A framework for constructing critical ultrasonic neuromodulation experiments

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Acknowledgments

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Why Neuromodulation?

Bypass inhibitions

Address poorly-connected regions

Pretest permanent (e.g., surgical) changes

Ultrasonic Neuromodulation

Conjecture 1: dose

Neuronal stimulus can be expressed
as a function of ultrasound dose.

The function has a root at a non-trivial dose,
where stimulus and inhibition are balanced.

Examples of single-valued dose: Ablation

Equivalent Time

Pennes Bio-Heat Transfer Equation

$$\partial T / \partial t = \kappa \nabla^2 T + Q - T / \tau$$

T temperature

t time

κ thermal diffusivity (typically 0.0014 cm^2/s)

Q heat

τ perfusion time constant (∞ in vitro)

$\rightarrow$ dose = equivalent time to reach e.g. 43°C

Thermal Index TI = power delivered / power for +1C°

Mechanical Index MI = Peak Neg. Pressure (MPa) / $\sqrt{f_C}$

f_C central frequency (MHz)

One-dimensional dose-response

dose, $d \in \mathbb{R}_+$ $\rightarrow$ response, $r(d) \in \mathbb{R}$

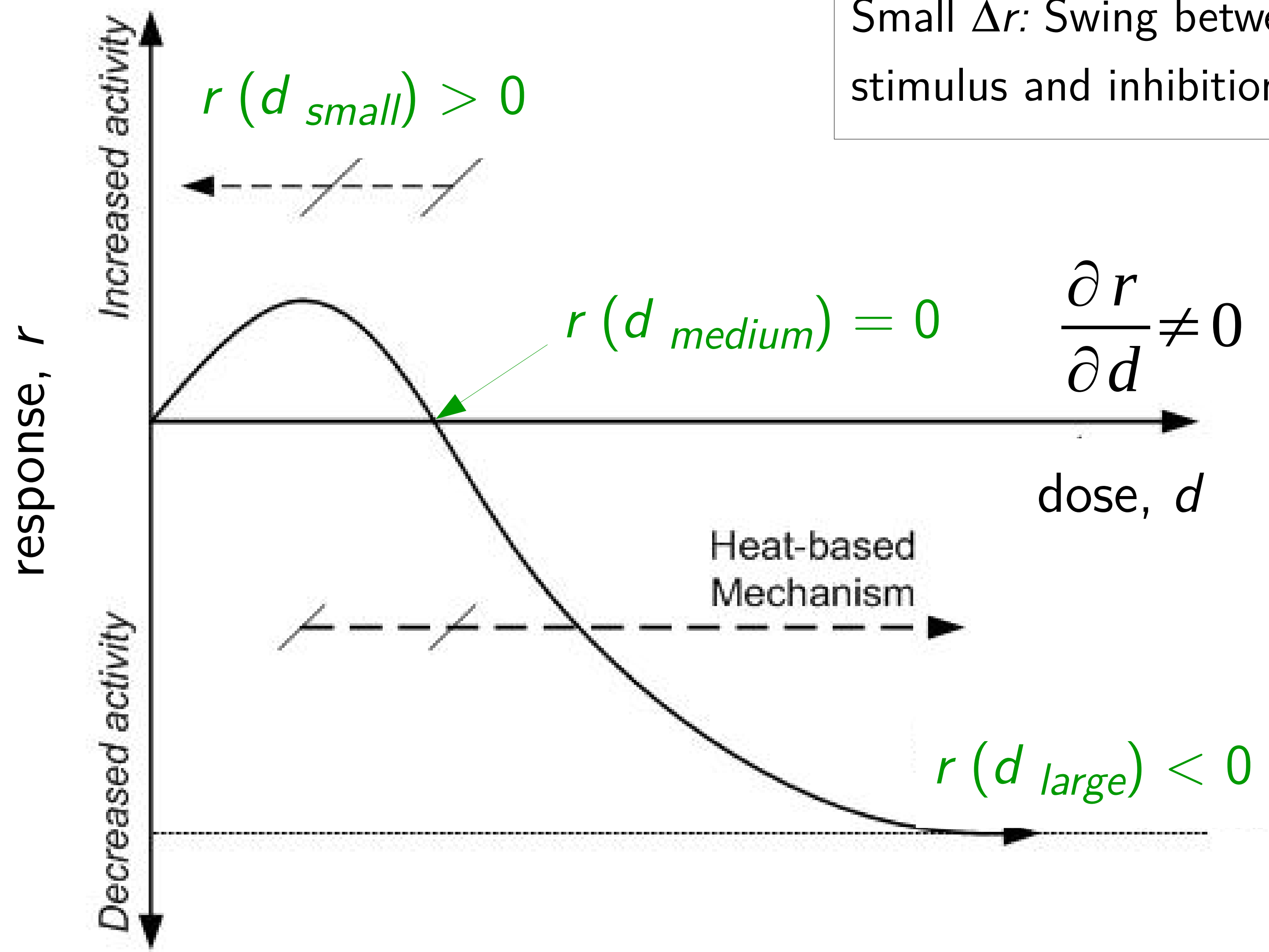
inhibition $r < 0$
stimulation $r > 0$

$$r\,(d_{\,small}) > 0 \qquad \cup \qquad r\,(d_{\,large}) < 0$$

intermediate value theorem $\Rightarrow\ \exists\ r\,(d_{\,medium}) = 0$
assuming $r(d)$ is well-behaved

