AUTONOMOUS NEURAL CONTROL OF GASTROPARESIS

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https://engineering.purdue.edu/CID

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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

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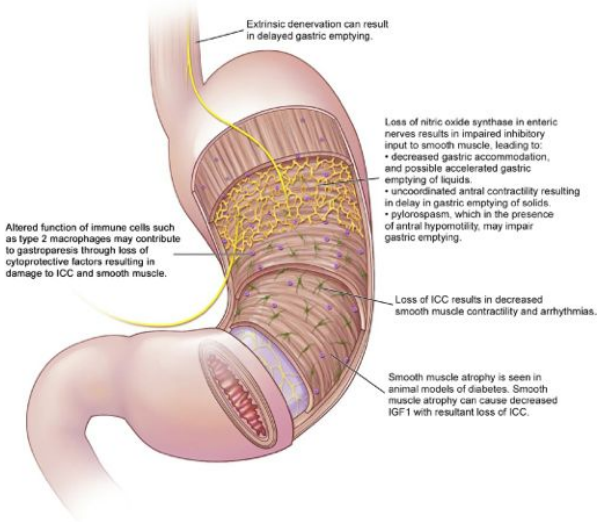
Etiology of Gastroparesis

- **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
(Medtronic, Inc.)

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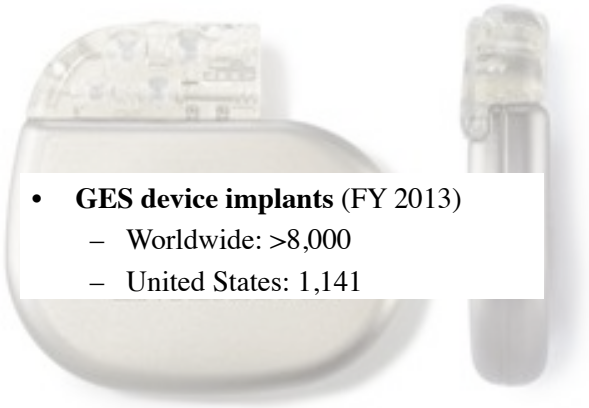
State of Gastric Electrical Stimulation

- 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

Enterra® II Gastric Electrical Stimulator
(Medtronic, Inc.)

COLLABORATE AND TRANSLATE

IU GASTROENTEROLOGY/HEPATOLOGY

PURDUE BIOMEDICAL/ELECTRICAL ENGINEERING

The Gastroparesis Team

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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

Central Hypothesis

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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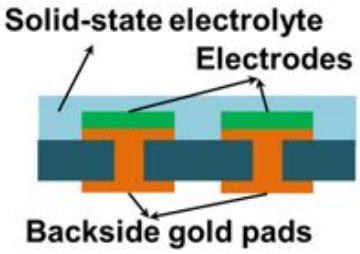
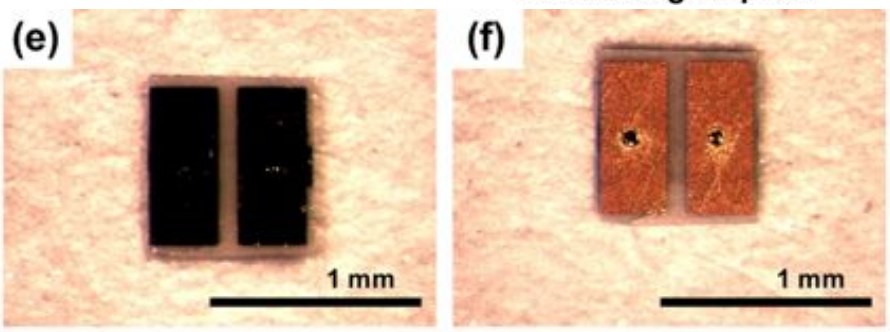
Demo: Wireless Power Transfer

