AUTONOMOUS NEURAL CONTROL OF GASTROPARESIS

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Characteristics of Gastroparesis

Diagnosis

- Symptoms
  - Nausea
  - Vomiting
  - Early satiety
- Delayed gastric empting on nuclear scintigraphy
- Absence of anatomic gastric outlet obstruction

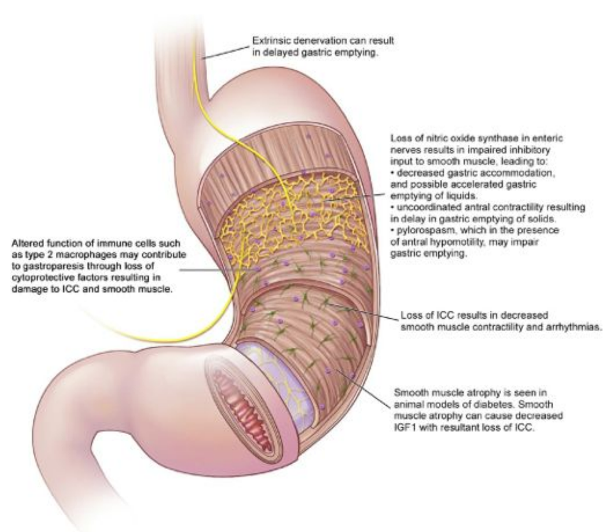
Epidemiology

- **Incidence (per 100,000)**
  - 2.4 (M)
  - 9.8 (F)
- **Prevalence (per 100,000)**
  - 9.6 (M)
  - 37.8 (F)
- **Survival** (5 year)
  - 80% ($p < 0.05$ vs. expected)

Jung et al. Gastroenterology 136:1225-1229, 2009

Etiology of Gastroparesis

- **Diabetes Mellitus**: neuropathy (?)
- **Idiopathic**: post-viral, myopathy, neuropathy, autoimmune
- **Post-surgical**: vagotomy, Nissen fundoplication



Gastroparesis Treatment Options

- Diet
- Promotility agents
- Anti-nausea medication
- GJ (gastrojejunostomy) tube
- TPN (total parenteral nutrition)
- **GES (gastric electrical stimulation)**

Enterra® II Gastric Electrical Stimulator
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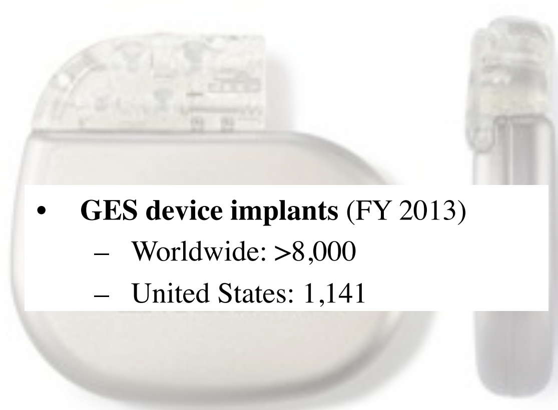
State of Gastric Electrical Stimulation

- Mechanism unknown
- Up to <u>six months</u> for symptom improvement
- No correlation between symptom improvement and improvement in gastric emptying rate
- **GES efficacy**
  - Diabetic: 80-90%
  - Idiopathic: 60-70%
  - Post-surgical: 60%



- **GES device implants** (FY 2013)
  - Worldwide: >8,000
  - United States: 1,141

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(Medtronic, Inc.)

Collaborate and Translate

IU Gastroenterology/Hepatology

Purdue Biomedical/Electrical Engineering

The Gastroparesis Team

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Indiana University School of Medicine

Goals for Gastroparesis

- Improve patient care
  - Enhance efficacy, reduce cost-of-care
  - Simplify device tuning protocols
- Translate promising biomedical tech to the clinic
  - Leading physicians/investigators
  - Leading engineering school
- Develop next-generation, personalized medicine
  - Biomarker/response marker discovery
  - Self-optimizing therapy

<u>Central Hypothesis</u>

Gastric electrical stimulation modulates nausea and vomiting through a vagal mechanism

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Problems with GES Therapy

- Variable (often short) battery life
- Stimulating lead failure
  - Dislodge from generator
  - Break
- No measurable ("objective") response marker
- No standard device tuning protocol

Enterra® II Gastric Electrical Stimulator
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Our Solution: Battery Life

• Variable (often short) battery life	⟺	Wireless power transfer and supercapacitor technology
• Stimulating lead failure – Dislodge from generator – Break		Miniature, leadless stimulation and measurement technology
• No measurable (“objective”) response marker		Noninvasive measurement of vagal nerve response to GES
• No standard device tuning protocol		Autonomous neural control technology