Single-valued zero

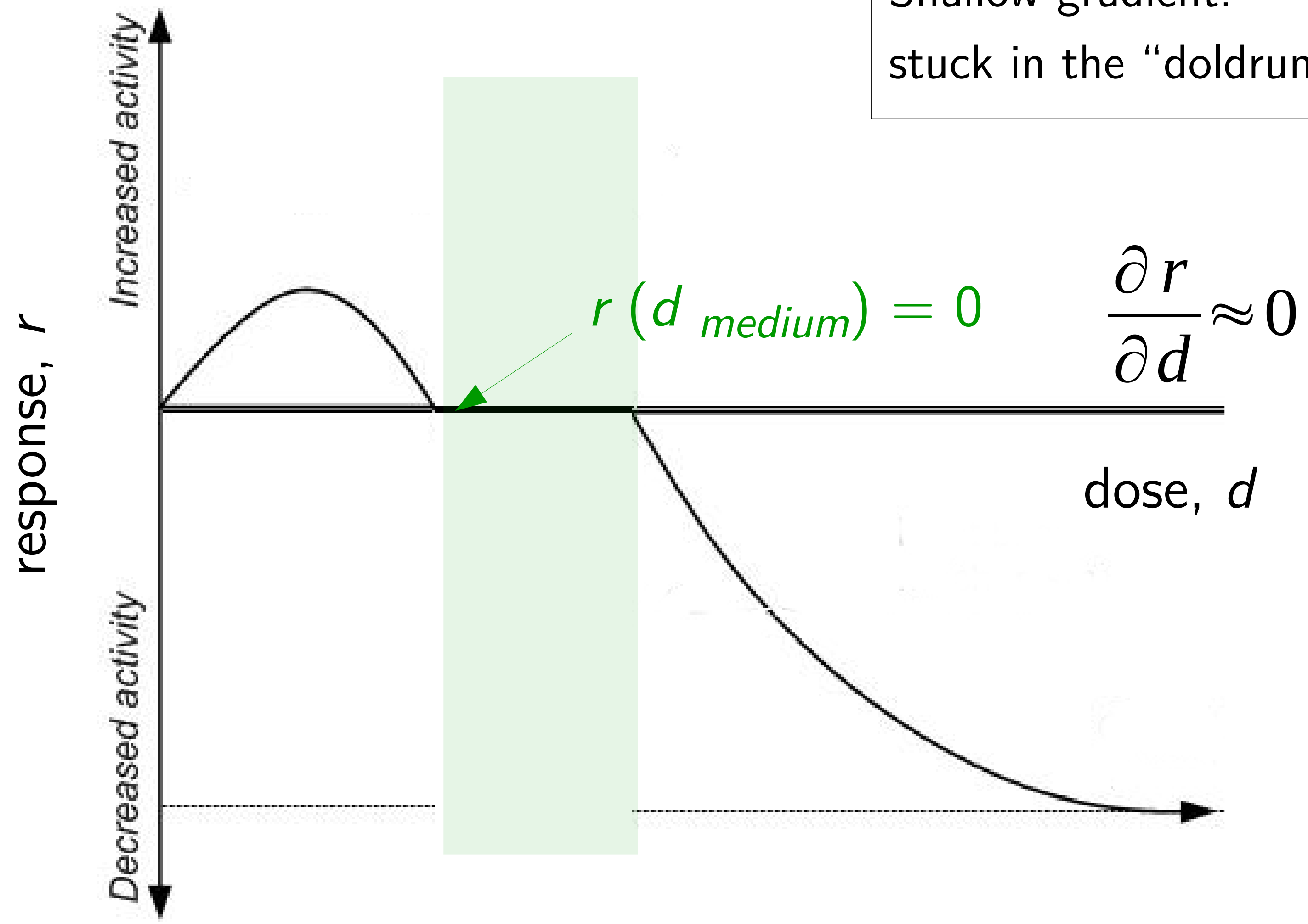
Small Δr: Swing between stimulus and inhibition.



Muratore & Vaitekunas 2013
Acoustics Today

Extended zero: No apparent response

Shallow gradient:
stuck in the "doldrums".



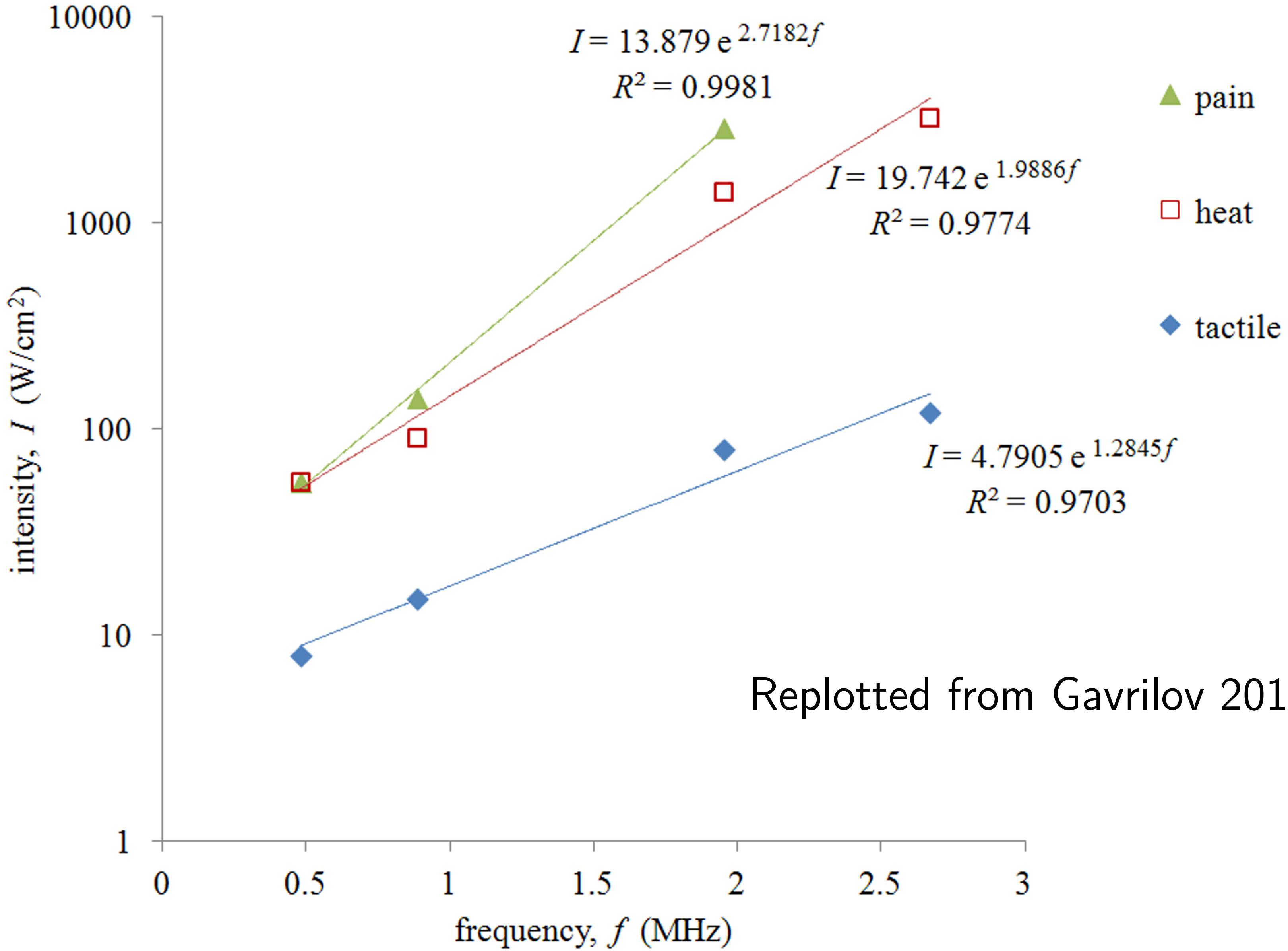
Multi-valued dose: Low-intensity stimuli

Neuronal tissue responds to many dose parameters:

- Frequency
  - carrier
  - pulse repetition frequency
  - modulation
- Intensity
- Time
  - duty cycle
  - total insonation

Are there zeros for multi-valued doses?