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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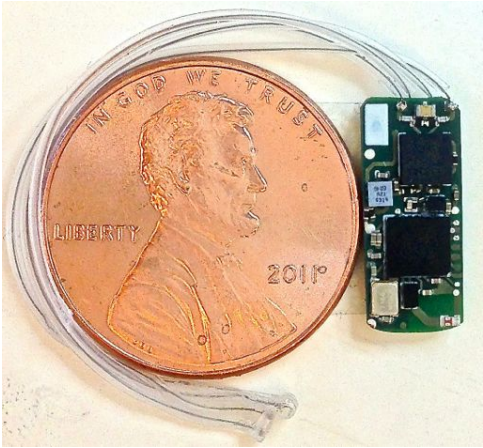
The Bionode (ZIPH Labs)

- 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 – Dislodge from generator – Break	Miniature, leadless stimulation and measurement technology
• No measurable ("objective") response marker ⟺	Noninvasive measurement of vagal nerve response to GES
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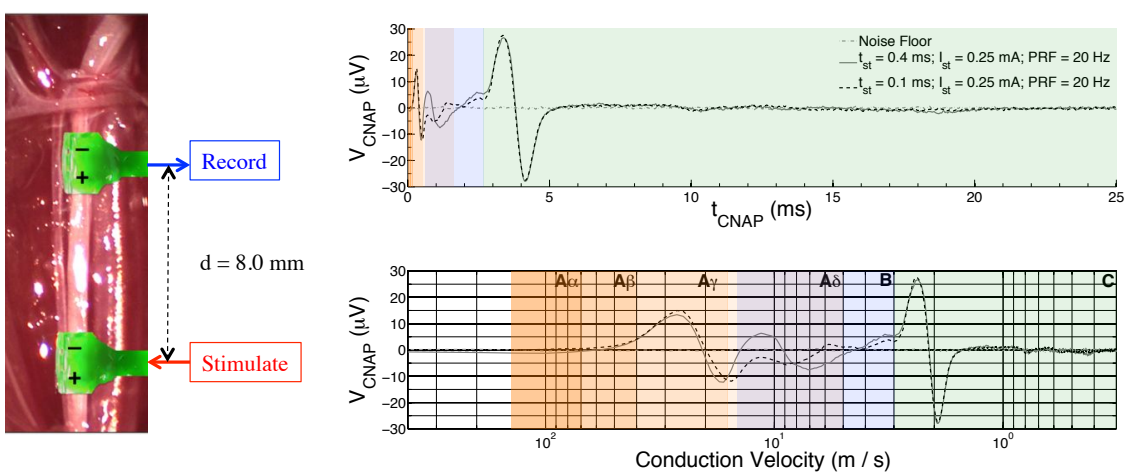
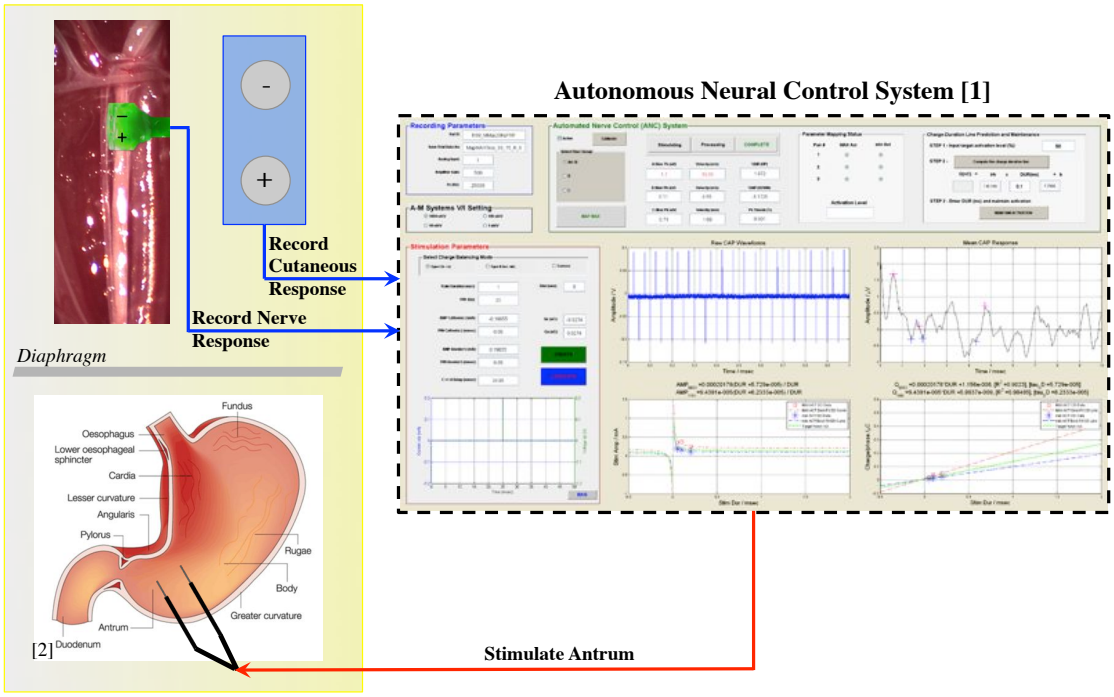
The Compound Nerve Action Potential