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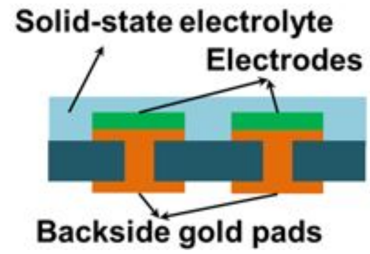
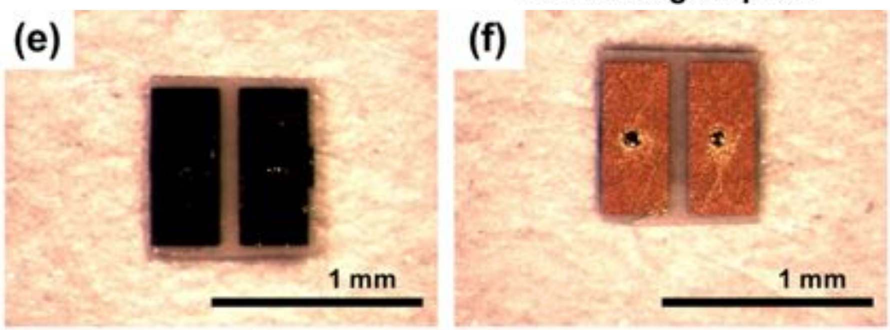
Demo: Wireless Power Transfer

Power Storage: Supercapacitor

- Integrated within package
- Size < 1 mm^2 relevant to buoy antenna design
- Capacity: 1 μW/hour for 16 hours on a single charge





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Our Solution: Stimulating Leads

- Variable (often short) battery life — Wireless powering technology
- Stimulating lead failure
  - Dislodge from generator
  - Break

  Miniature, leadless stimulation and measurement technology
- No measurable ("objective") response marker — Noninvasive measurement of vagal nerve response to GES
- No standard device tuning protocol — Autonomous neural control technology

Demo: Leadless Pressure Sensor

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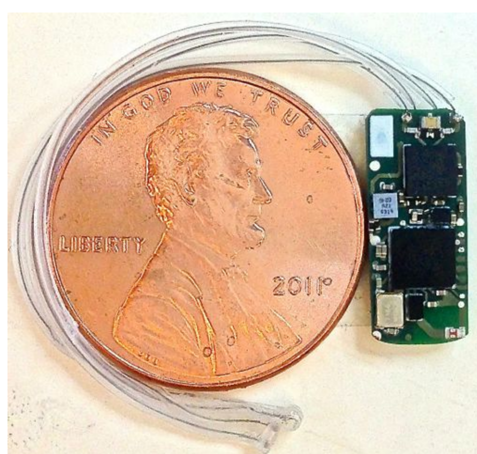
The Bionode (ZIPH Labs)

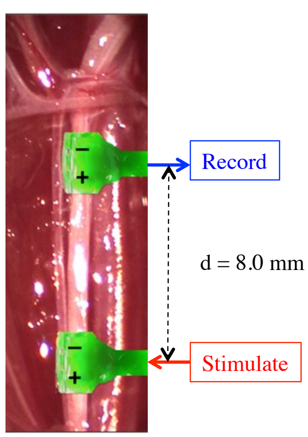
- Wireless power and data transfer
- Light (<4g) fully implantable, 5x8.5x2 mm package
- Electrical stimulator option, pulses as short as 8us, 2mA
- Fiber optic stimulator option for optogenetic research
- 1 or 2 recording channels up to 5K samples/s
- Input signal amplitude range of 35uV - 10mV
- Frequency response of 5 - 2500 Hz
- Wave Stage compatible with Windows, OS X, and Linux

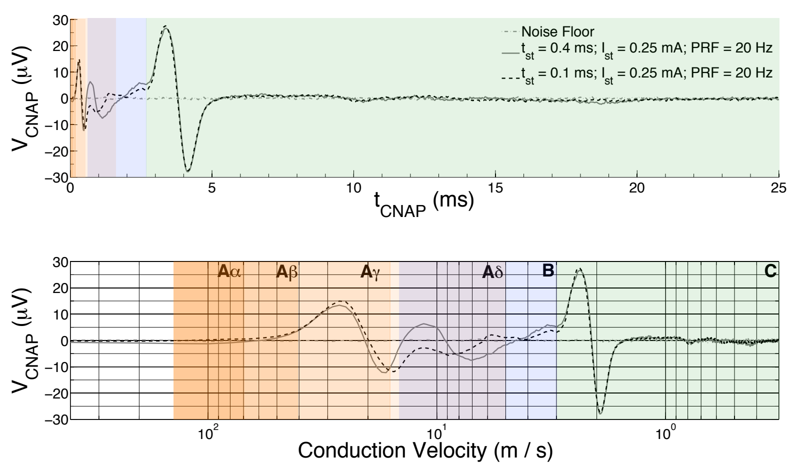


Our Solution: Response Markers

- Variable (often short) battery life — Wireless powering technology
- Stimulating lead failure — Miniature, leadless stimulation and measurement technology
  - Dislodge from generator
  - Break
- No measurable ("objective") response marker ⟺ Noninvasive measurement of vagal nerve response to GES
- No standard device tuning protocol — Autonomous neural control technology