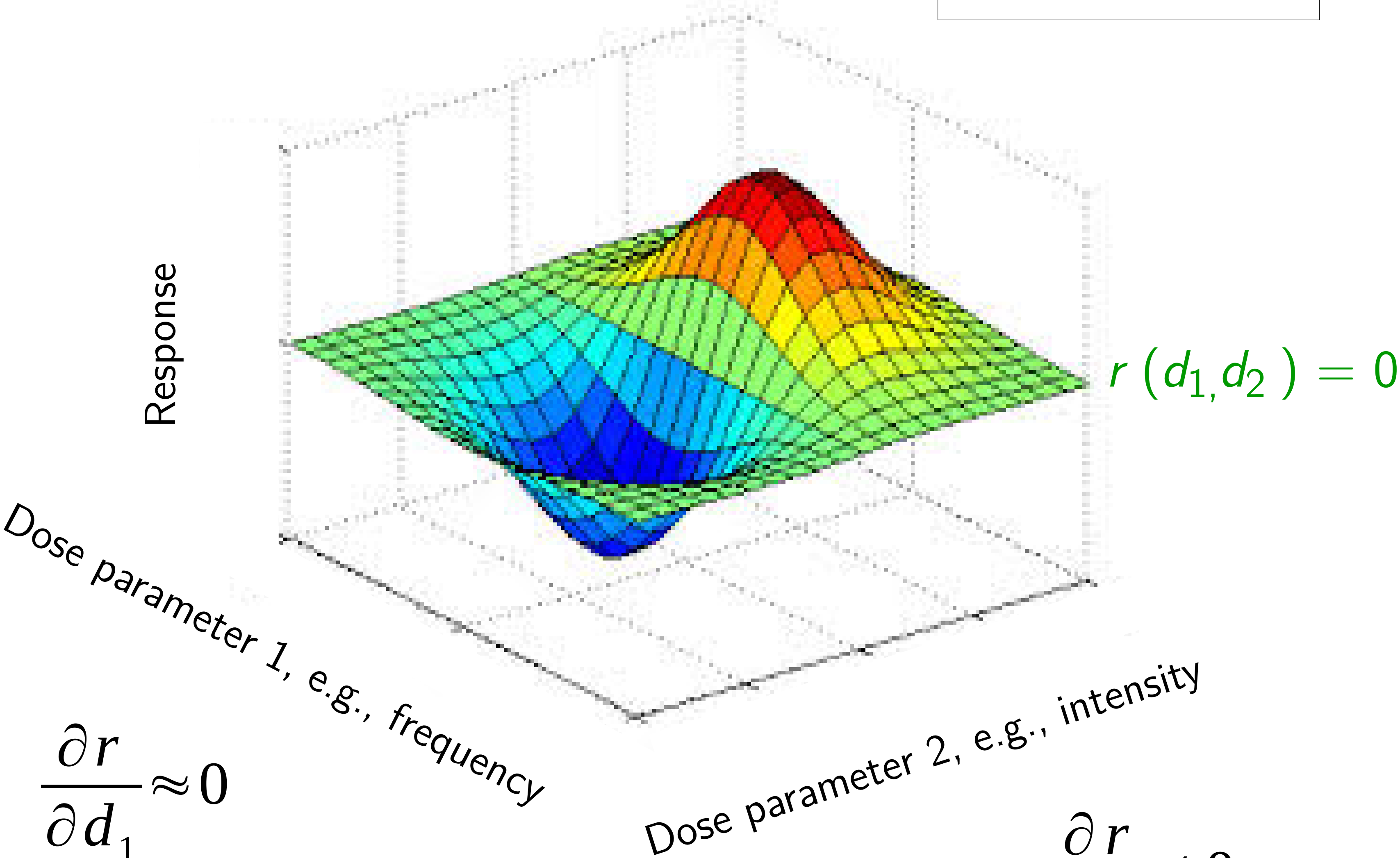
Fingertip responses to intensity and frequency



