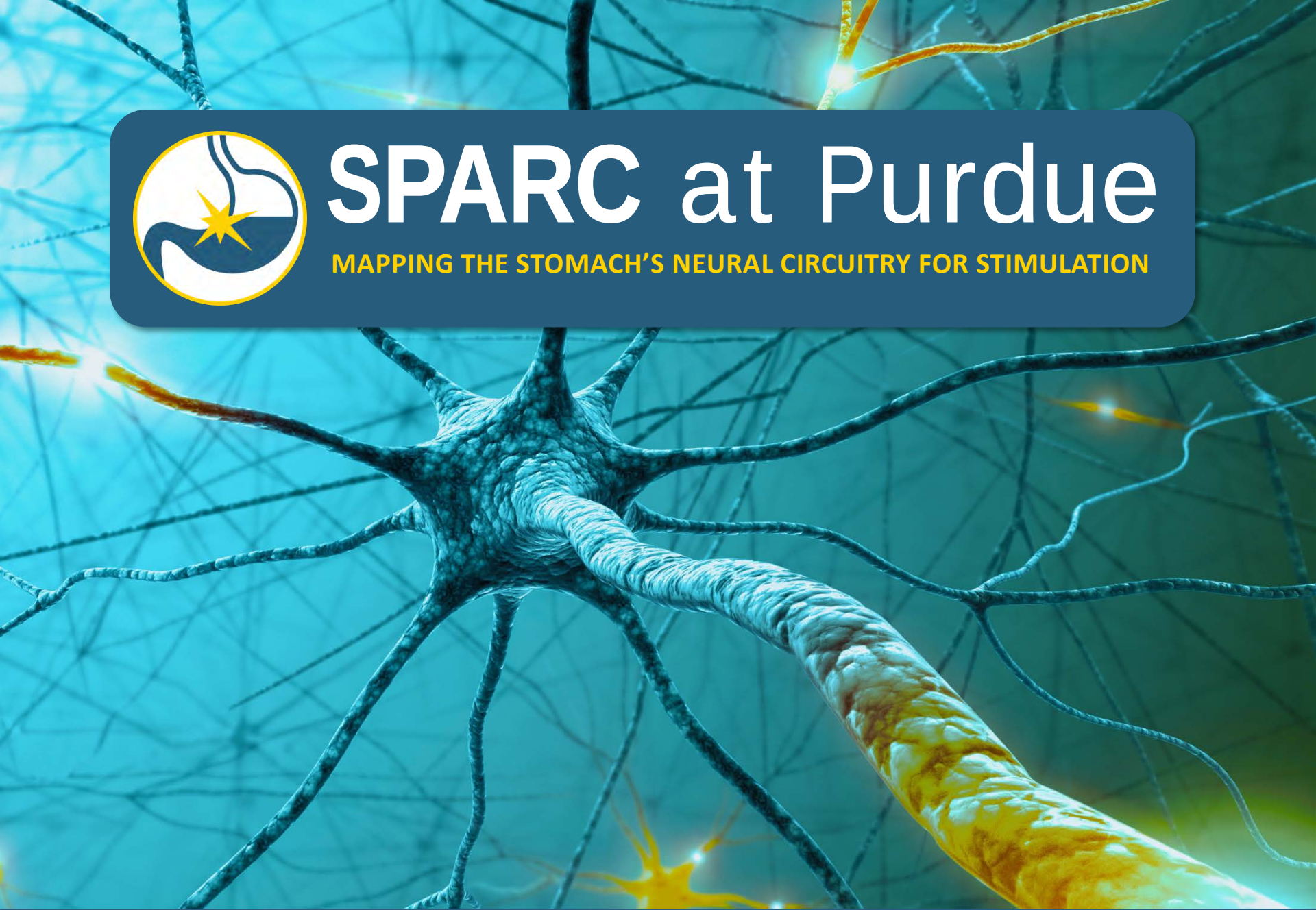


PURDUE UNIVERSITY

THE UNIVERSITY OF MELBOURNE

SCHOOL OF MEDICINE
INDIANA UNIVERSITY

UT DALLAS

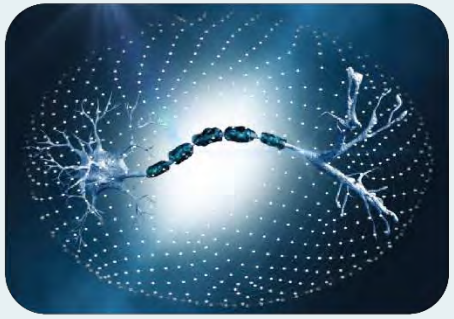
SPARC at Purdue

Therapeutic Approaches: Problems

- **Drugs:** Off-target effects; drug-drug interactions; drug refractory conditions
- **Surgery:** Irreversible; non-specific; drastic
- **Stimulation:** Promising but problematic (1st Generation)