[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.

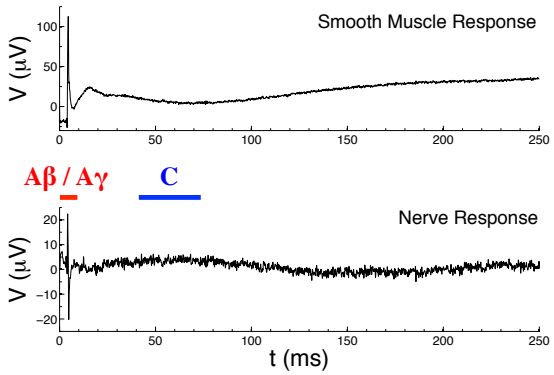
Experimental Setup: Gastric Electrical Stimulation in Rat

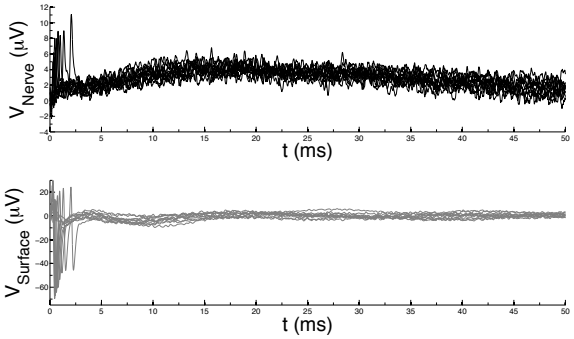


[1] *In press* - M. P. Ward *et al*., "A flexible platform for rapid biofeedback control and personalization of electrical nerve stimulation therapy," Aug 2014.
[2] Richard M. Peek, Jr & Martin J. Blaser. (2002). "Helicobacter pylori and gastrointestinal tract adenocarcinomas." Nature Reviews Cancer **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