Replotted from Gavrilov 2012

Two-dimensional dose; One-dimensional response

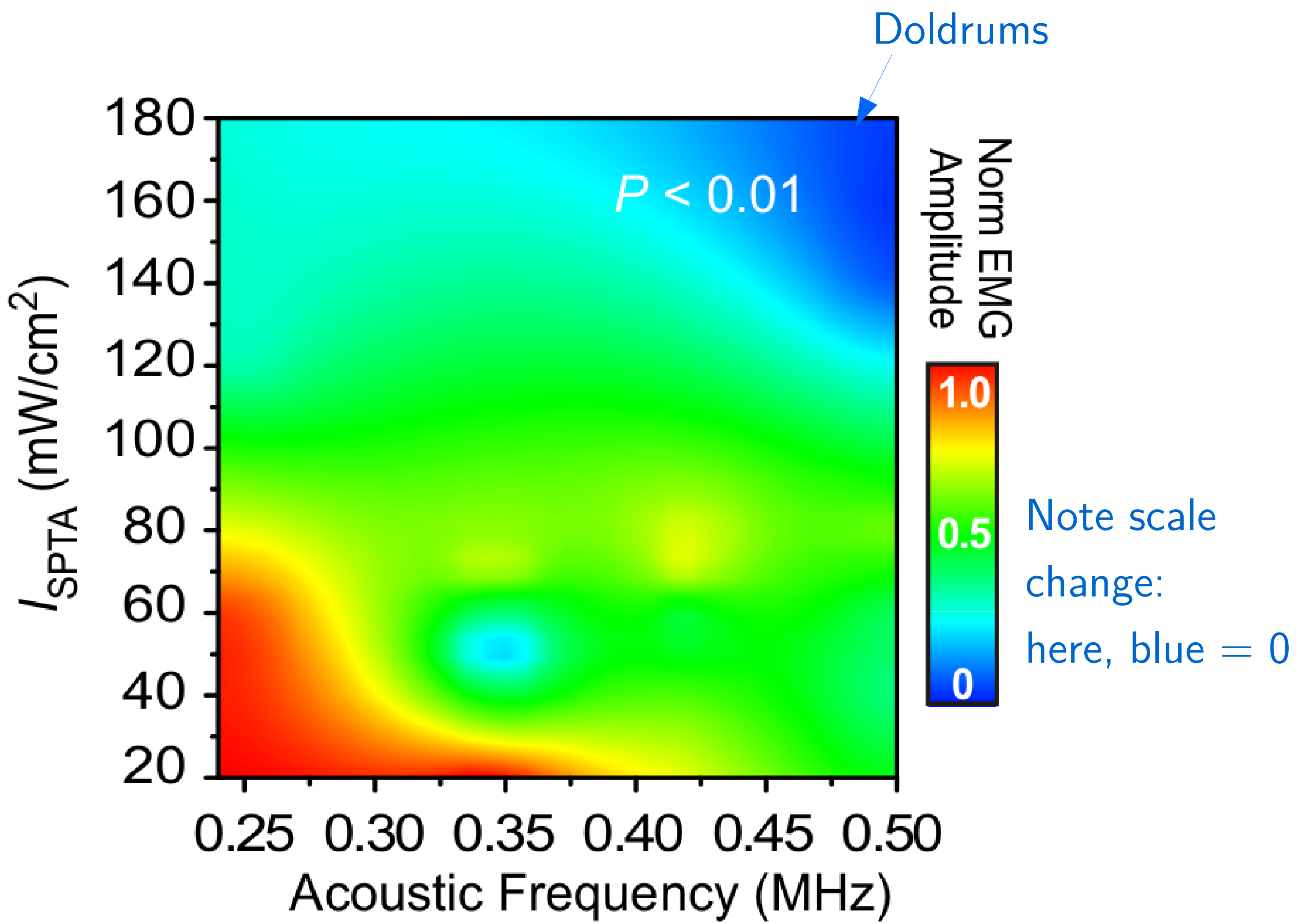
Doldrums remain



$$\frac{\partial r}{\partial d_1} \approx 0$$

$$\frac{\partial r}{\partial d_2} \neq 0$$

Mouse brain responses to intensity and frequency



Tufail et al. Neuron 2010

n-dimensional dose; one-dimensional response

does parameter $d_i \in \mathbb{R}$

dose vector $(d_1, d_2, \ldots d_n) \in \mathbb{R}^n$

response $r(d_1, d_2, \ldots d_n) \in \mathbb{R}$

Graph of $r\ (d_1, d_{2,\ldots} d_n)$:

$(n+1)$ dimensional vector $(d_1, d_{2,\ldots} d_{n,}\ r\ (d_1,\ d_2,\ \ldots d_n))$

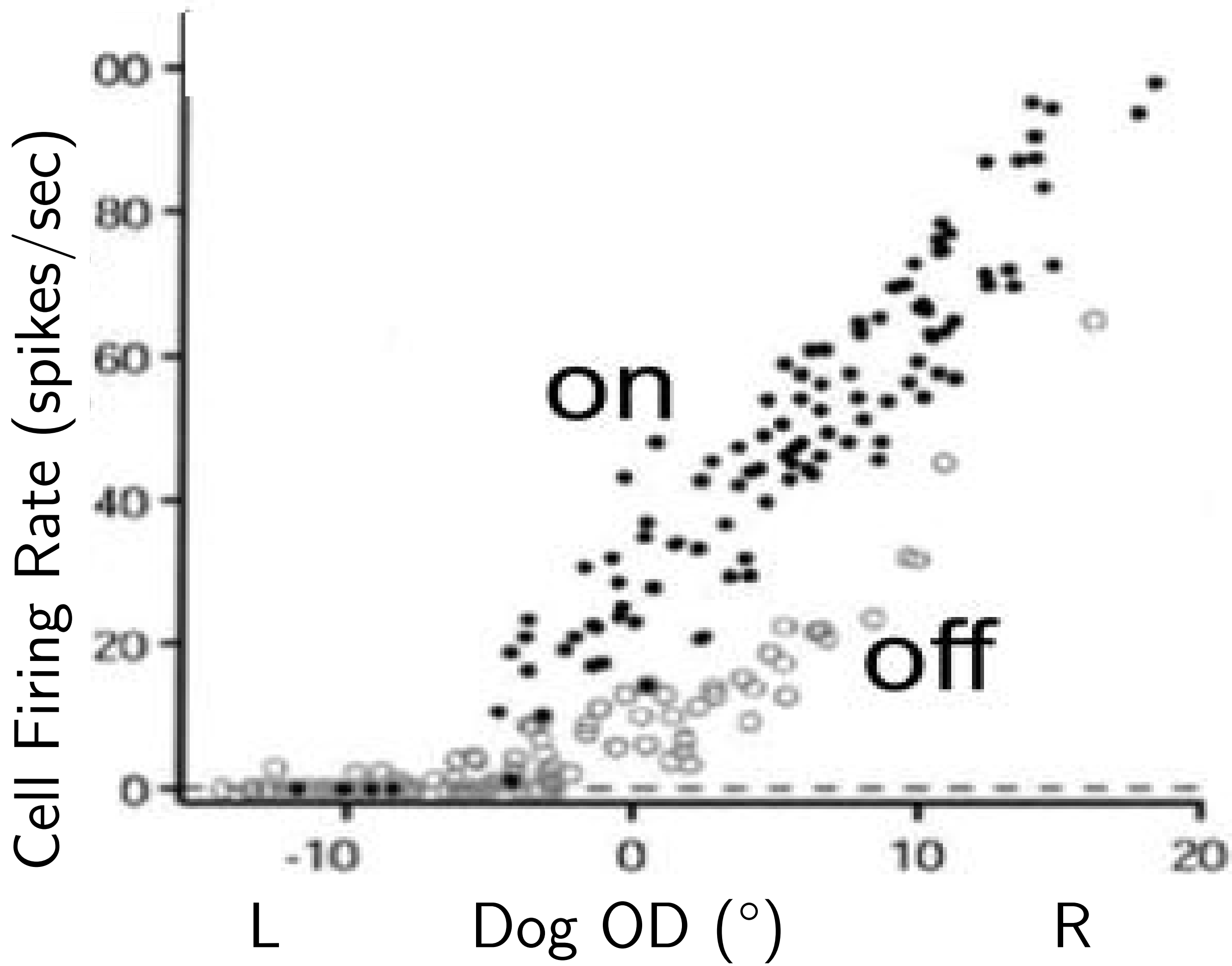
0-level set: $(n+1)$ dimensional vector $(d_1, d_{2,\ldots} d_{n,}\ 0)$