Experimental Needs

- Interdisciplinary, programmatic research
- Rapid data sharing



SPARC

Stimulating Peripheral Activity to Relieve Conditions

VAGUS NERVE STIMULATION (VNS) FOR GASTROINTESTINAL DISORDERS

FDA APPROVED

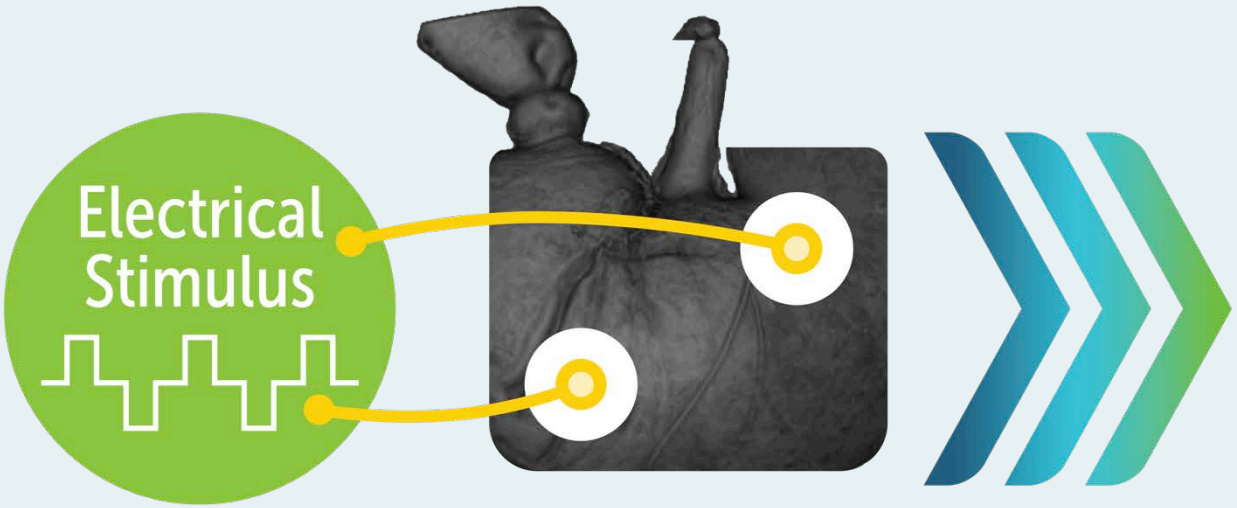
- Medtronic - Enterra II Gastric electric stimulation (2000).*

  ** Humanitarian Device: ..... The effectiveness of this device for this use has not been demonstrated.*

- EnteroMedics – Maestro Rechargeable System (Vbloc) (2015).

CE MARK

- Intrapace – Abiliti Gastric Pacemaker (2011).
- Endostim – Endostim LES Stimulator for GERD (2012).
- Metacure – Diamond (2007)



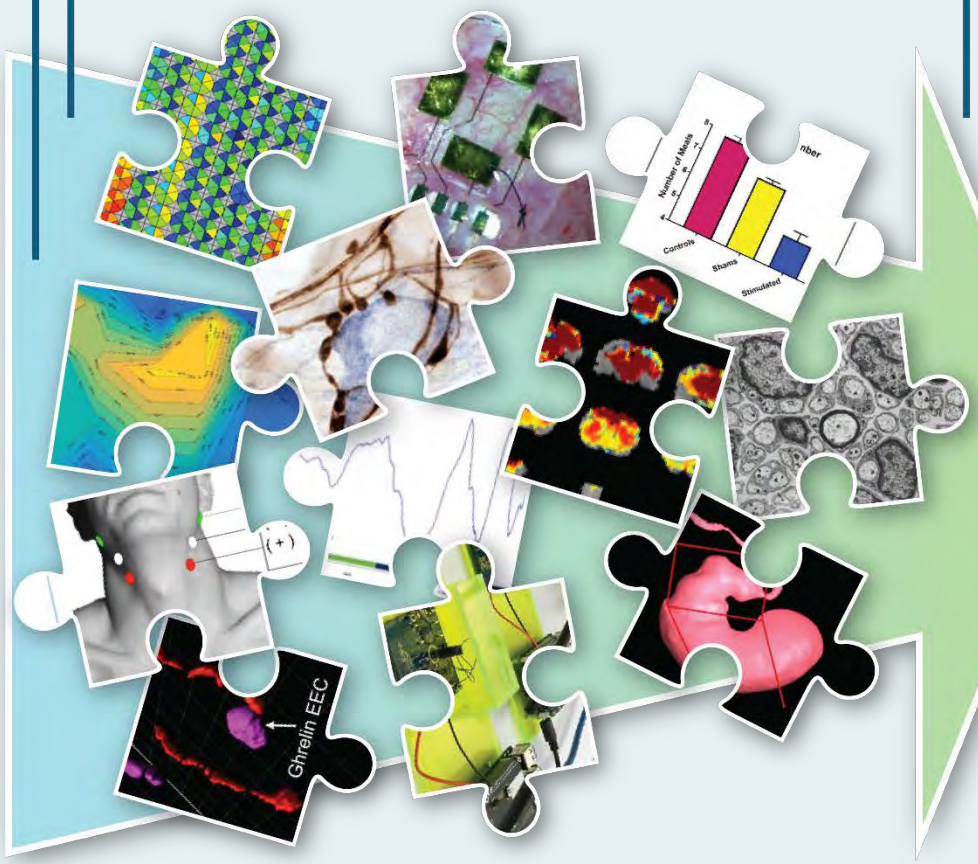
1st Generation

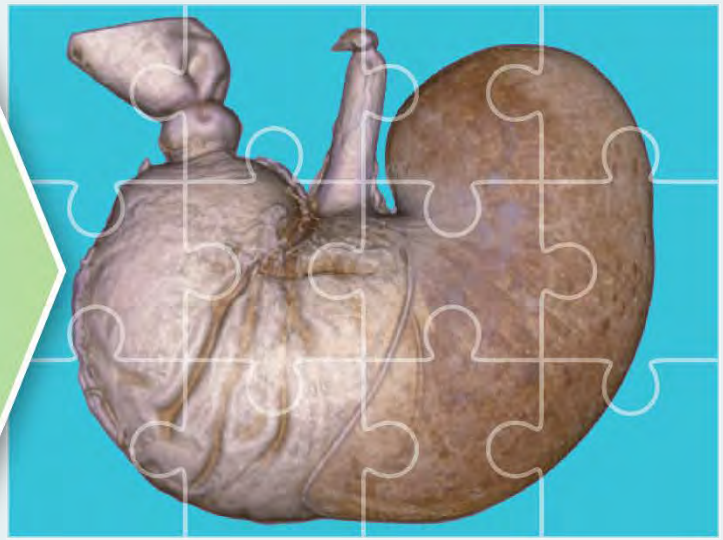
- Gastroparesis
- Gut Dysmotility
- Dyspepsia
- Visceral Pain
- Nausea, Emesis
- Obesity
- Pyloric Stenosis
- Dumping
- Reflux
- Anorexia Nervosa