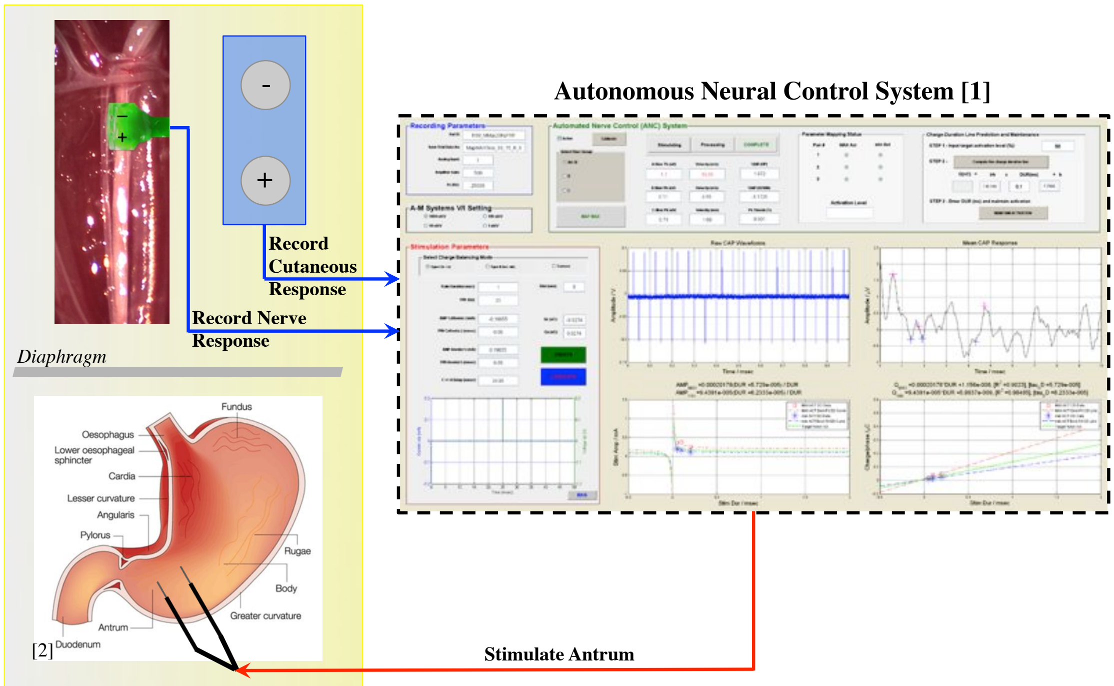
The Compound Nerve Action Potential





[1] *In press* - M. P. Ward *et al*., "A flexible platform for rapid biofeedback control and personalization of electrical nerve stimulation therapy," Aug 2014.
[2] Herbert S. Gasser. (1941). *The classification of nerve fibers*. Ohio J Sci 41, p. 145-159.

Experimental Setup: Gastric Electrical Stimulation in Rat



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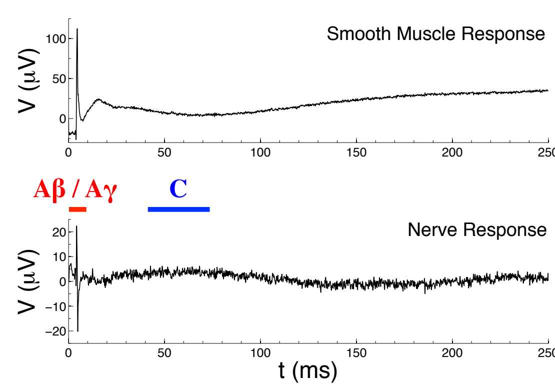
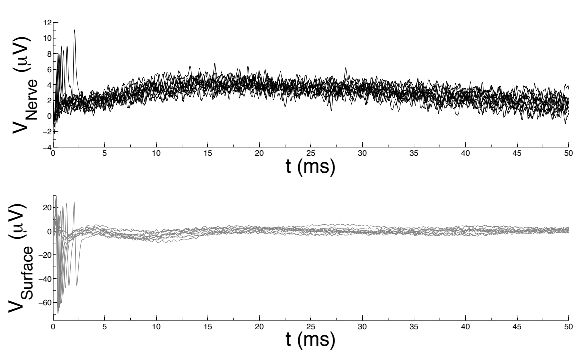
[2] Richard M. Peek, Jr & Martin J. Blaser. (2002). "Helicobacter pylori and gastrointestinal tract adenocarcinomas." Nature Reviews Cancer **2**, pp. 28-37.