Solution set: n dimensional vector $(d_1, d_{2,\ldots} d_n)$

doldrum dimension ≤ dose dimension

Hysteresis: Out of the doldrums

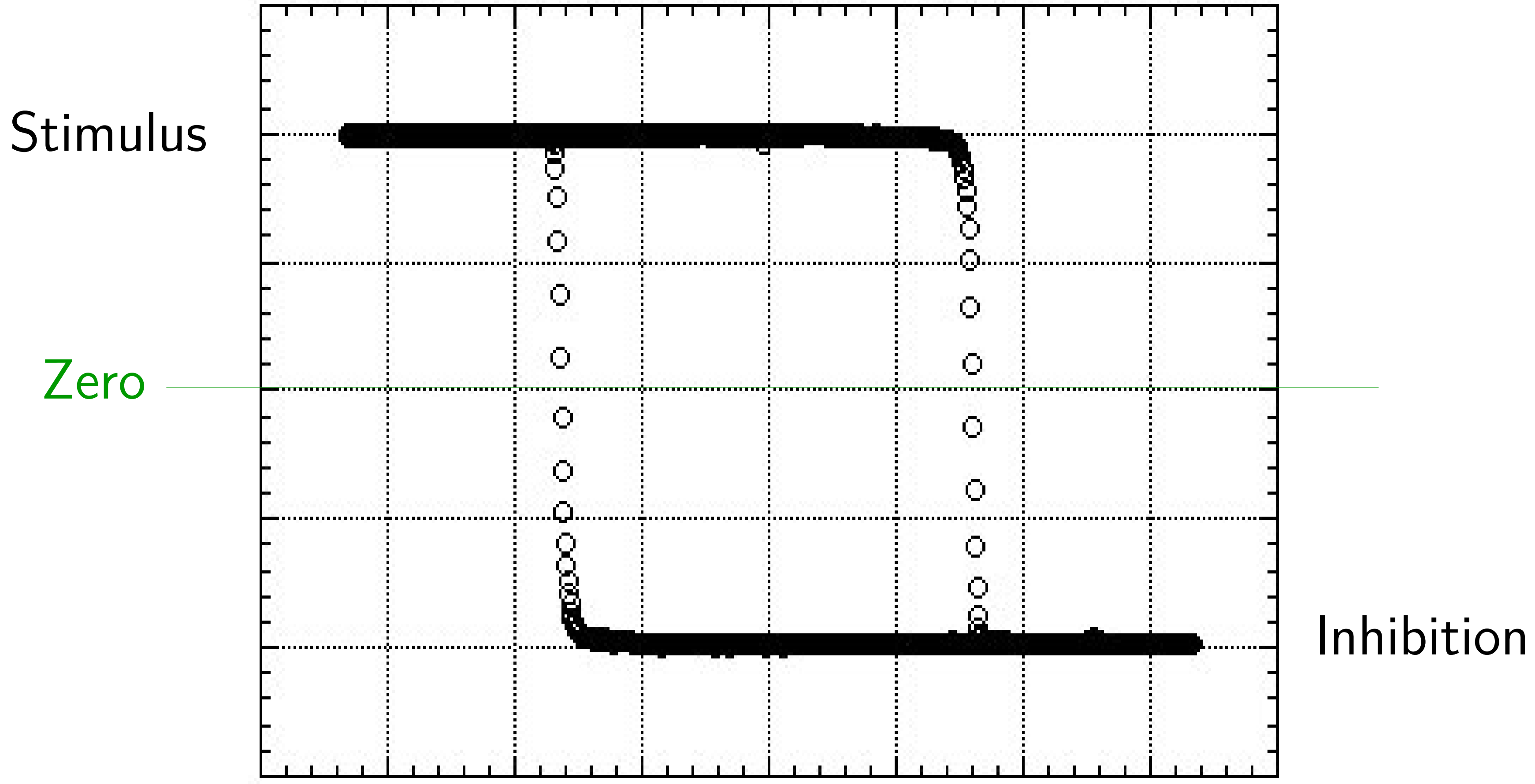
neuronal history → hysteresis



Nikitchenko 2010 Neural Comput.

Hysteresis: Out of the doldrums

Idealized model



Schrader 2006 U W Australia

Conjecture 2: time

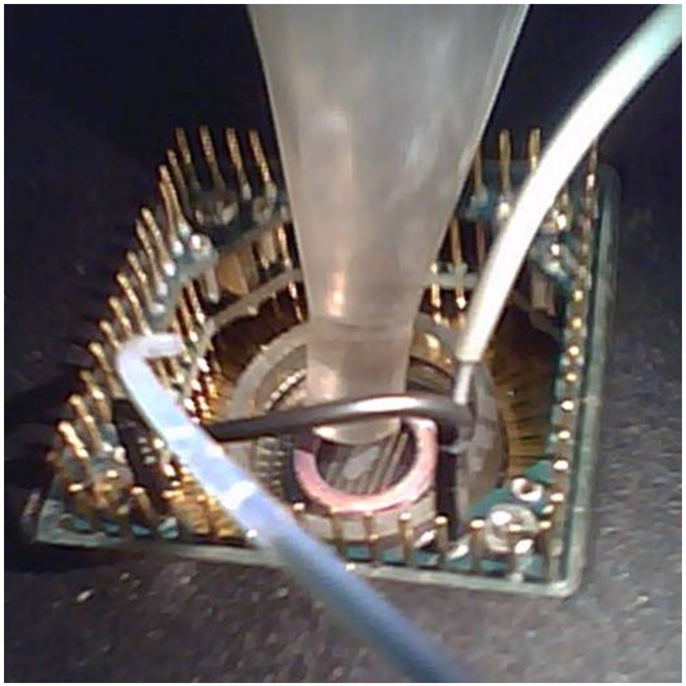
An acoustic beam can modulate a neuronal region for longer than the duration of the insonation.

$$\text{Beam duration} < \text{Modulation time}$$

Converse An acoustic beam can modulate a neuronal region for shorter than the duration of the insonation.