SPARC at Purdue

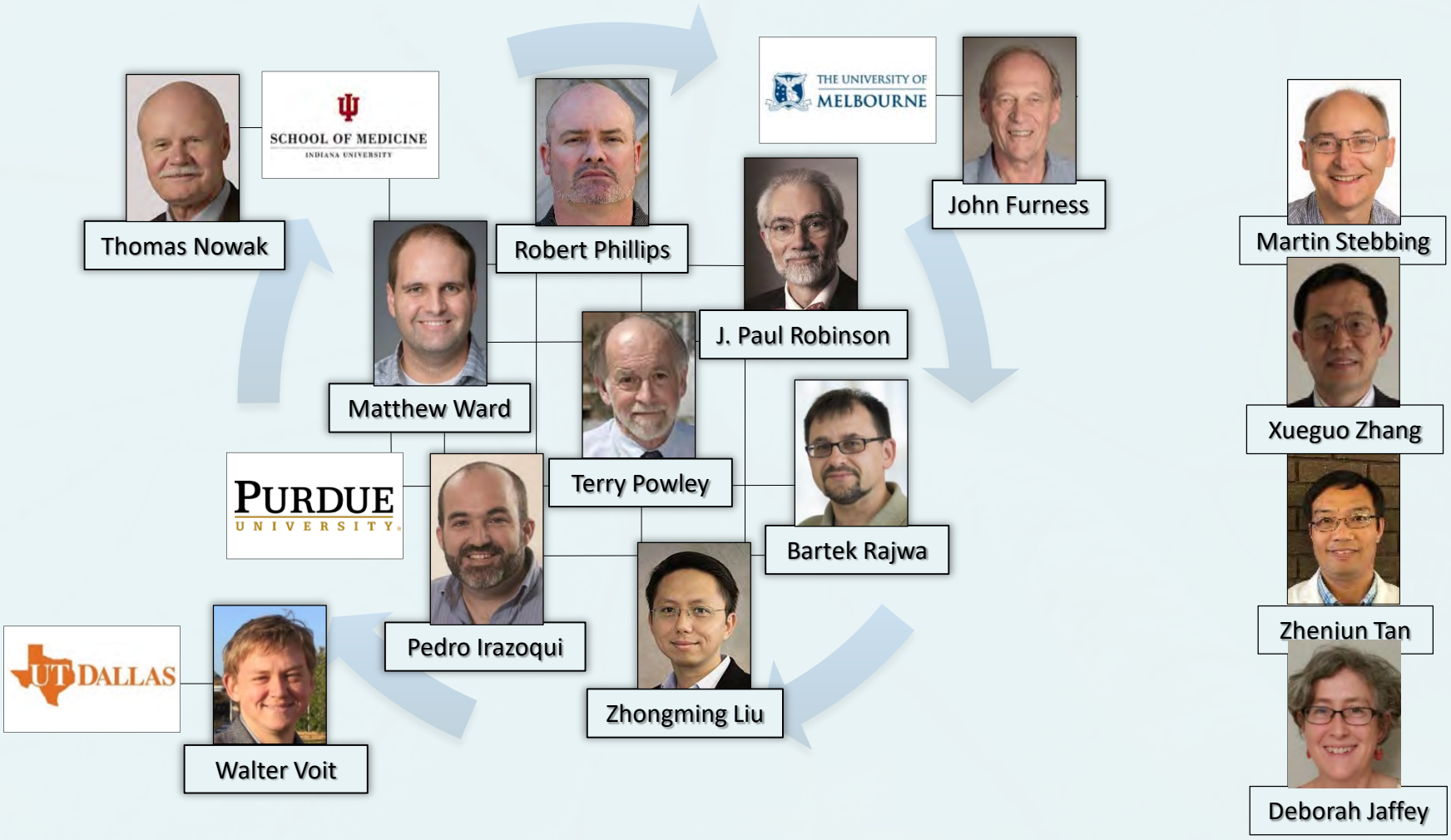
OT2 (Integrative)

RO1s (Tunnel Vision)