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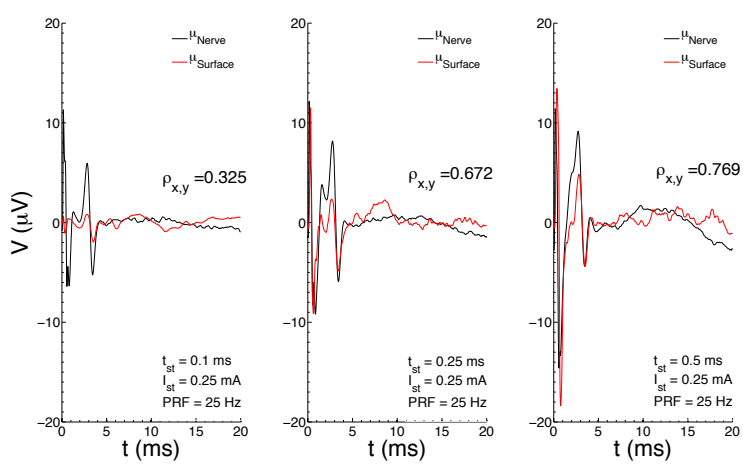
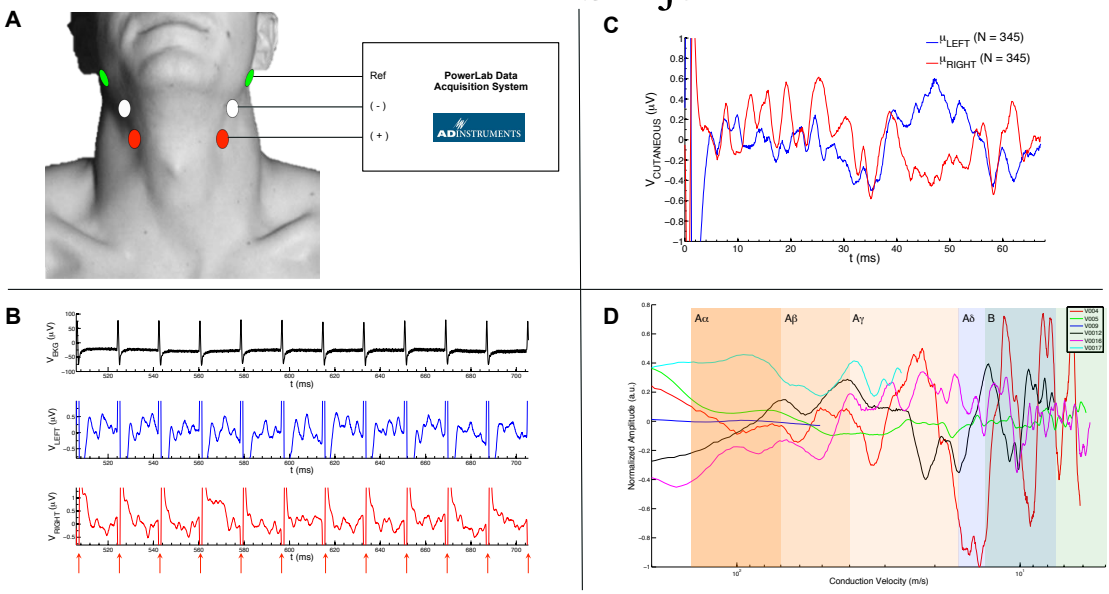
Vagal CAP Measurement with Cutaneous Electrodes in Rat



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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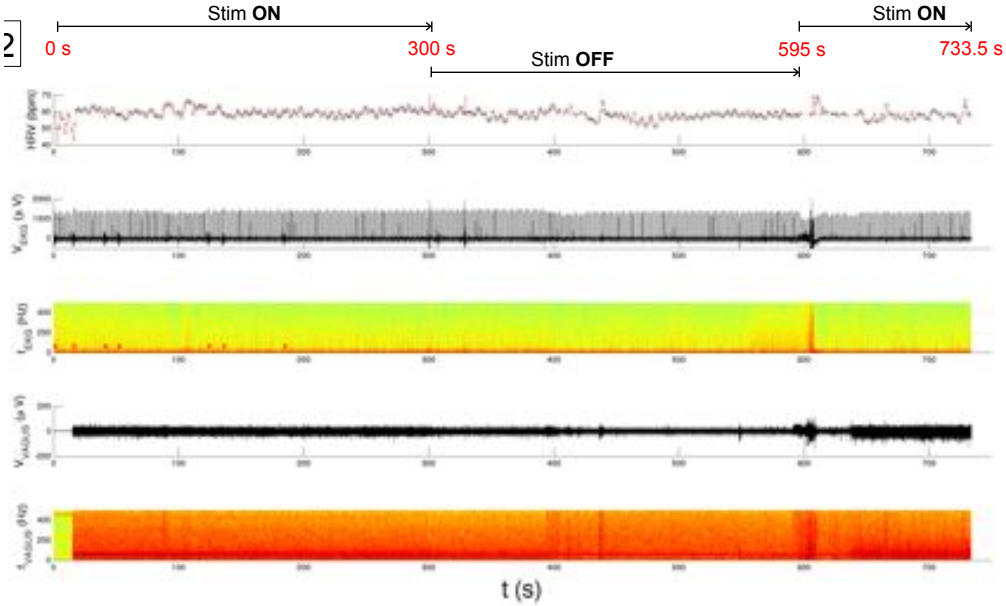
Ex. Summary of 15-min Recording Session



