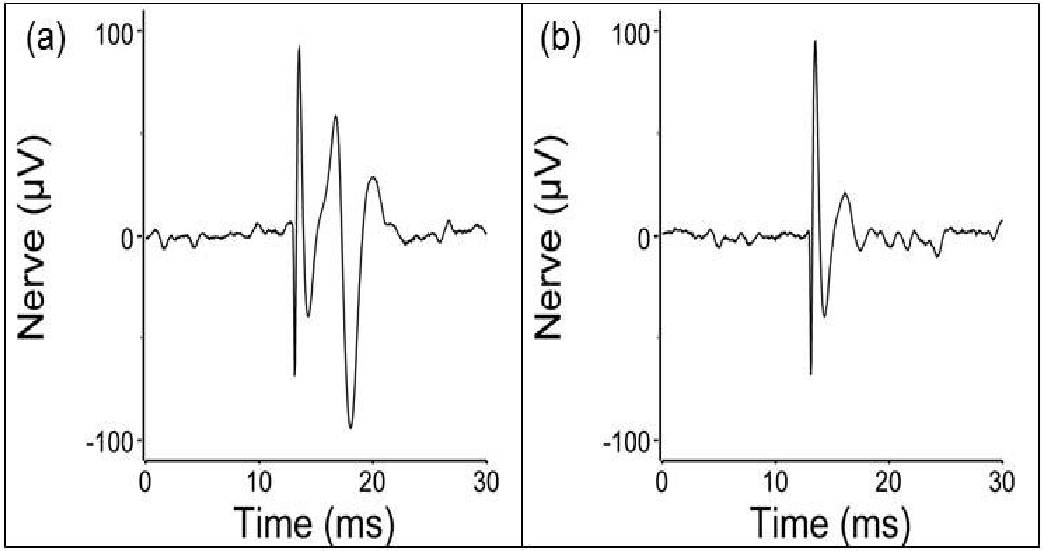
- Spatial overlap
- Temporal overlap
- Drift in threshold

Optimize n-dimensional parameter space

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

Optical Inhibition





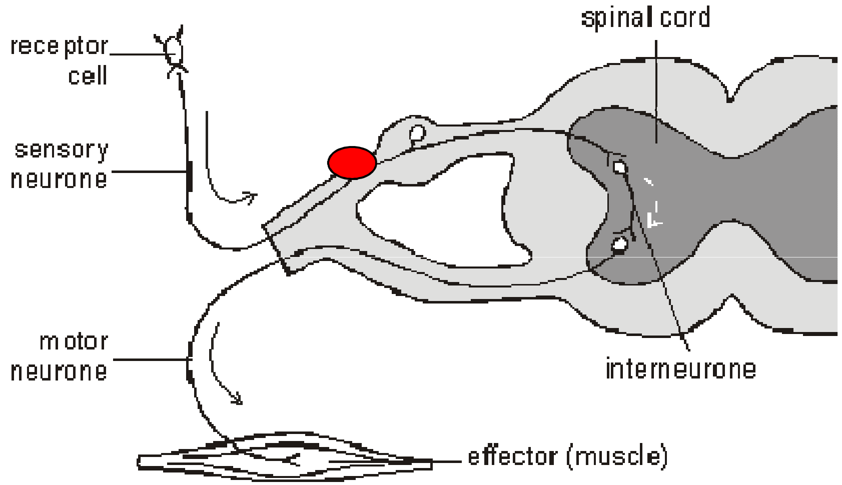
- A novel enabling tool in neuroscience
- Clinical utility to 'silence' (over)active neurons?
  - Parkinson's, Epilepsy, ET, etc.