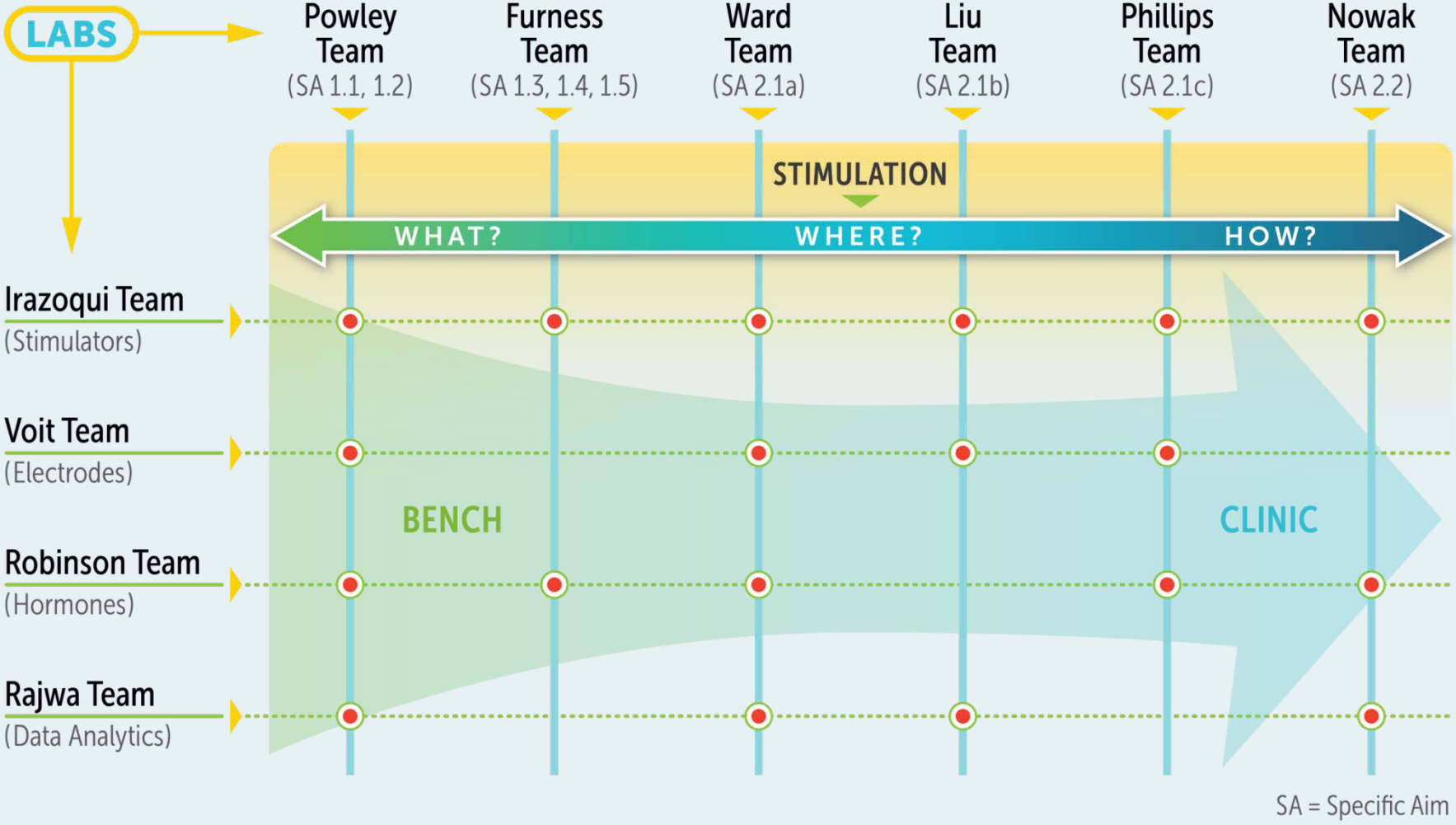




INTERDISCIPLINARY SYNERGY

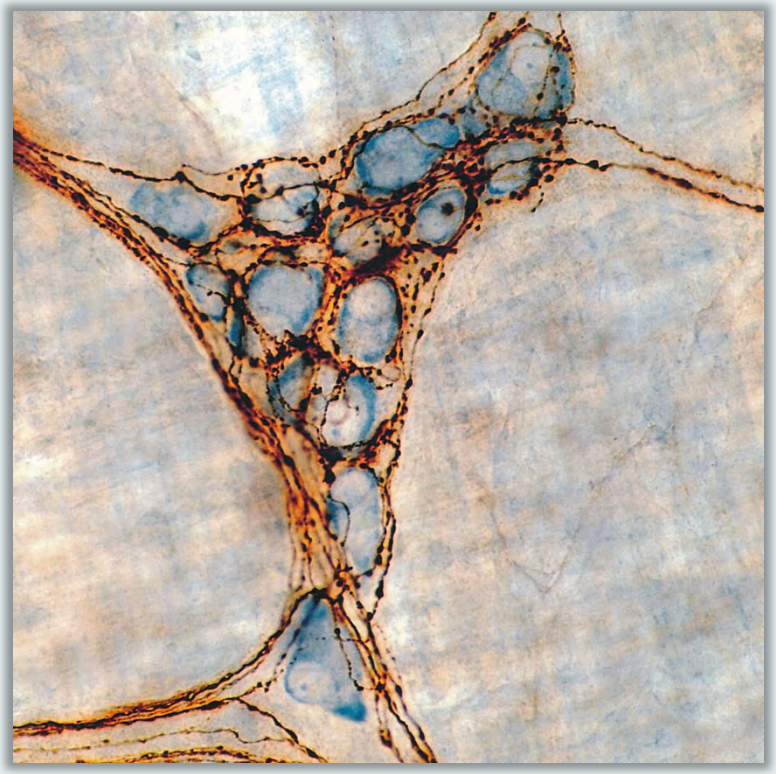


SPARC at Purdue

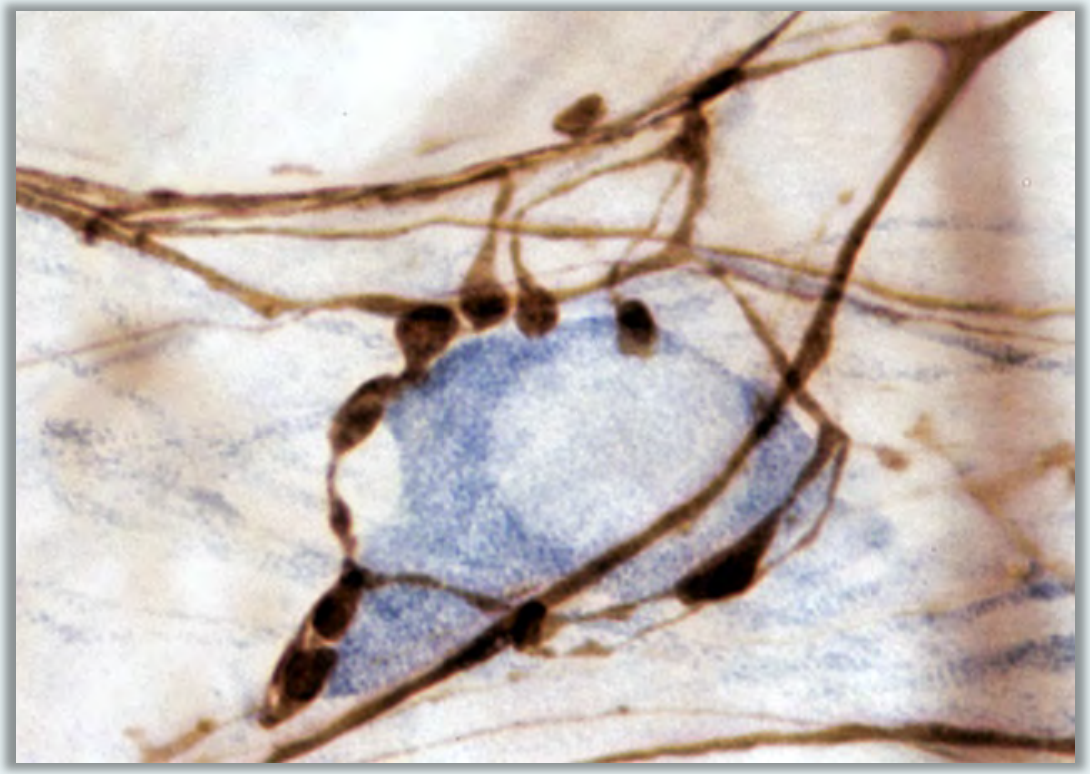


If we don't know
what, where, how
to stimulate,
we don't know what
we are doing.