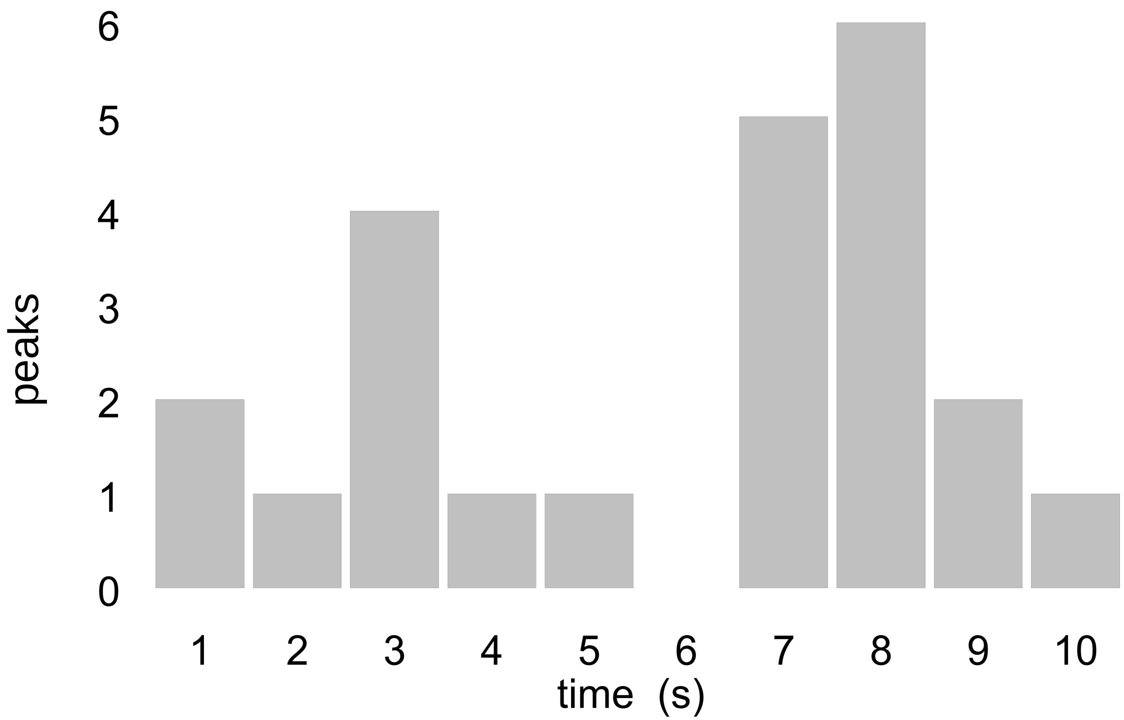
$$\text{Modulation time} < \text{Beam duration}$$

Beam duration < Modulation time



time until rat hippocampal response

following 30 ms 3 kPa ultrasound stimulus



4.04 MHz

42 mm diameter, 90 mm focal length, f/2.1

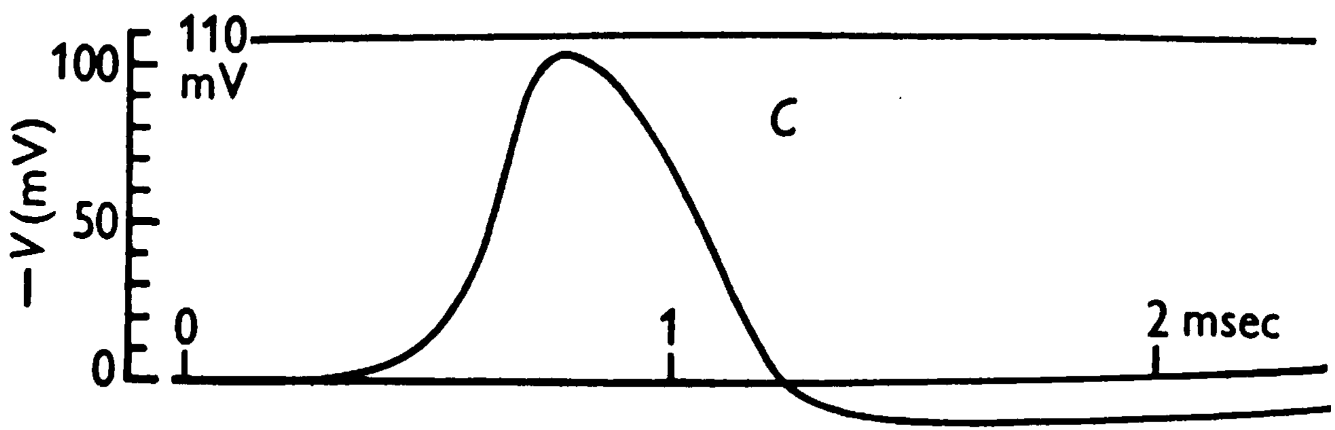
2 W, 240 W/cm^2 nominal

Muratore Acoustics08 Paris

Modulation time < Beam duration

Refractory periods

Hodgkin-Huxley	milliseconds
ATP depletion	minutes
inhibition	hours



squid action potential, Hodgkin-Huxley 1952

Conjecture 3: space

An acoustic beam can modulate a neuronal region larger than that which it insonifies.

$$\text{Beam width} < \text{Modulation area}$$

Converse The spatial precision of ultrasonic neuromodulation can be considerably finer than the incident acoustic beam width.