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

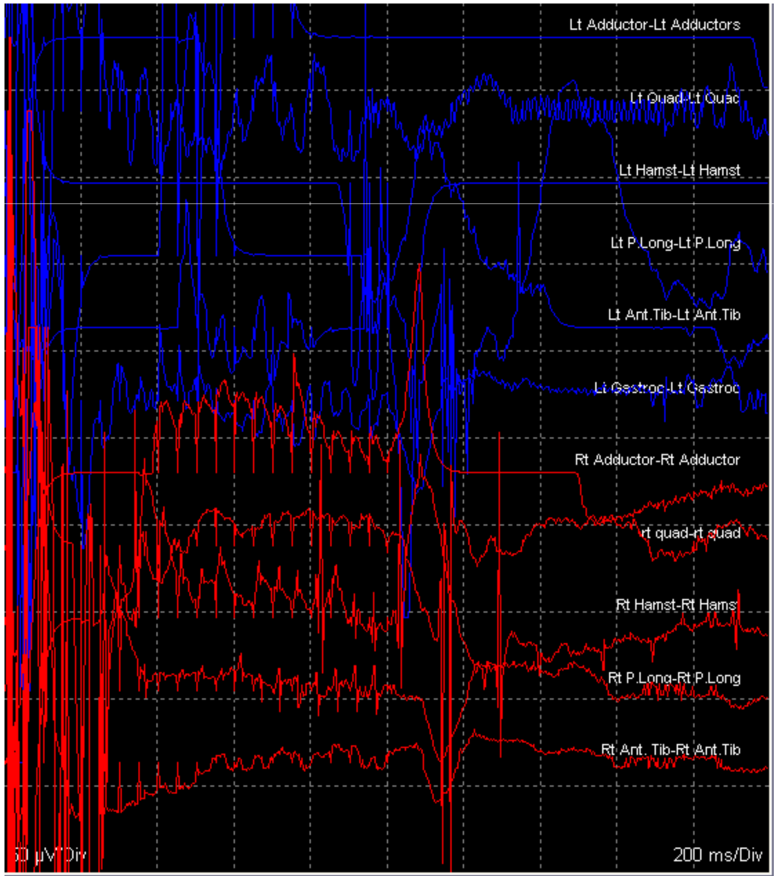
Translation to Human: Dorsal Rhizotomy



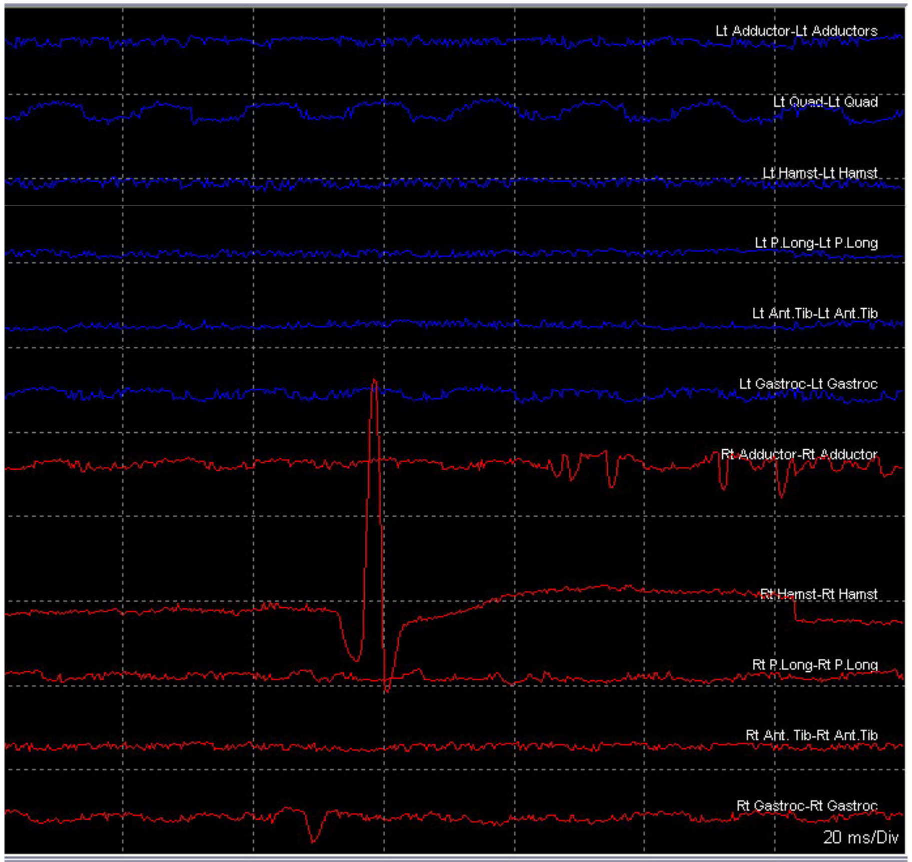
- Perfect procedure for clinical trial
  - Safety Study
  - Efficacy Study
- Employ Ho:YAG
  - 2.12 µm, 2 Hz, 0.2 - 1.5 J/cm^2, 20 pulses, 600 micron fiber probe
  - 7 cases to date

Results:

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



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



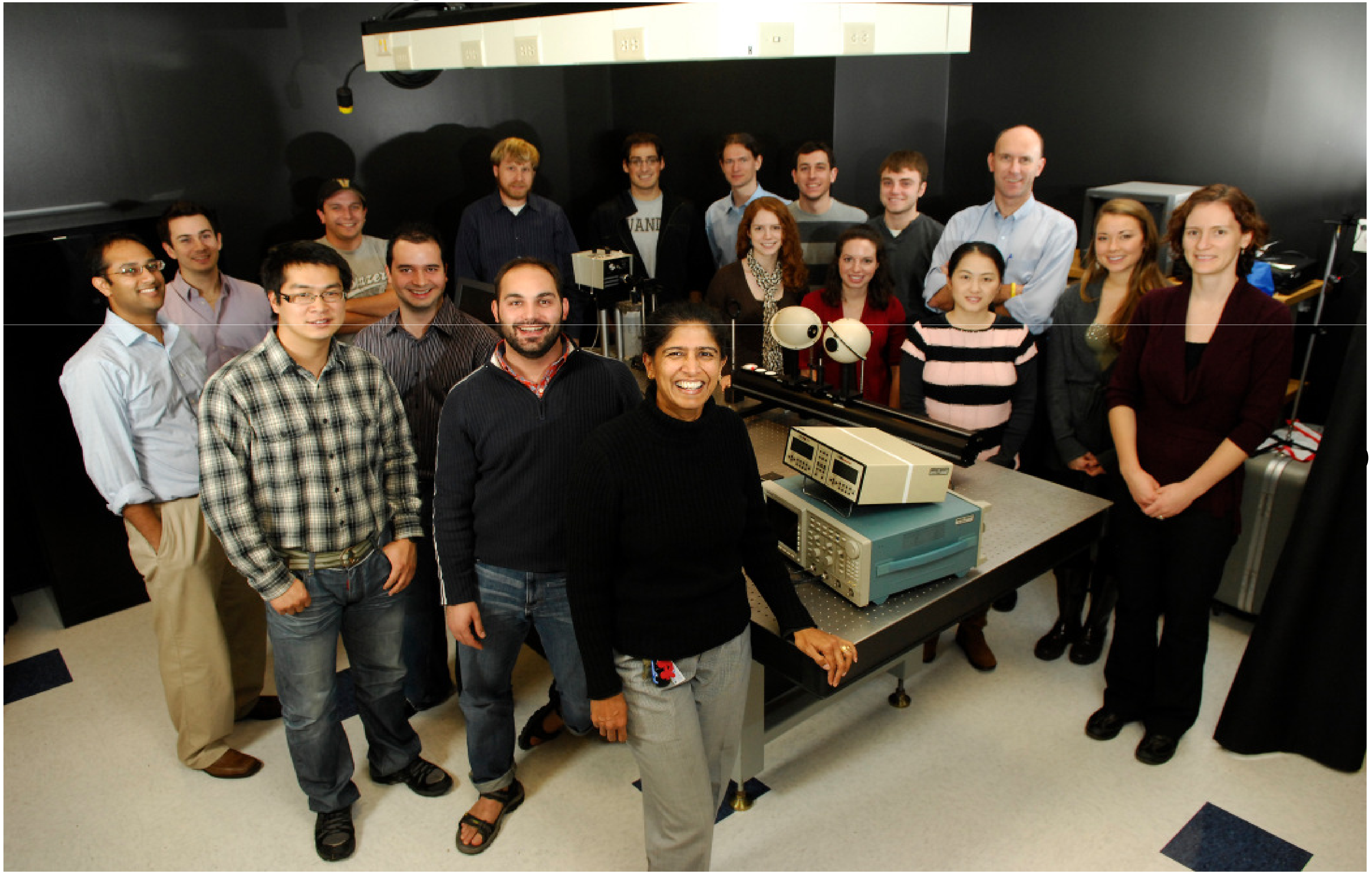
Conclusions:

- **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

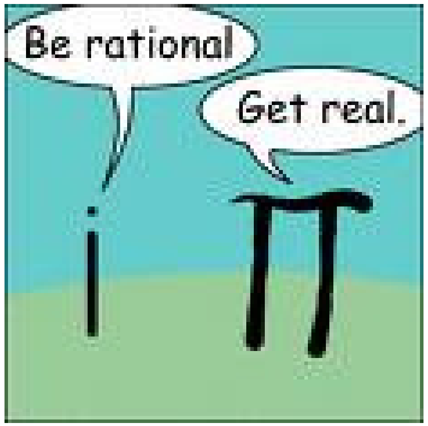


Translation to Human: Dorsal Rhizotomy

Mechanisms

By now you're probably wondering…..

how does INS work?