Preliminary Observations in Rat

- Reproducible bioelectric activity from left cervical vagus (antral stimulation)
  - Smooth muscle component
  - Nerve component
- Activation threshold depends on stimulating electrode placement





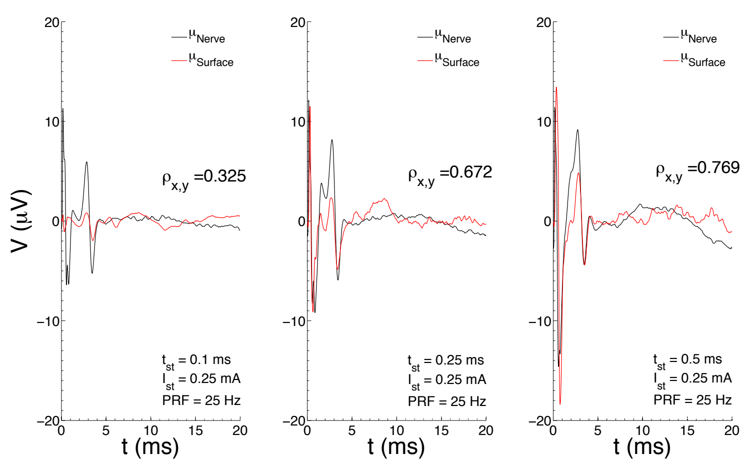
- Response latency is inversely related to stimulus pulse amplitude
- The response marker is measurable from the nerve and skin surface
- Response averaging required to enhance signal-to-noise ratio

No GES-evoked Response Following Vagotomy

Pre-Vagotomy

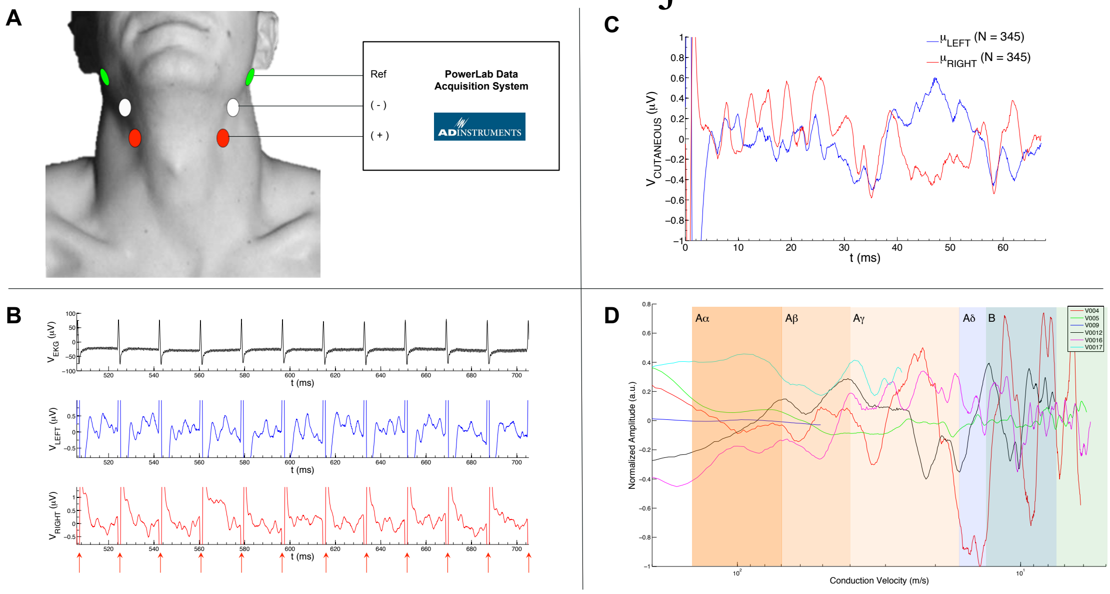
Post-Vagotomy

Vagal CAP Measurement with Cutaneous Electrodes in Rat



Black trace: Cuff electrode recording (N = 20)
Red trace: Cutaneous electrode recording (N = 20)