Our Solution: Objective Tuning

• Variable (often short) battery life	Wireless powering technology
• Stimulating lead failure – 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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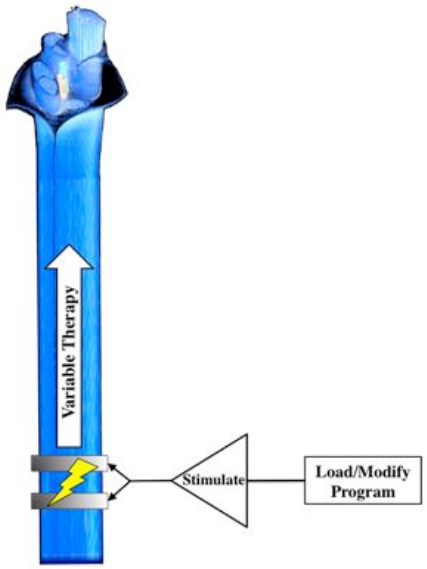
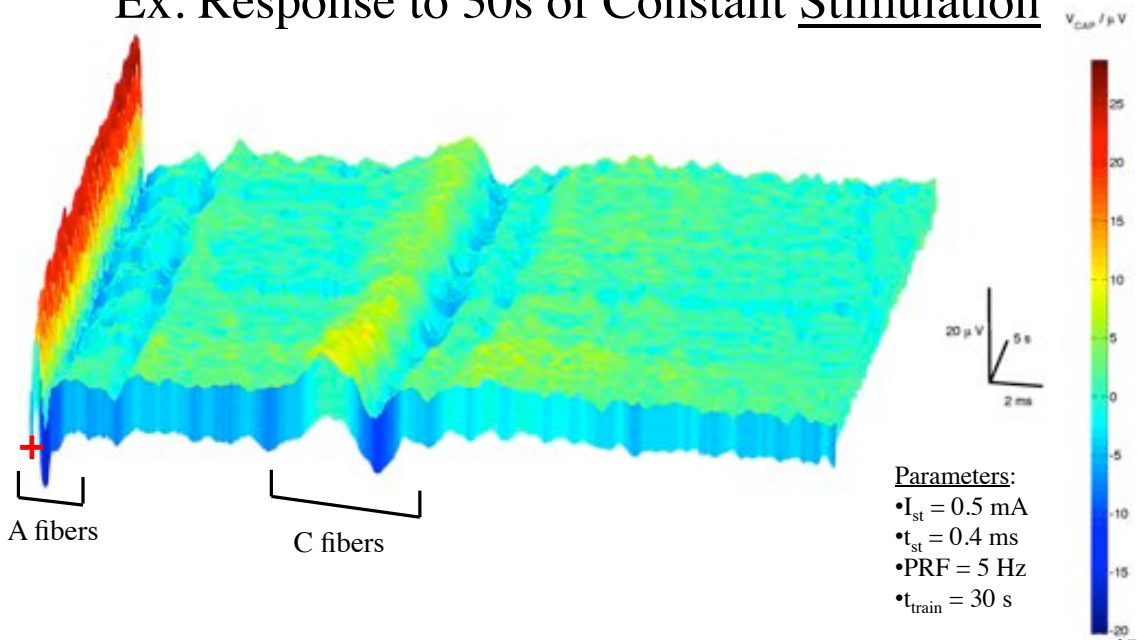
The Gold Standard in Neurostimulation