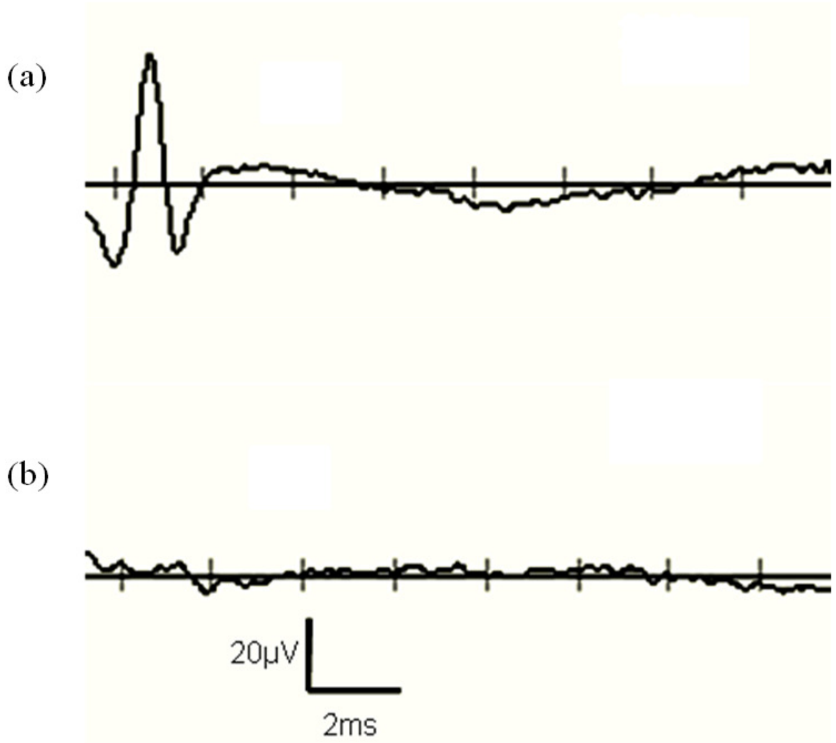
Mechanisms: Summary

- 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

Wells JD, et al. – Biophysical J, 93:2567-80 (2007).

Spatial selectivity is maintained

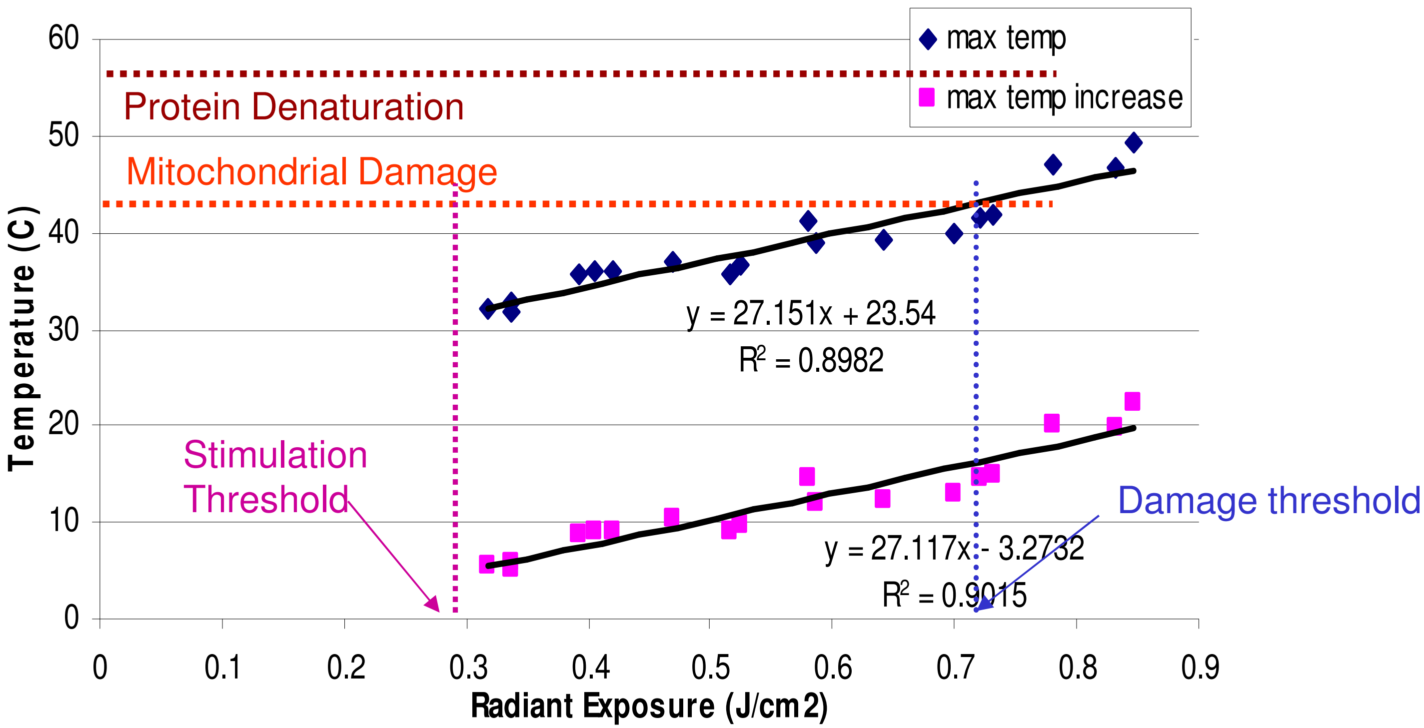


CMAP from gastrocnemius (target)