$$\text{Modulation area} < \text{Beam width}$$

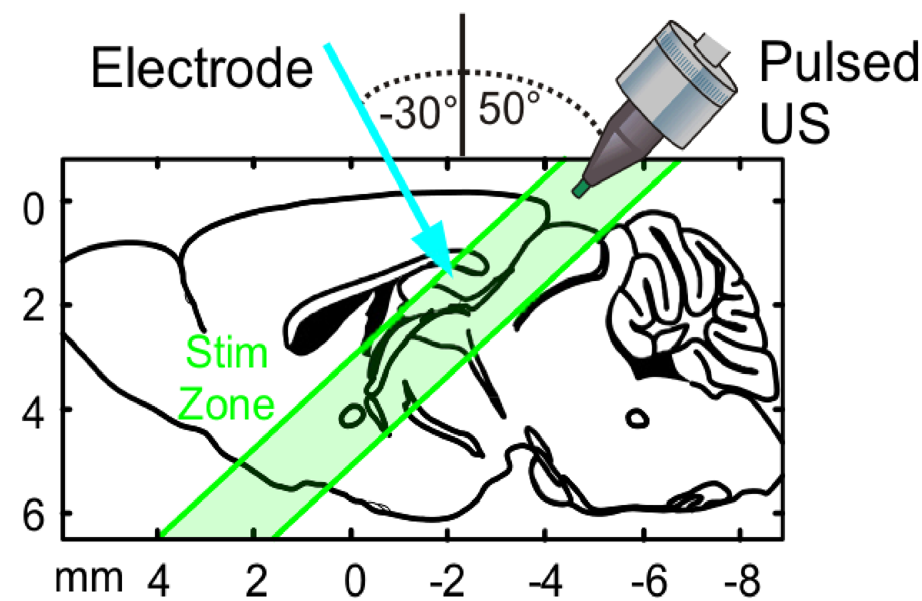
Beam width $<$ Modulation area

The <u>brain</u> exhibits widespread responses to localized insonification.

Vykhodtseva and Koroleva ISTU 2005 - spreading depression in rat

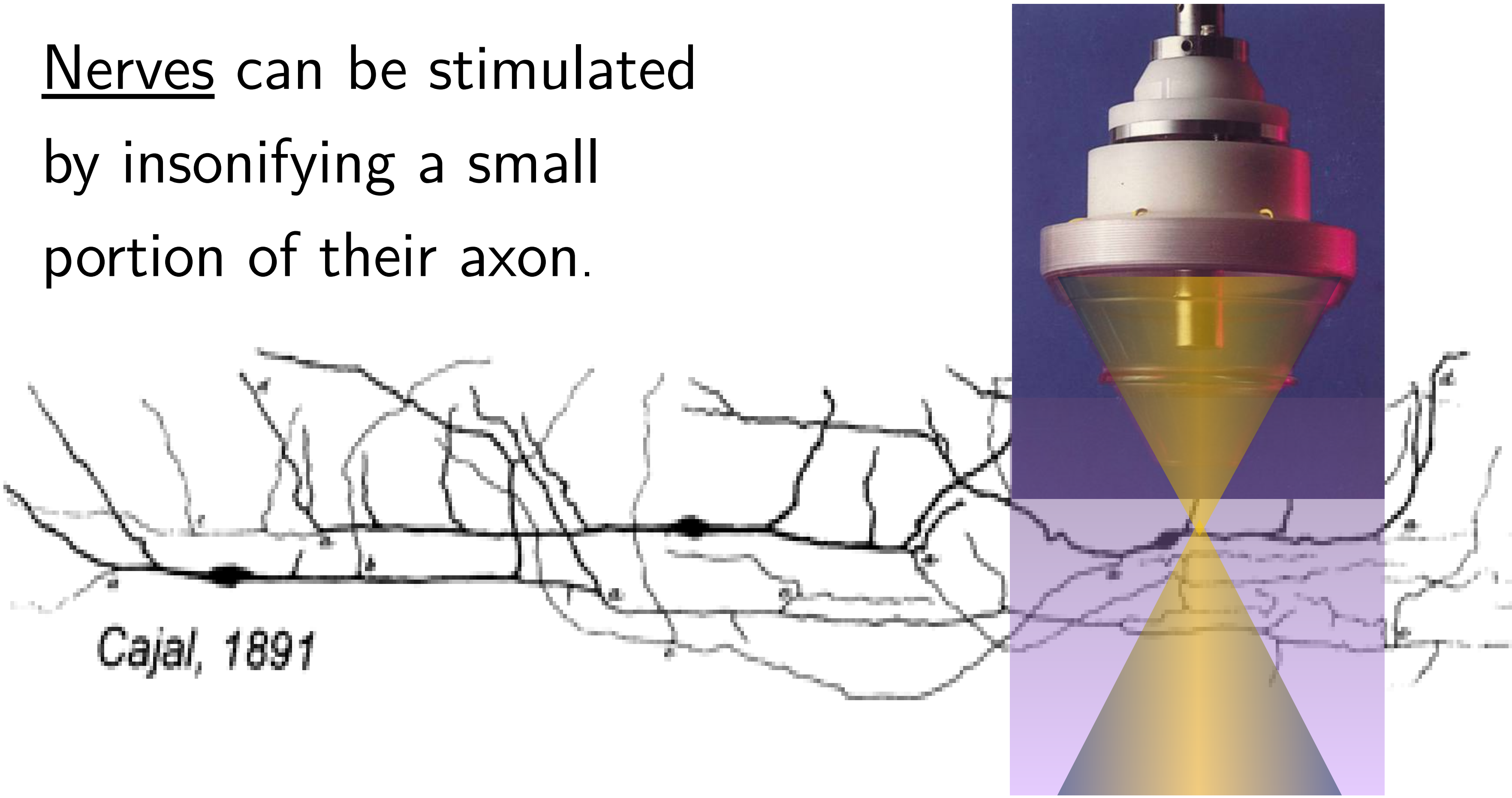
Muratore et al. ISTU 2008 - hippocampus responds beyond beam

Tufail et al. 2010 Neuron - rat responds to narrow beam:



Beam width < Modulation area

<u>Nerves</u> can be stimulated by insonifying a small portion of their axon.