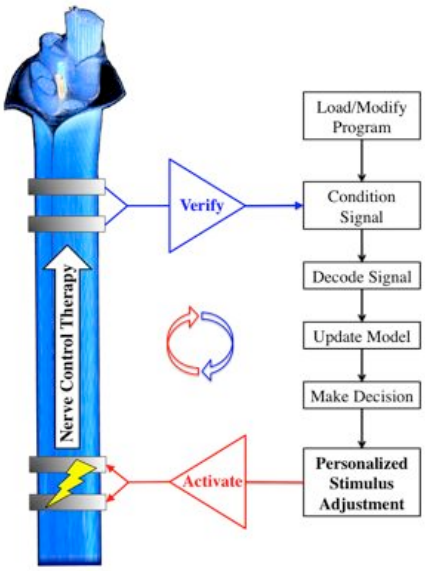
- Increase stimulus until:
  1. Adverse effects occur
  2. Average setting is reached
  3. Patient reports symptom relief
- Repeat every few weeks
- Major limitations:
  1. Body ignores stimulus over time
  2. No control over target neuron type
  3. No true "dosing" method

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

The New Standard: Autonomous Neural Control

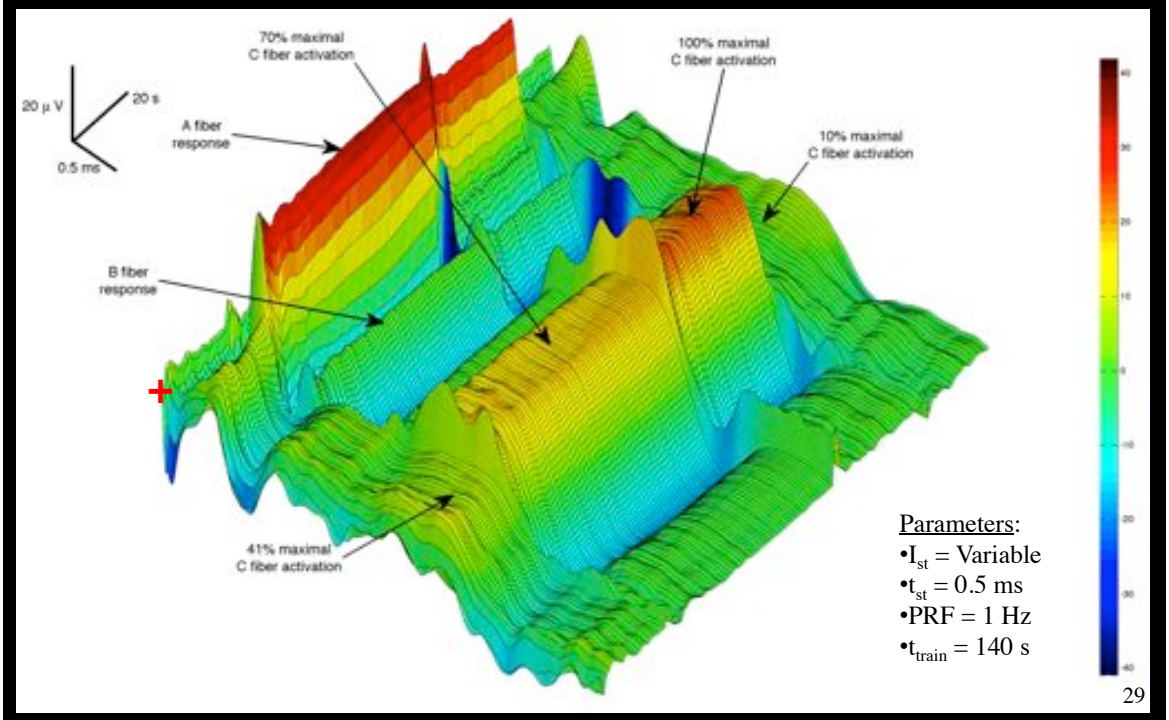


The Autonomous Neural Control System

- 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



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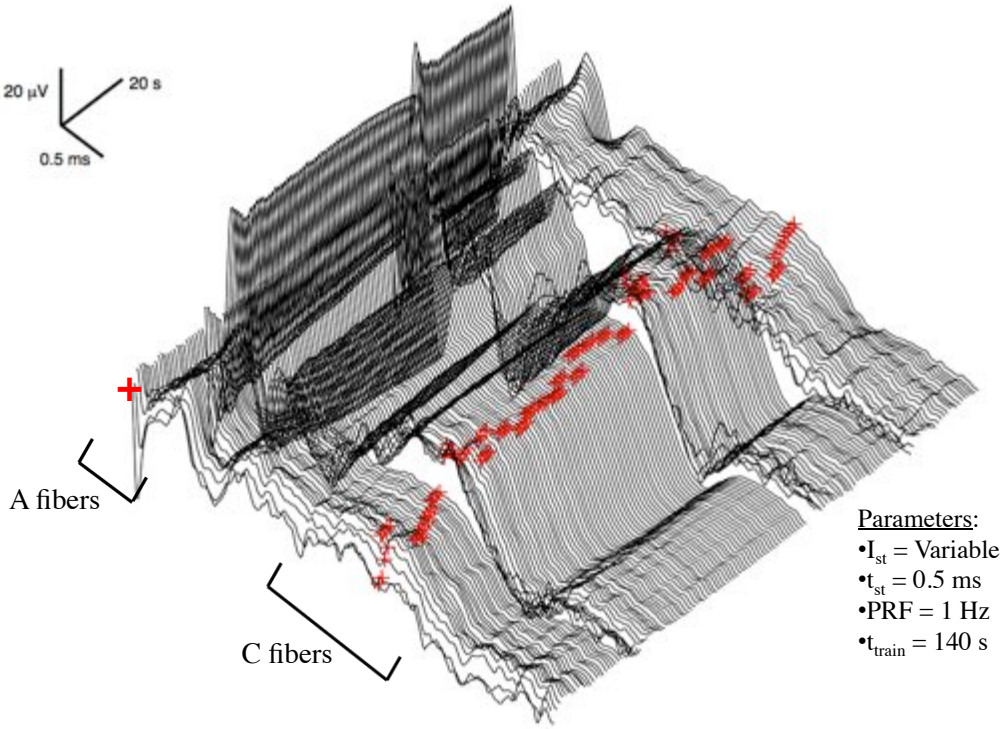
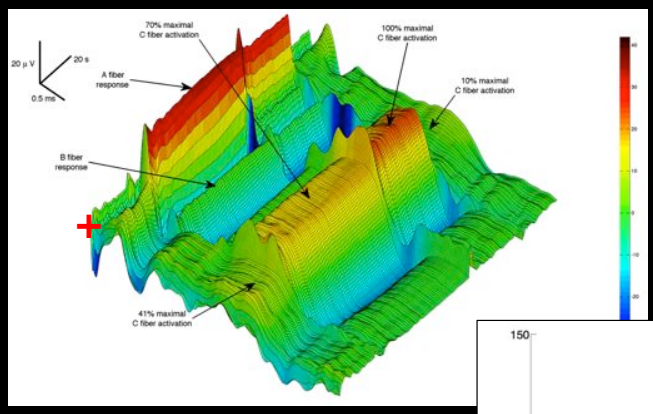
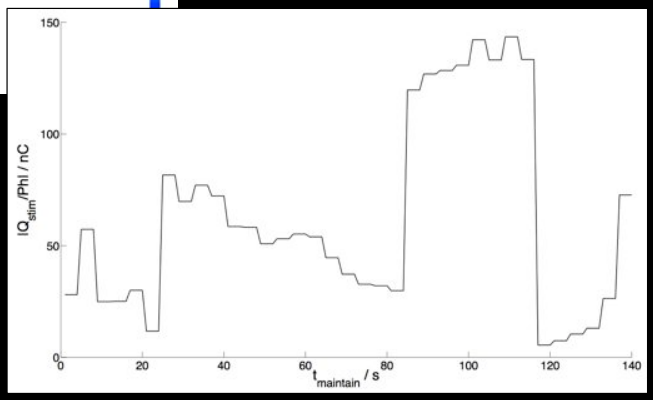