Vagal CAP Measurement with Cutaneous Electrodes in Human Subjects



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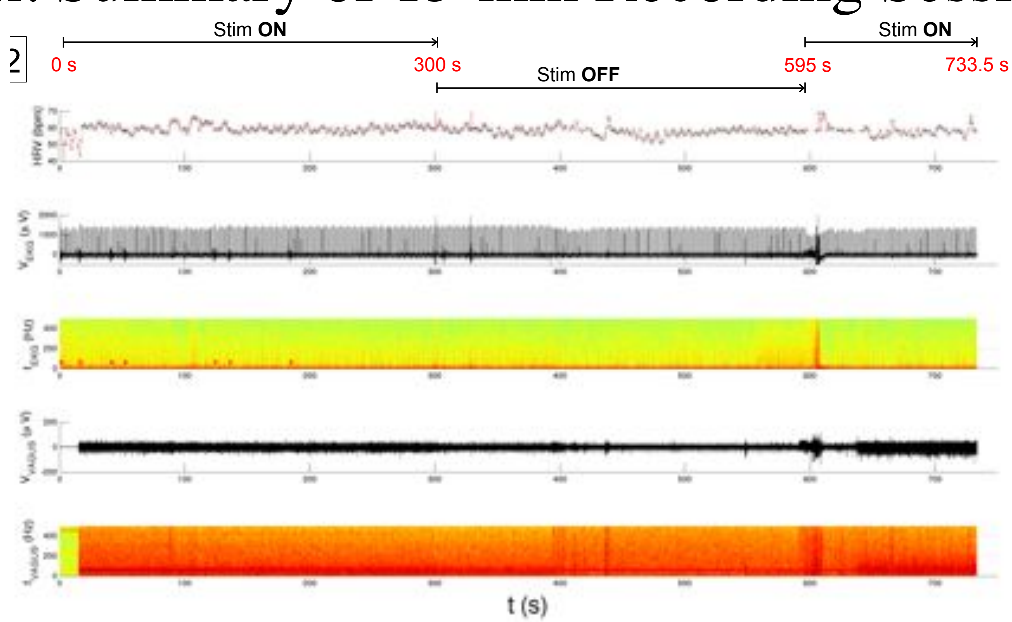
Ex. Summary of 15-min Recording Session



Our Solution: Objective Tuning

- Variable (often short) battery life — Wireless powering technology
- Stimulating lead failure — Miniature, leadless stimulation and measurement technology
  - Dislodge from generator
  - Break
- No measurable ("objective") response marker — Noninvasive measurement of vagal nerve response to GES
- No standard device tuning protocol ⟺ Autonomous neural control technology

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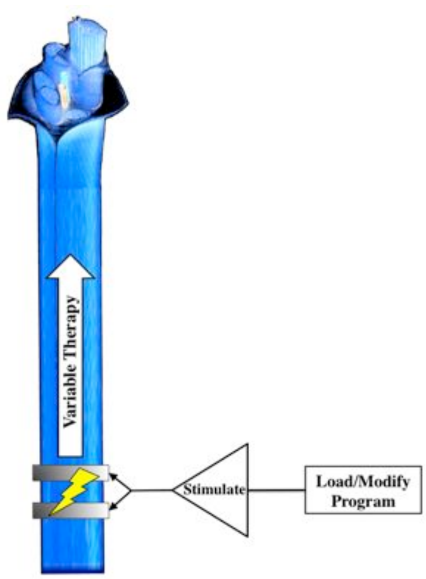
The Gold Standard in Neurostimulation



- Increase stimulus until:
  1. Adverse effects occur
  2. Average setting is reached
  3. Patient reports symptom relief
- Repeat every few weeks
- Major limitations:
  1. Body ignores stimulus over time
  2. No control over target neuron type
  3. No true "dosing" method

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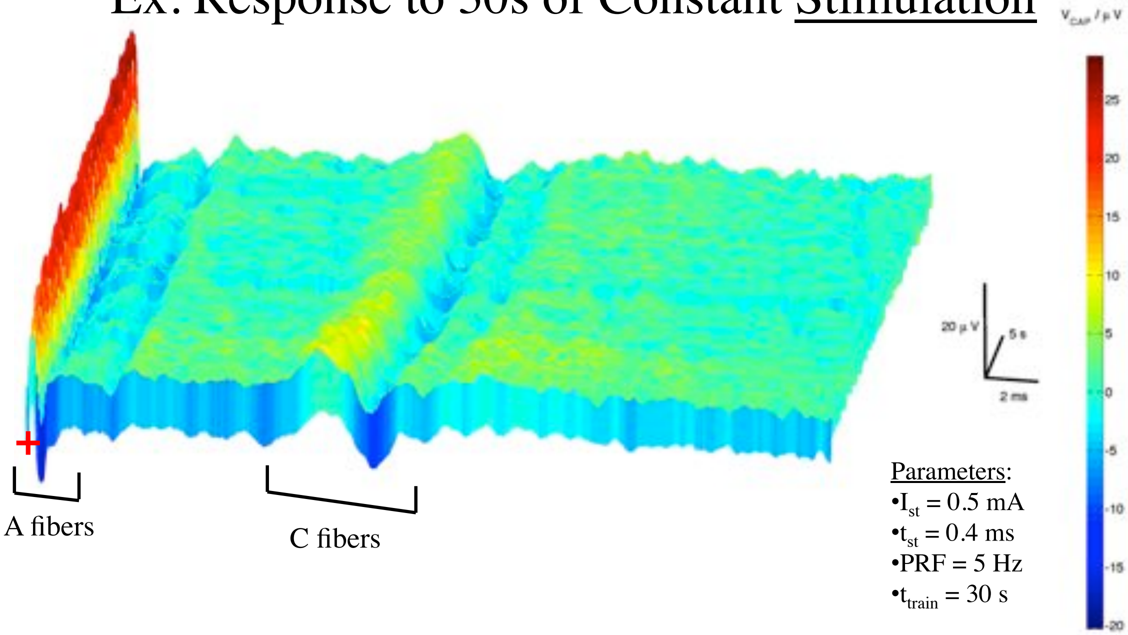
Ex. Response to 30s of Constant Stimulation