CMAP from biceps femoris

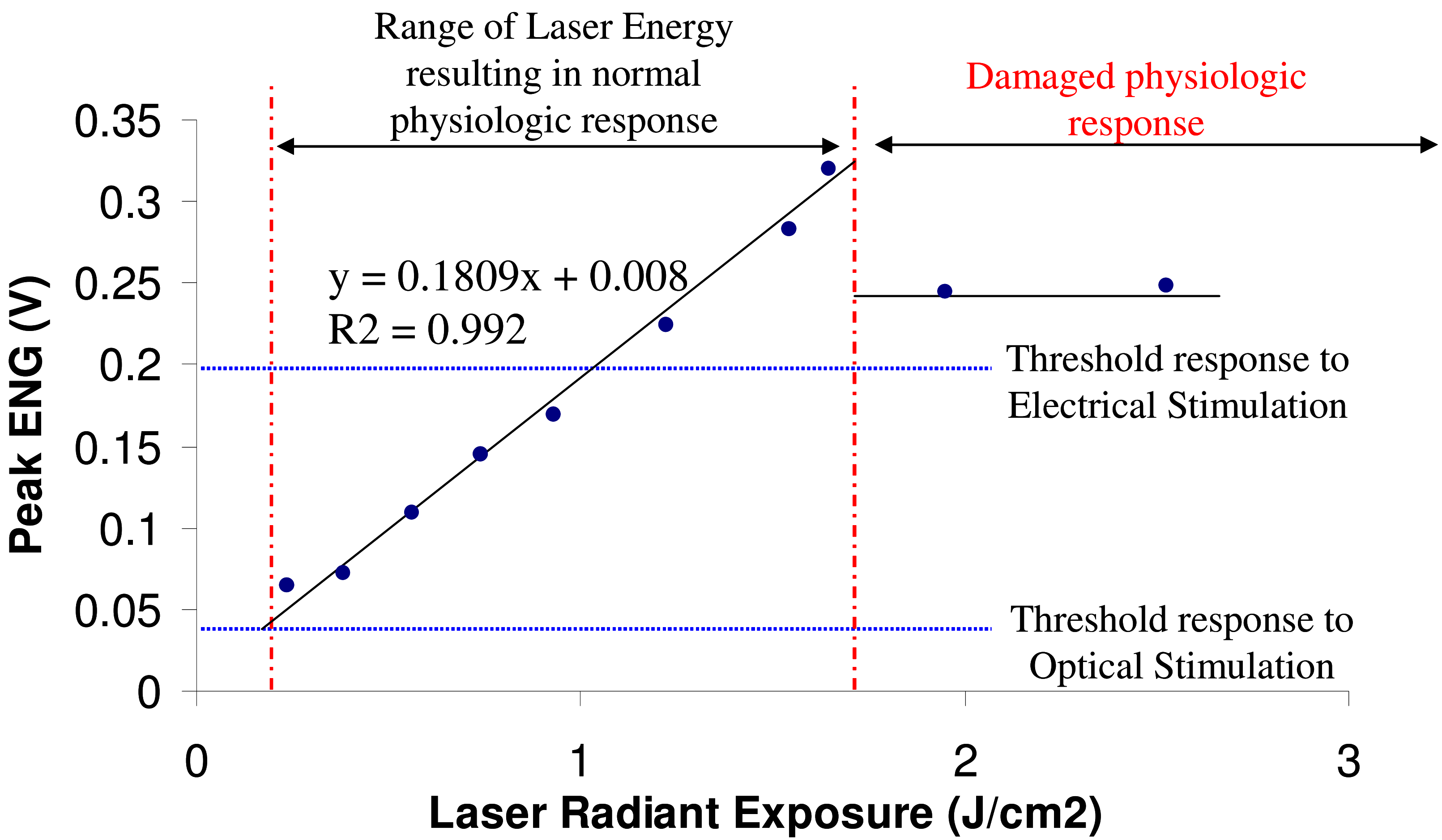
Combined optical and electrical stimulation in nerve

Thermal response

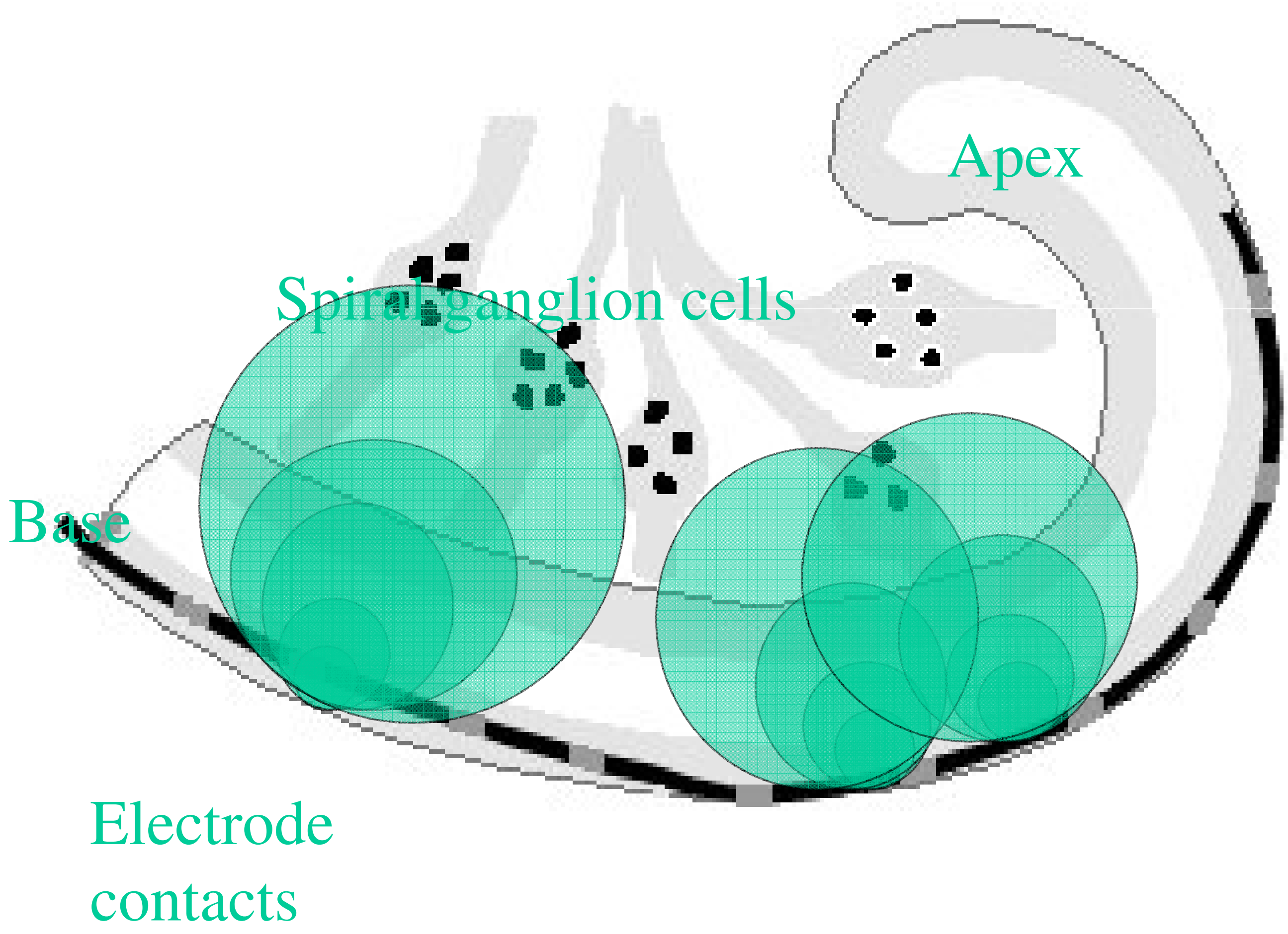


Wells et al. - Biophysical Journal 93(7) 2567–2580 (2007)