Constant Activation with Variable Stimulation Strength





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Solutions for GES Therapy

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

Wireless power transfer and supercapacitor technology

Miniature, leadless stimulation and measurement technology

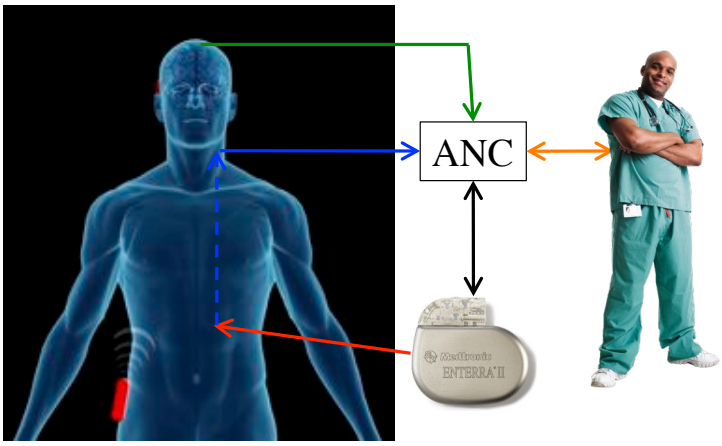
Noninvasive measurement of vagal nerve response to GES

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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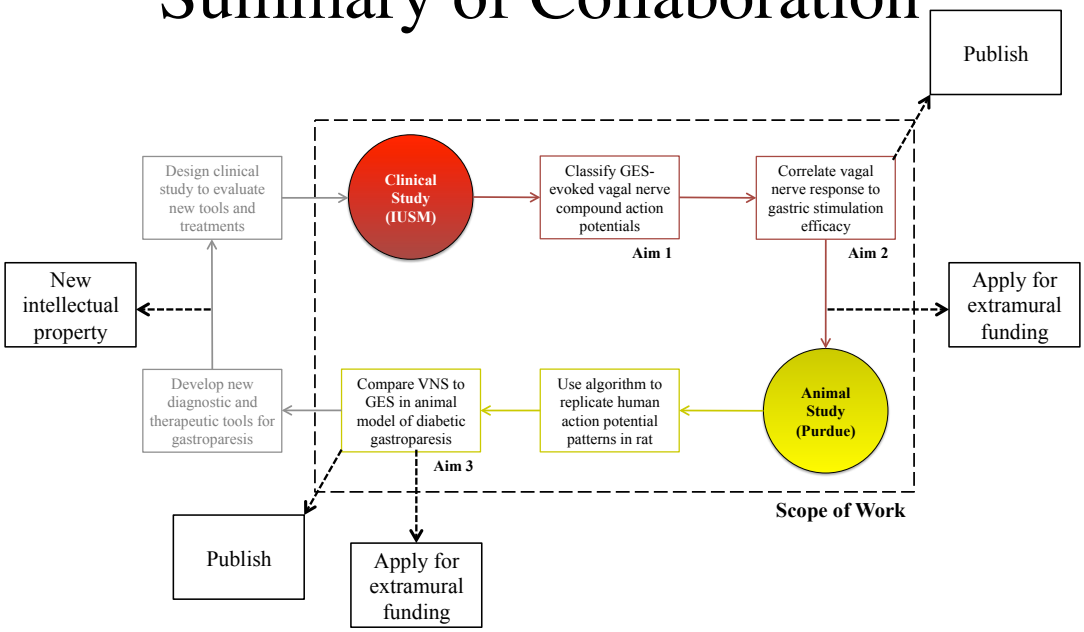
Summary of Collaboration



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  - Targeted Muscle Reinnervation
    - Todd Kuiken, M.D./Ph.D. Levi Hargrove, Ph.D.
    - Rob Burgess, Ph.D. Greg Cox, Ph.D.
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    - Da Ting Lin, Ph.D. DFTx, Inc.
  - Glaucoma
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  - Graduate Students
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    - Jack Williams

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  - Technical staff
    - Gabriel Albors, Managing Director
    - Henry Zhang, Engineer

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Thank You