Parameters:
- I_{st} = 0.5 mA
- t_{st} = 0.4 ms
- PRF = 5 Hz
- t_{train} = 30 s

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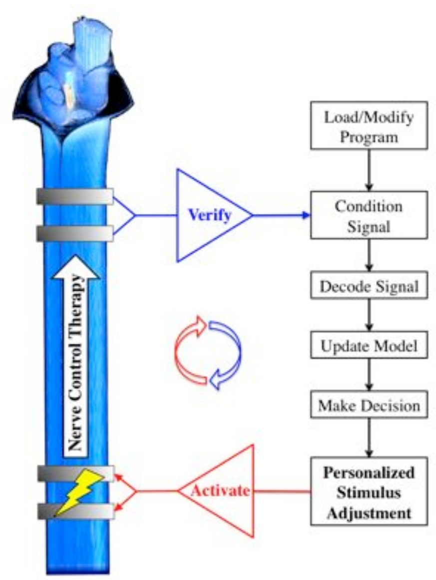
The New Standard: Autonomous Neural Control

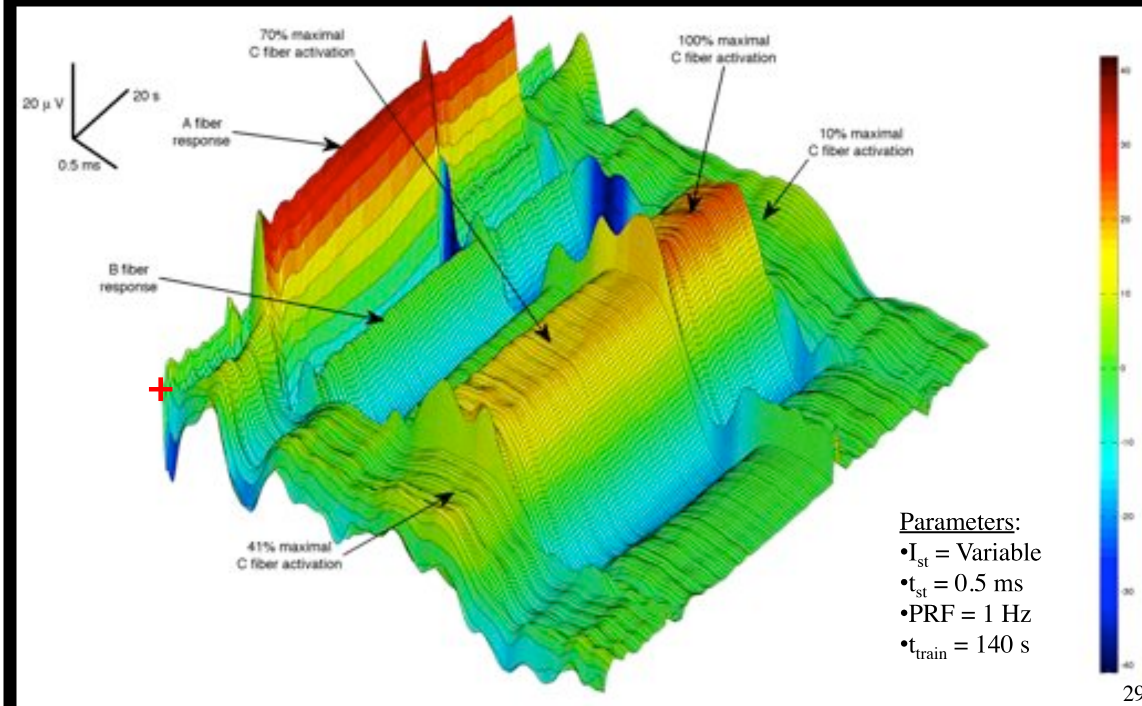


The Autonomous Neural Control System

- Personalized medicine
- Amenable to any:
  - Patient
  - Nerve
  - Neuron type
- Therapy based on activation level maintenance
  - e.g., 0 to 100% activation
- Utilizes a nerve activation prediction model

M.P. Ward and P.P. Irazoqui. (2011). *An Automated Stimulus Parameter Prediction Tool and its use as a Nerve Activation*...US Patent Application No. 61/550,584 (Filed 24 Oct 2011).