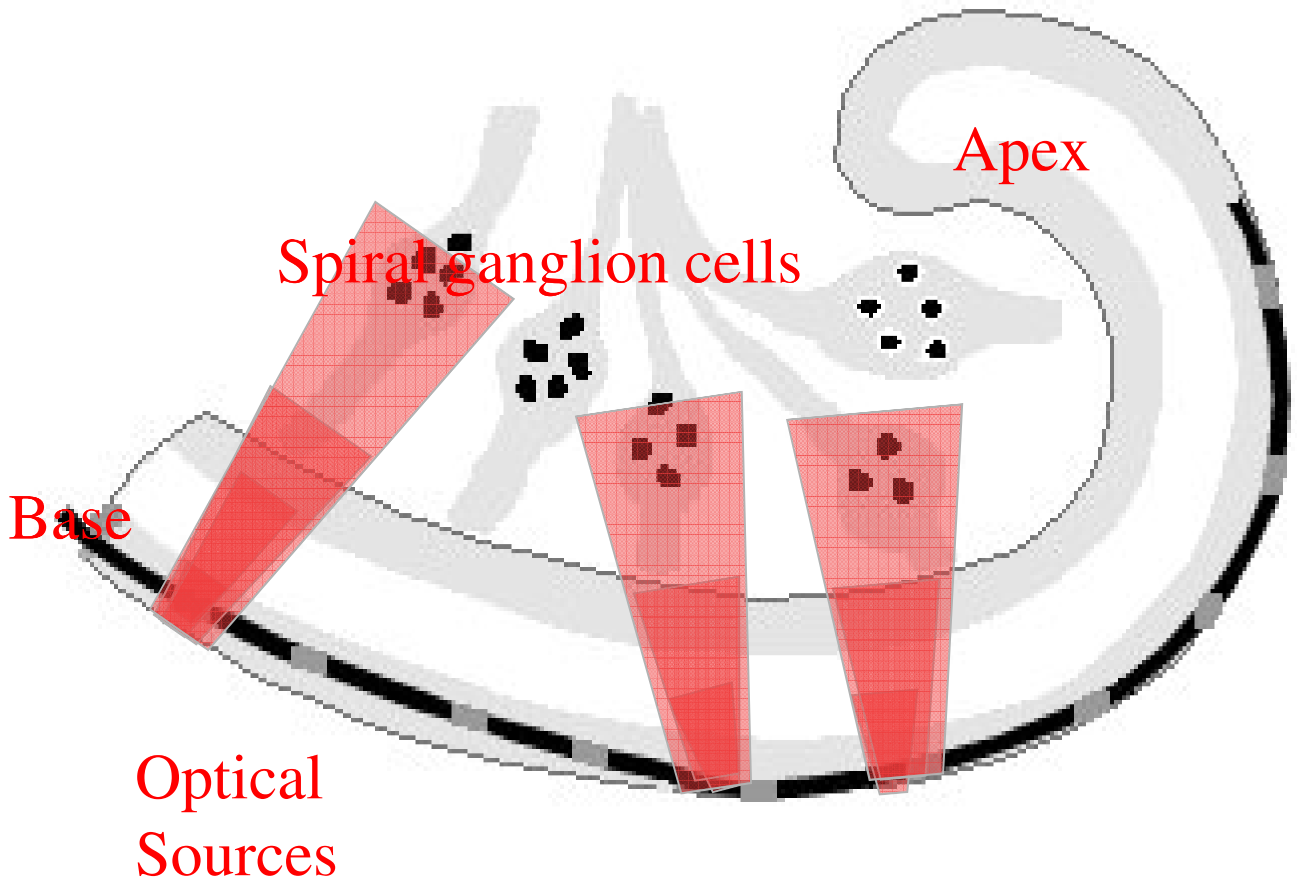
Optical Stimulation: Strength-response curve