Gavrilov *Use of Focused Ultrasound* 2014

Vaitekunas 2009 US Patent 7553284

Modulation area < Beam width

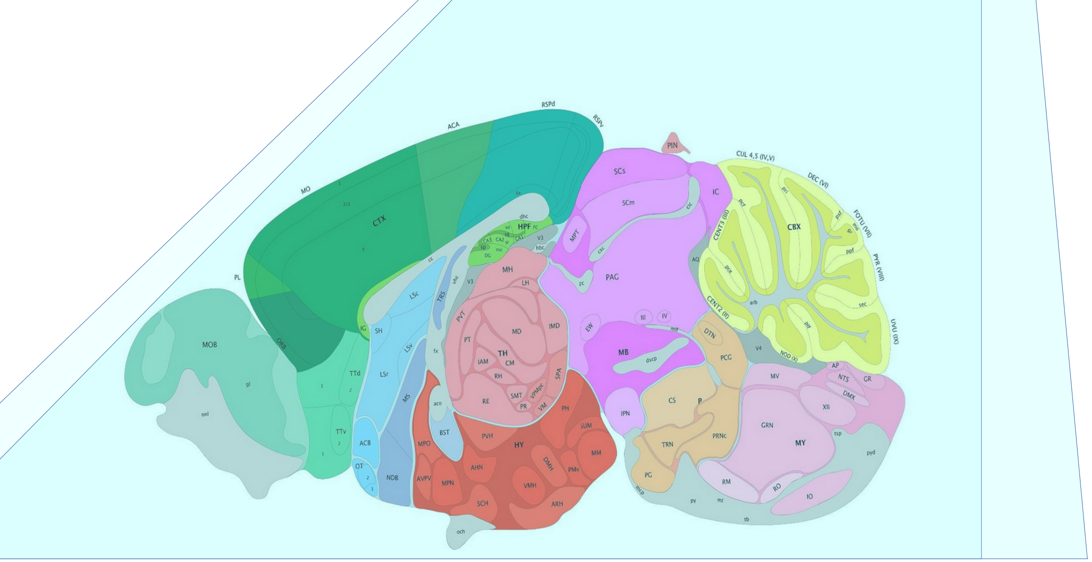
<u>Brain</u>: Across the cortex, displacements of acoustic beams smaller than the beam width can achieve fine motor control in the mouse.

- ISTU Heidelberg

edge effect

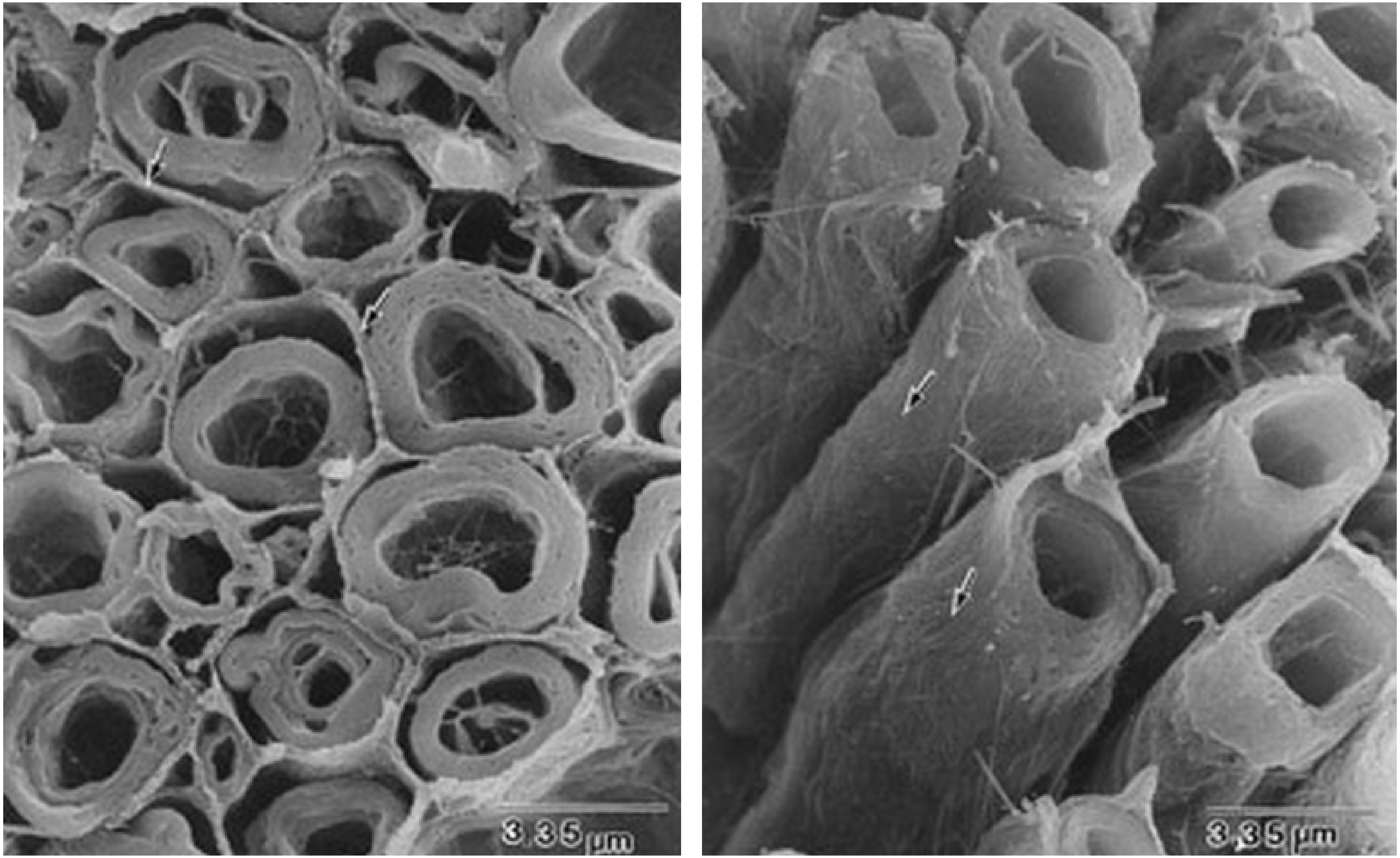
or

centroid?



Allen Mouse Brain Atlas

Modulation area < Beam width



3 μm

Nerve Fibers: Tanisaki et al. Int. J. Morphol. 2005.

Modulation area $<$ Beam width

Nerves classified by Erlanger-Gasser system

Type	Aα	Aβ	Aγ	Aδ	B	C
Conduction velocity	120					0.6 m/s
Diameter	25					0.1 μm
Myelination	thick			thin		none
Function	motor --$>$					
		$<$---				sensory
Bioeffective US dose	high					low

Bioeffects

Ablation Montieth et al. J Neurosurgery 2013

Reversible Blocking Jabbary 2011, Colucci UMB 2009, Foley UMB 2004

Conclusions

In peripheral and central nervous systems:

- Balance of stimulus and inhibition can mask bioeffects.
- Mismatch of beam and response times can be exploited for experimental effects.
- Mismatch of beam and target sizes can be exploited for clinical effects.