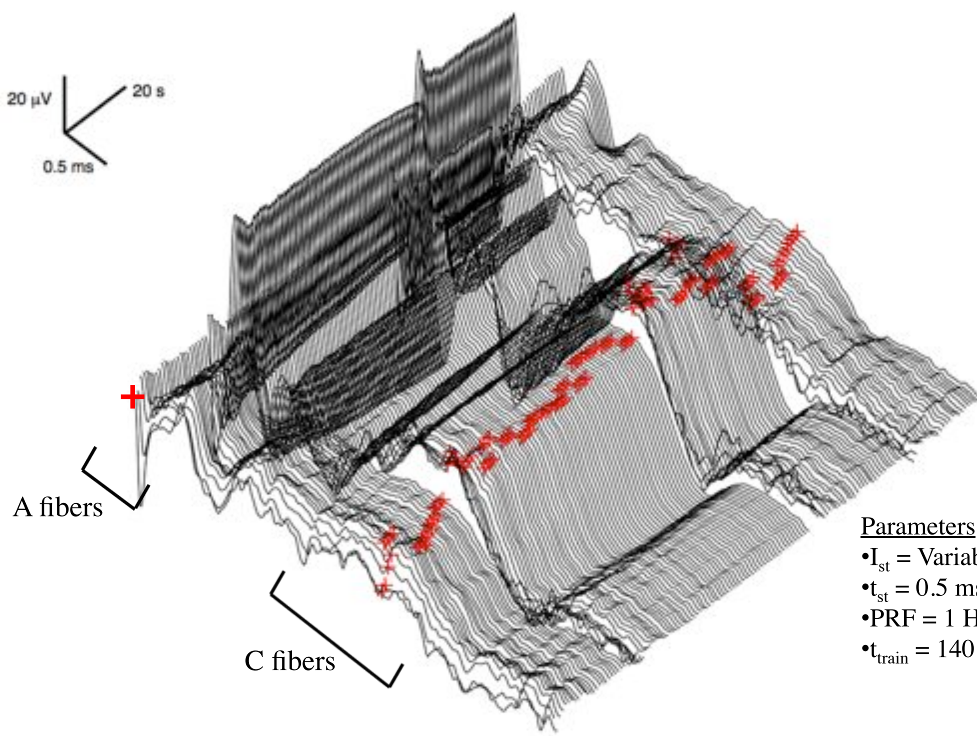
Ex. Response to 140s of Constant Activation



Parameters:
- I_{st} = Variable
- t_{st} = 0.5 ms
- PRF = 1 Hz
- t_{train} = 140 s

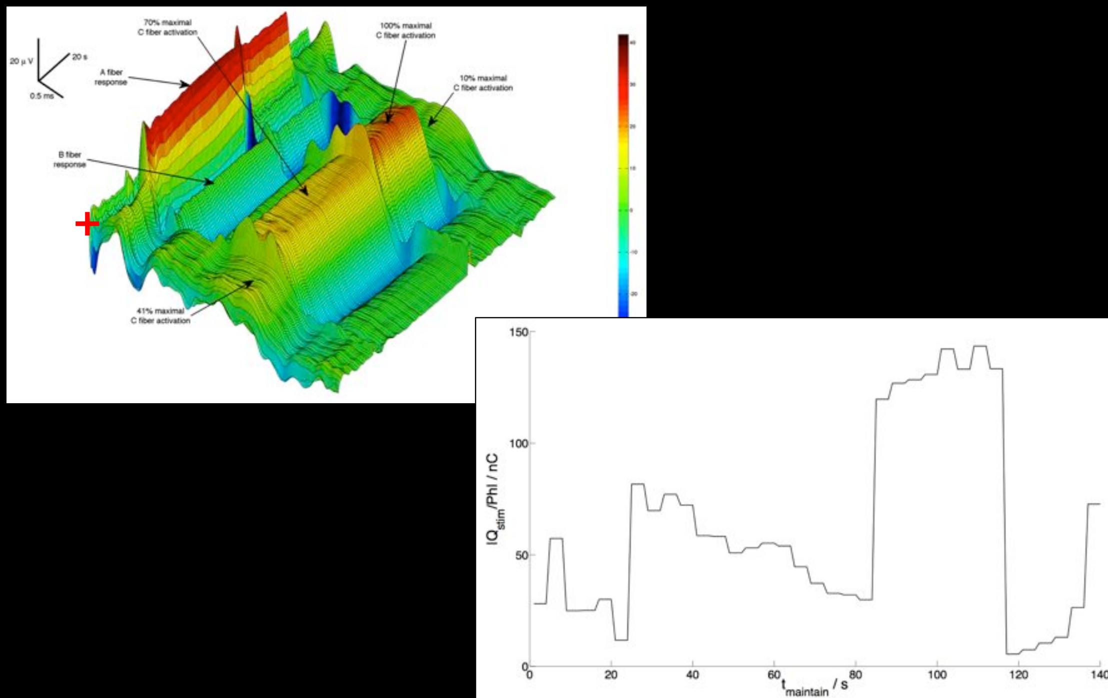
M.P. Ward and P.P. Irazoqui. (2011). *An Automated Stimulus Parameter Prediction Tool and its use as a Nerve Activation*...US Patent Application No. 61/550,584 (Filed 24 Oct 2011).