Electrical Stimulation



Optical Stimulation



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

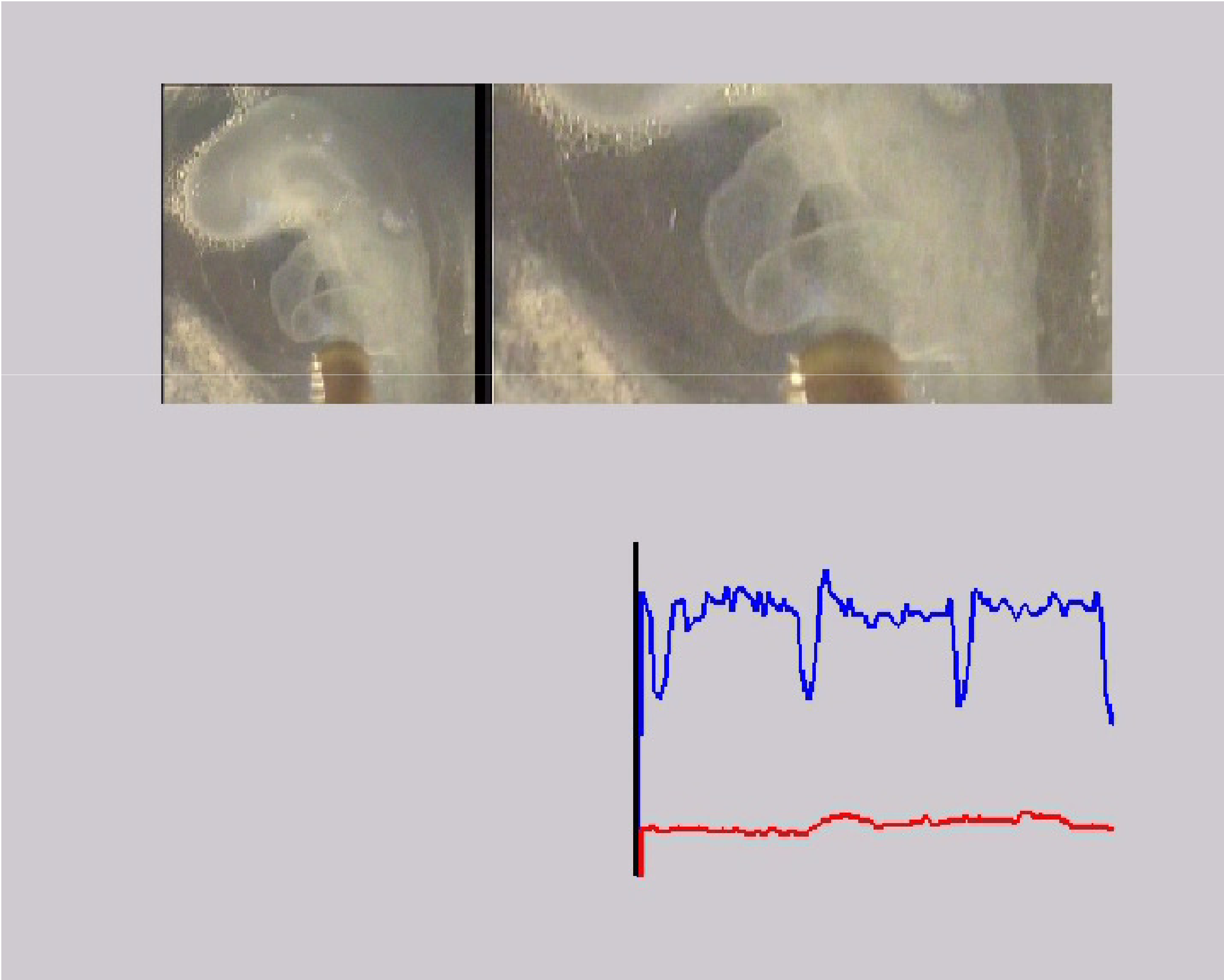
16.08.2010

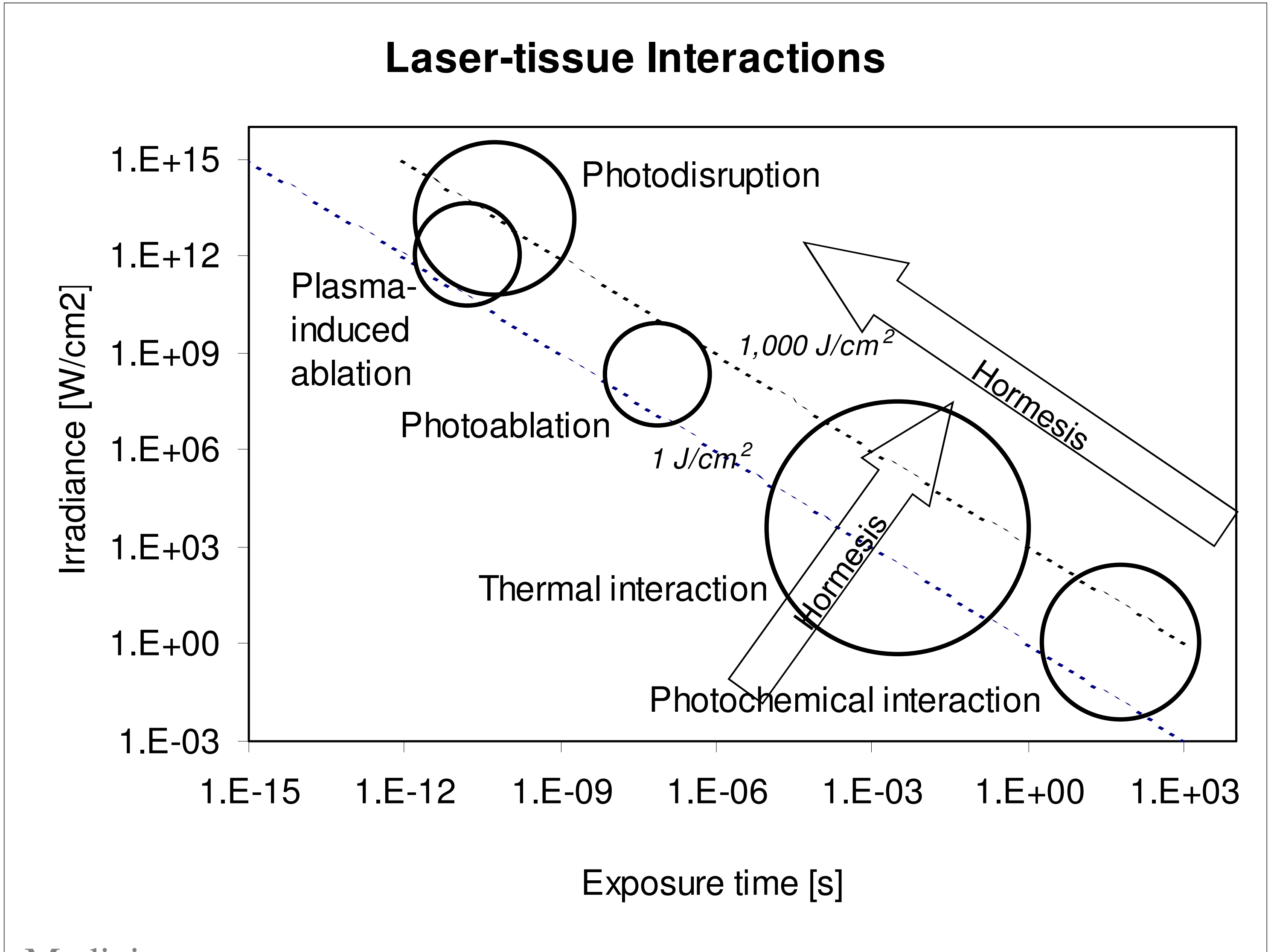
Researchers pace embryonic heart with laser

Laser mends broken heart

Jenkins MW, Duke AR, Gu S, Chiel HJ, Watanabe M, Jansen ED, Rollins AM – Optical pacing of the embryonic heart – Nature Photonics, Aug 15, doi:10.1038/nphoton.2010.166 (2010).

Pacing Movie




Laser-tissue Interactions
Photodisruption
Plasma-induced ablation
Photoablation
Thermal interaction
Photochemical interaction
Hormesis
Hormesis
1,000 J/cm2
1 J/cm2
Irradiance [W/cm2]
1.E+15
1.E+12
1.E+09
1.E+06
1.E+03
1.E+00
1.E-03
1.E-15
1.E-12
1.E-09
1.E-06
1.E-03
1.E+00
1.E+03
Exposure time [s]