TRACERS FOR PHENOTYPING EXTRINSIC PROJECTIONS: EFFERENTS

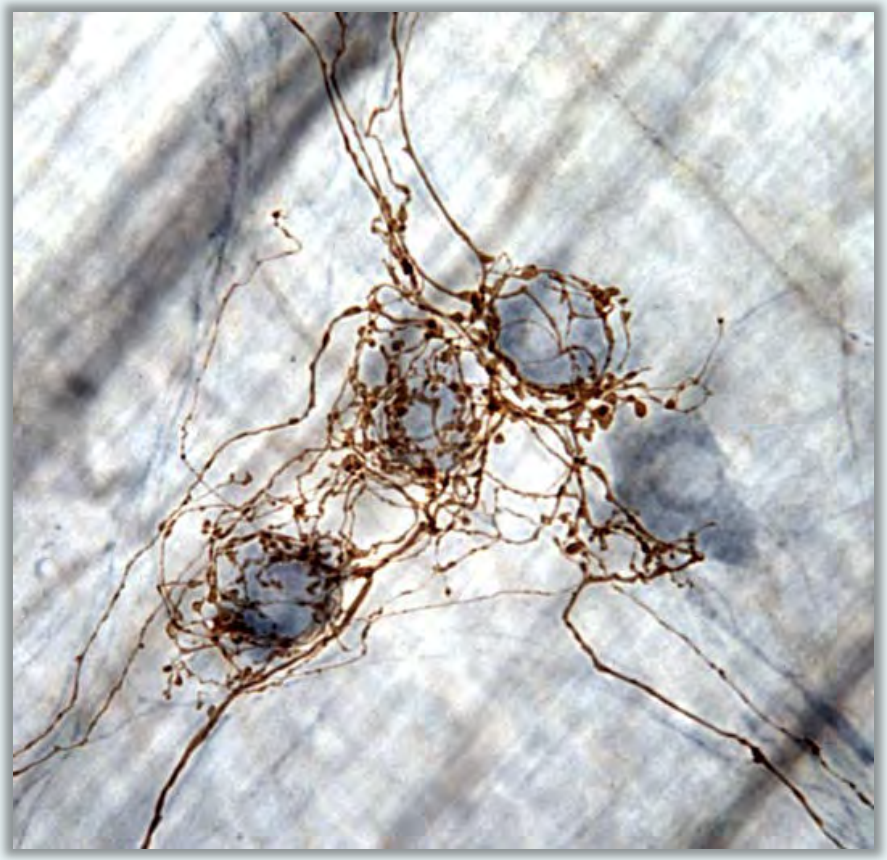


PHA-L / Cuprolinic Blue

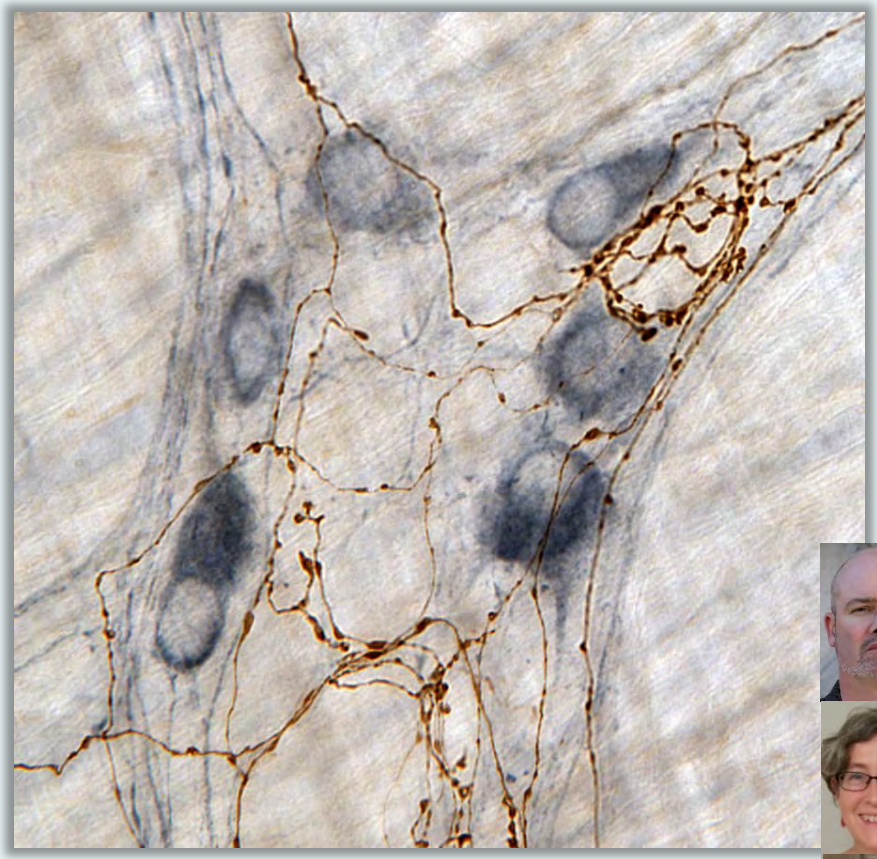


Dextran-Biotin / nNOS