Ex. Response to 140s of Constant Activation



Parameters:
- I_{st} = Variable
- t_{st} = 0.5 ms
- PRF = 1 Hz
- t_{train} = 140 s

Constant Activation with Variable Stimulation Strength



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Solutions for GES Therapy

- Variable (often short) battery life
- Stimulating lead failure
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Wireless power transfer and supercapacitor technology

Miniature, leadless stimulation and measurement technology

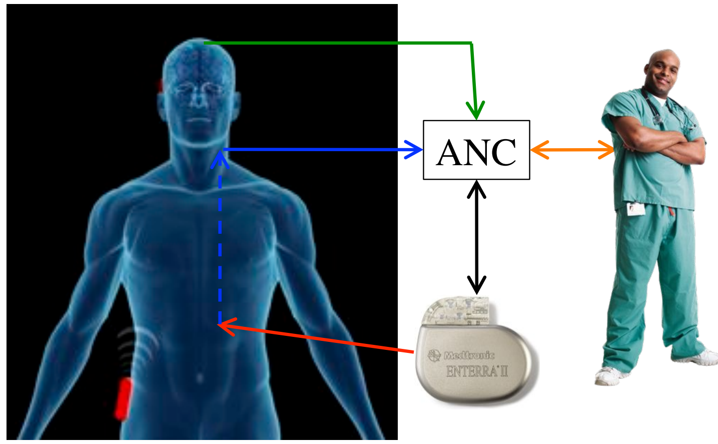
Noninvasive measurement of vagal nerve response to GES

Autonomous neural control technology

Dynamic Control of Gastroparesis

Approach

- Innovate with the end user in mind
- Fit device to patient, not patient to device
- Use ANC to link vagal response marker to:
  - Patient symptom surveys
  - Gastric output
  - Blood biomarkers
  - Exams
  - Other health data?



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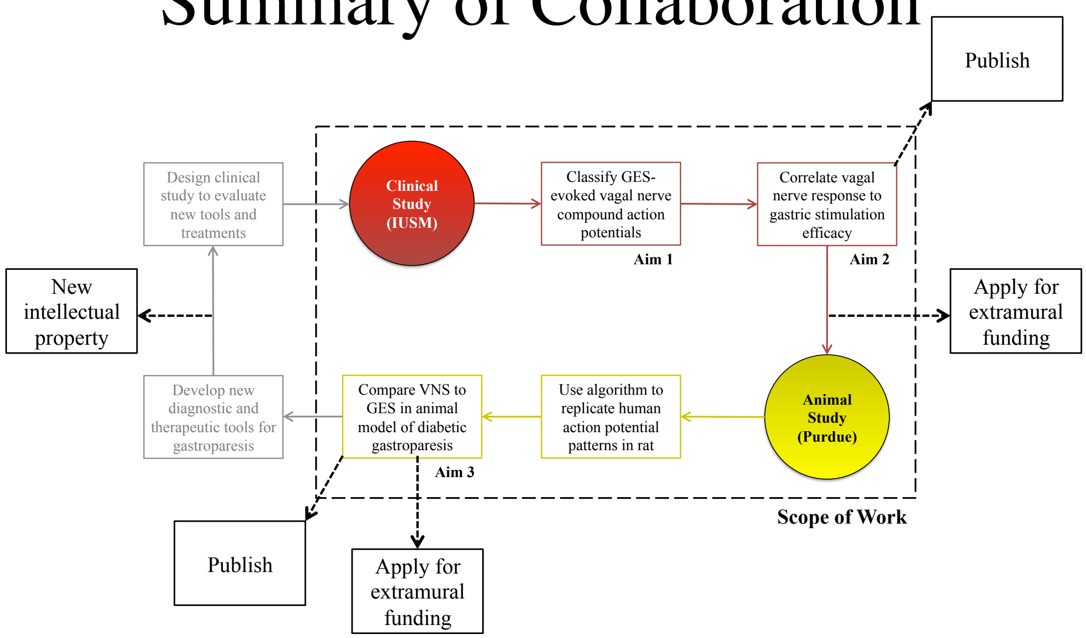
Summary of Collaboration



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  - Glaucoma
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  - Epilepsy Research UK

- Director
  - Pedro P. Irazoqui, Ph.D.
- Center student members
  - Research Scientists
    - Matthew Ward, Ph.D.
    - Quan Yuan, Ph.D.
  - Post-doctoral students
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    - Jimin Maeng, Ph.D.
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    - John Lynch Henry Mei
    - Dan Pederson Kurt Qing*
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    - Jack Williams

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    - Henry Zhang, Engineer

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Thank You