Mechanisms: Hypotheses

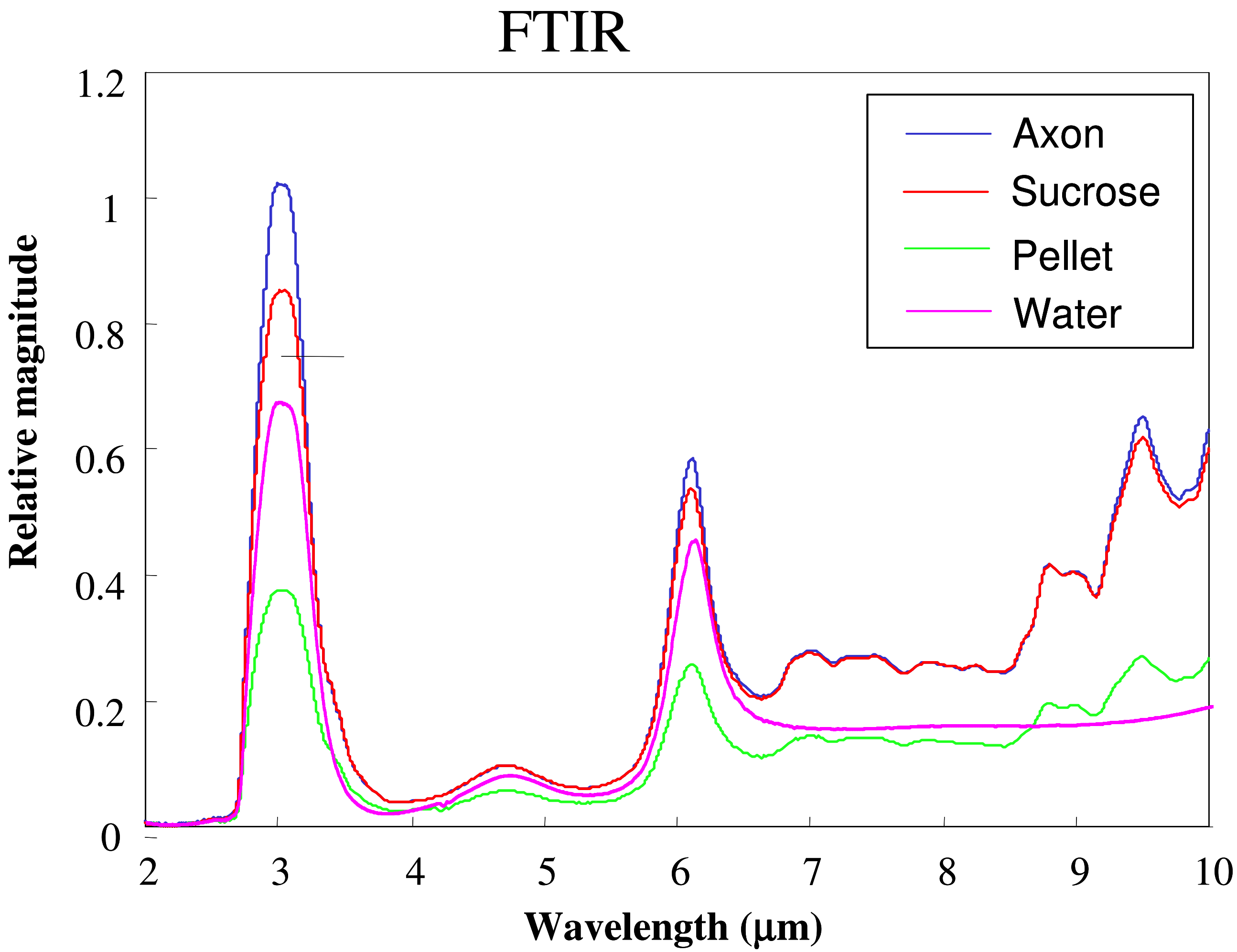
- Electric field effect?
- Photochemical
  - Alteration in the state of the ion channels?
  - Targeting specific neuro-transmitters?
- Photothermal
  - Transient membrane permeability?
  - Alteration of transmembrane proteins?
  - T or ΔT (dT/dx or dT/dt)??
- Photomechanical
  - Light induced stress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

Electric field effect

- Theoretical calculations do not predict voltage increase sufficient to produce current needed to drive action potential
  - $S_{threshold} = ½ c\varepsilon_o E_{max}^2$
  - $E_{max} = 0.155$ V/mm^2 → 0.05 mA/mm^2 (surface)
  - Field oscillations at ~10^{14} Hz
- Excite with Alexandrite laser (λ = 760 nm, 350 μs)
  - Fiber delivered (600 μm spotsize)
- Observations:
  - No stimulation for $E_p < 200$ mJ (70.7 J/cm^2)

- Conclusion: electric field effect is not the mechanism for optical stimulation

Do axons have unique optical properties?