TRACERS FOR PHENOTYPING EXTRINSIC PROJECTIONS: EFFERENTS WITH nNOS COUNTERSTAIN

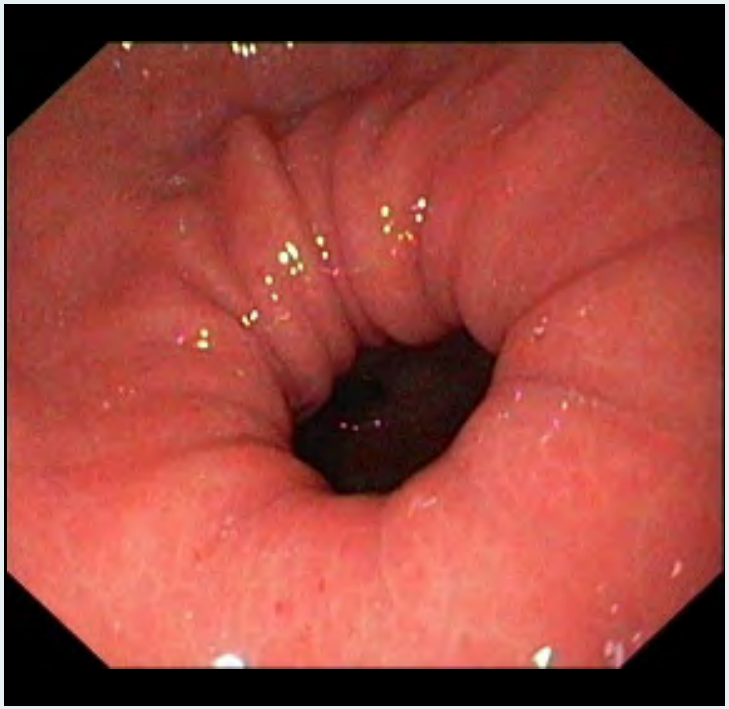


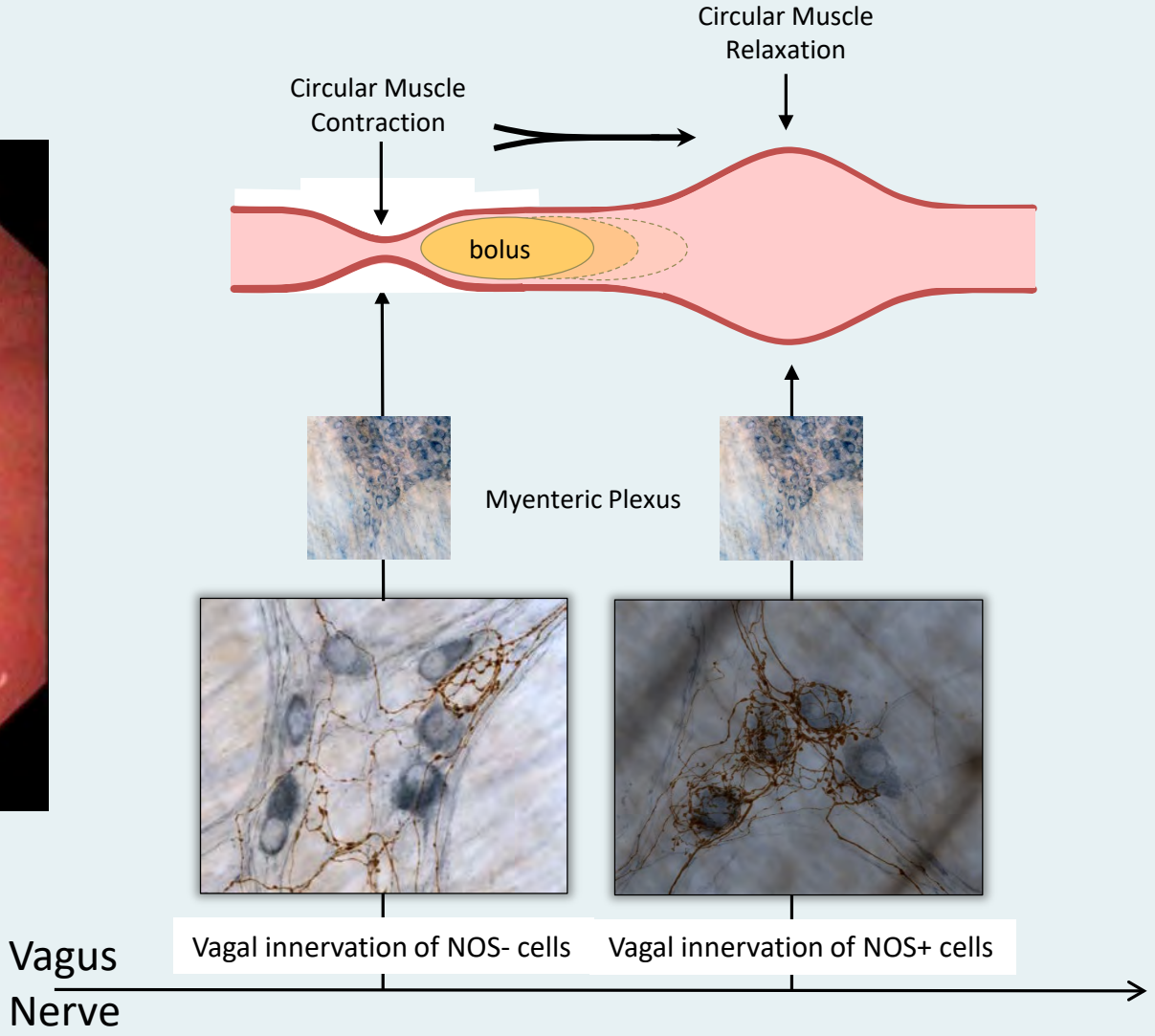
Contacting NOS+ cells



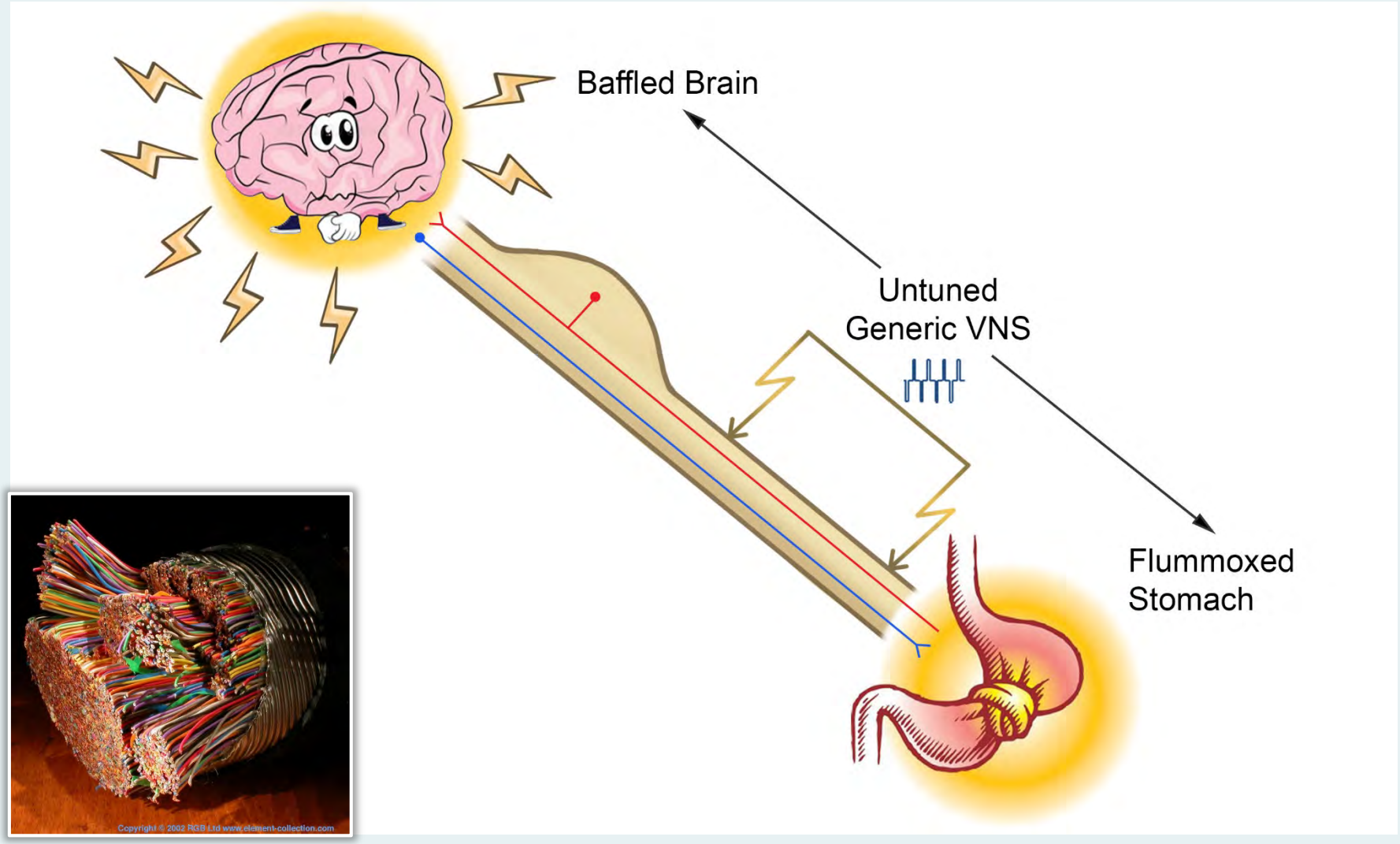
Contacting NOS- cells

PHASING PERISTALTIC PROPULSIVE MOTION *via* VAGAL COORDINATION?

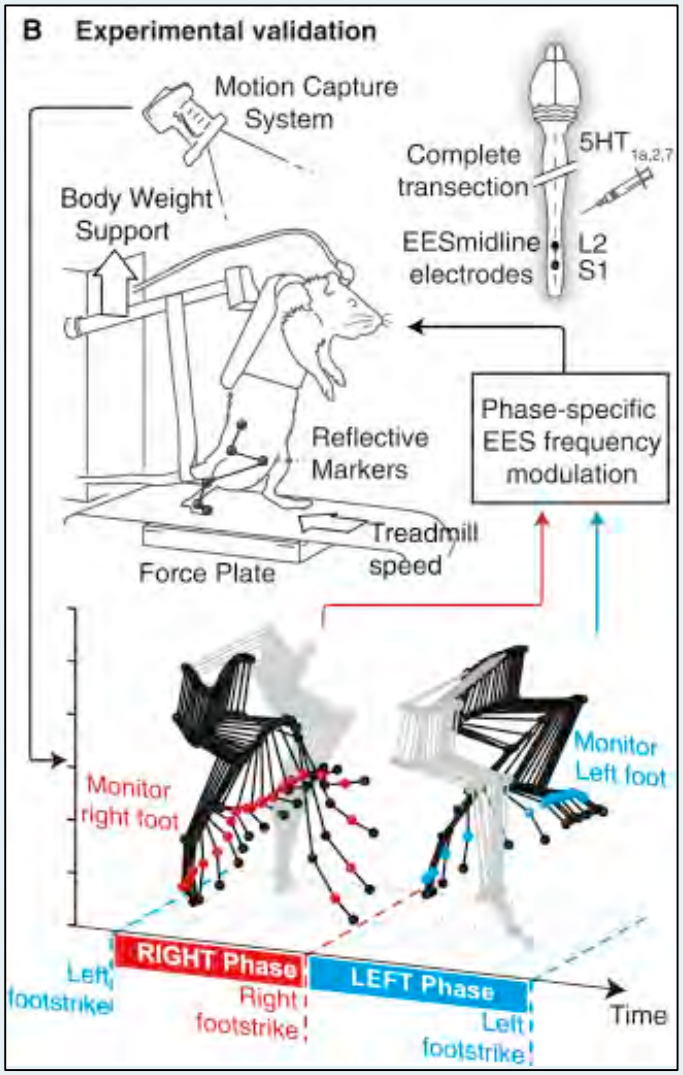




FIRST GENERATION DEVICES



ANALOGUE FOR VNS ENHANCEMENT OF STOMACH FUNCTION?