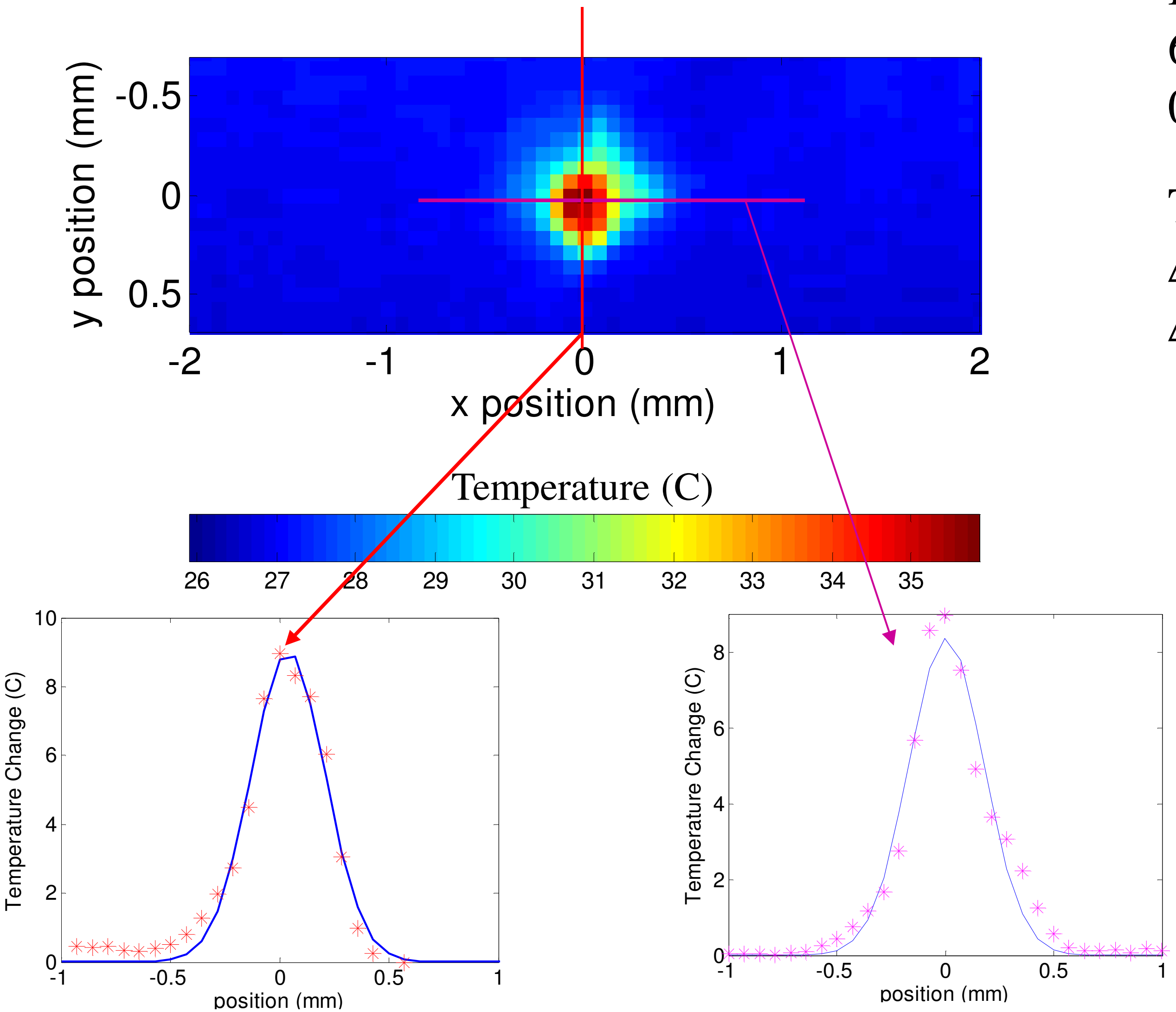


Photochemical effect

- 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

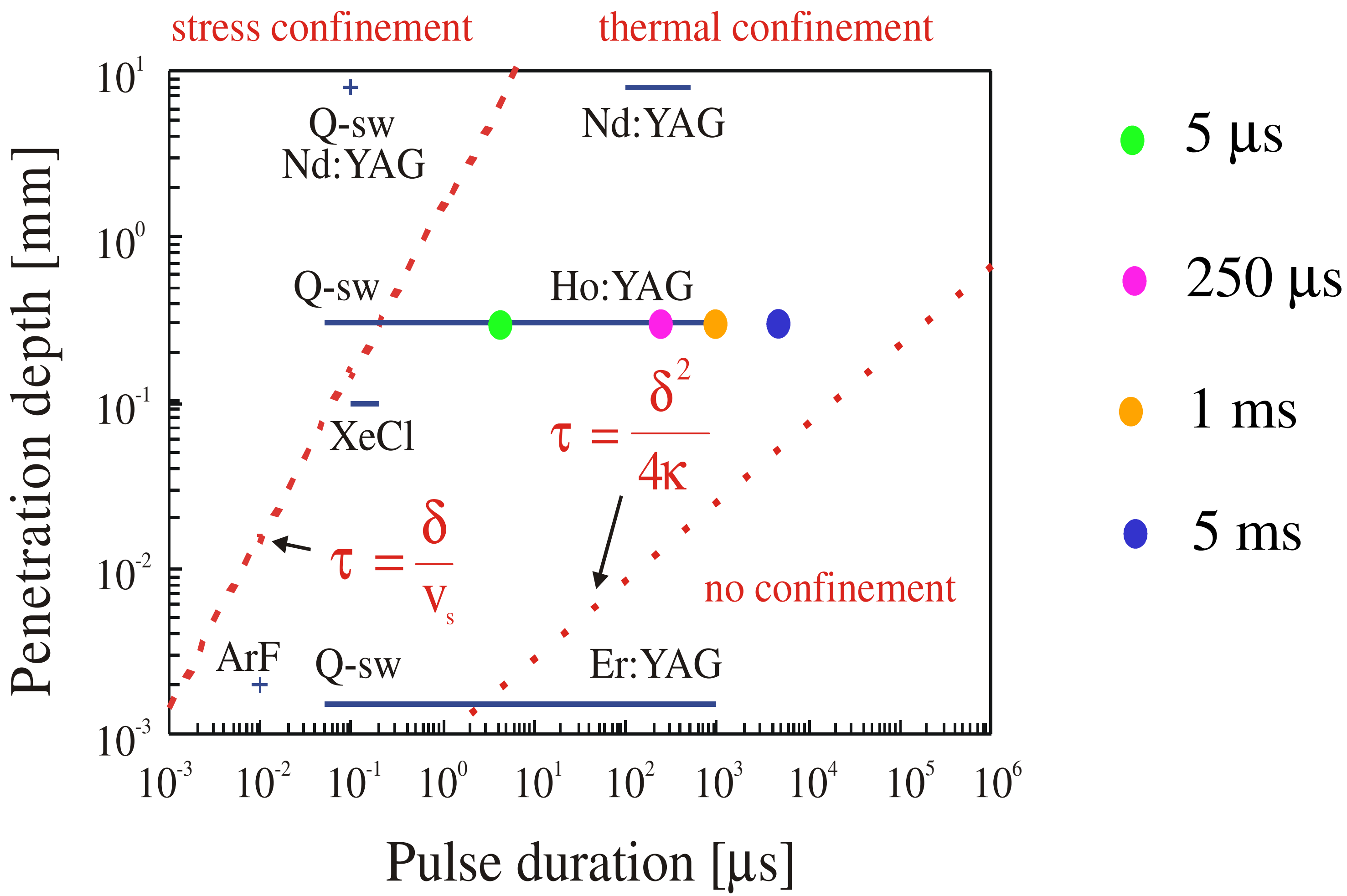
Thermal response



Ho:YAG
600 μm fiber
0.4 J/cm^2

T_{max} = 35.9 °C
ΔT_{max} = 8.9 °C
$\Delta T_{average}$ = 3.6 °C

Confinement Zones



Current Nerve Stimulator Areas of Activity

Vestibular infrared nerve stimulation	Univ of Washington (Harris)
CNS stimulation	MIT (Boyden)
Eye pain sensor	Univ of Maryland (Kao)
Cochlear scanner	Baylor (Saggau)
Vestibular nerve stimulation	Harvard (Merfeld/Lee)
Sweat gland neuropathy study	Mayo
Central and renal nerve	Johns Hopkins
Cavernous nerve	NC State (Fried)
Whisker nerves	Washington State University (Rector)
CNS and PNS	Vanderbilt (Jansen)
Cochlear INS	Northwestern University (Richter/Walsh/Izzo-Matic)
Facial nerve monitor	Northwestern University (Richter)
Facial nerve	UC Irvine (Wong)
Cardiac stimulation	CWRU (Rollins/Chiel)
Aplysia studies	CWRU/Vanderbilt (Chiel/Jansen)