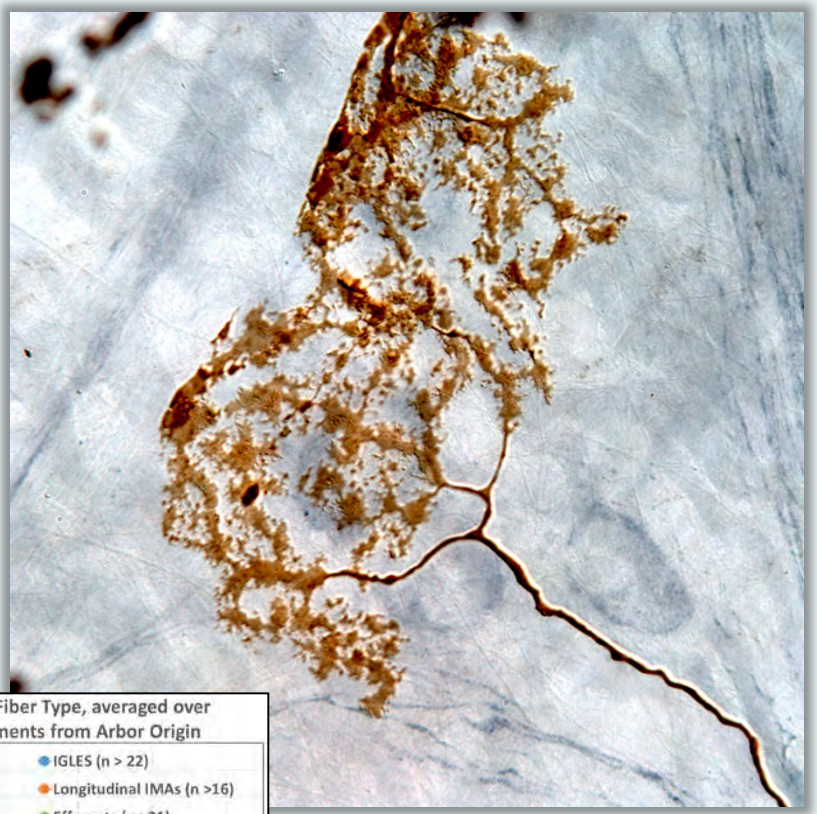


Stimulation to Restore Spinal Motor Function Requires:

- Afferent stimulation engaging reflex arcs
- Patterned stimulation

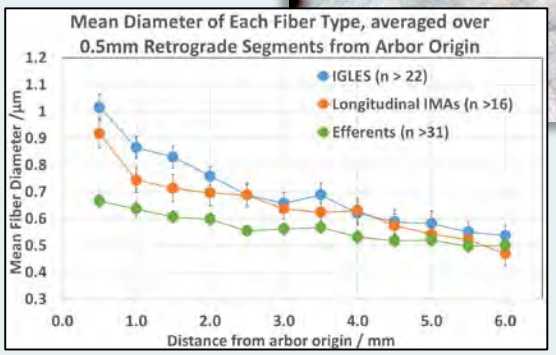
From: Moraud et al., Mechanisms Underlying the Neuromodulation of Spinal Circuits for Correcting Gait and Balance Deficits after Spinal Cord Injury, Neuron 89 (2016) 1, http://dx.doi.org/10.1016/j.neuron.2016.01.009

TRACERS FOR PHENOTYPING EXTRINSIC PROJECTIONS: AFFERENTS

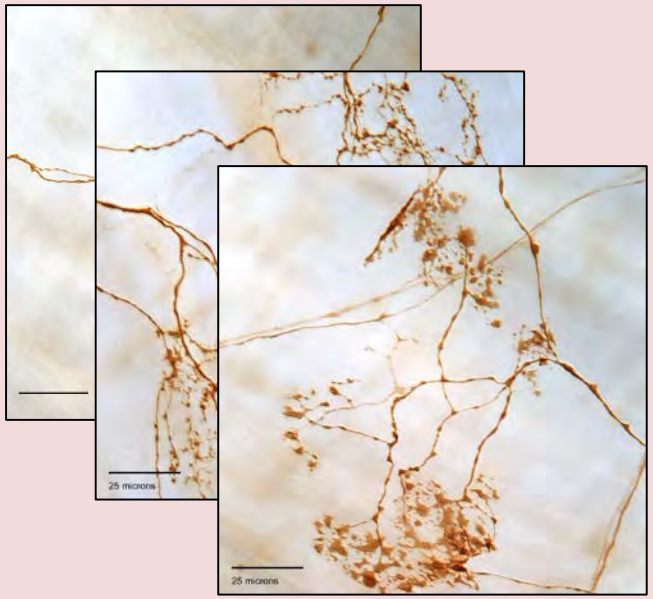


IGLE

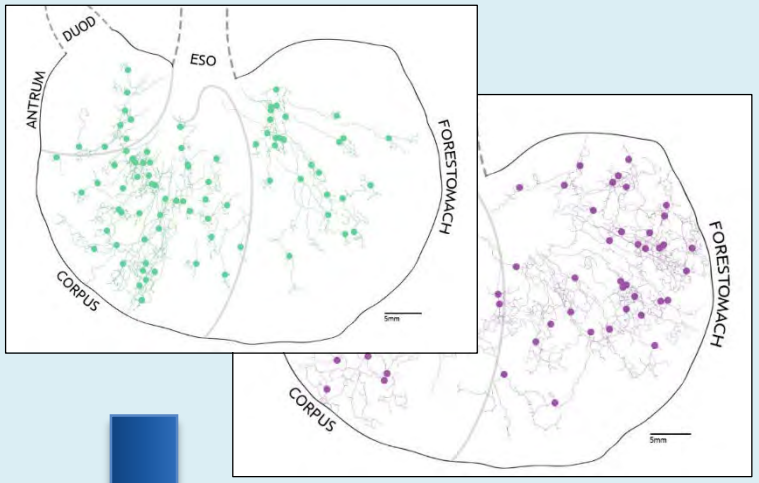
IMA



SPARC at Purdue

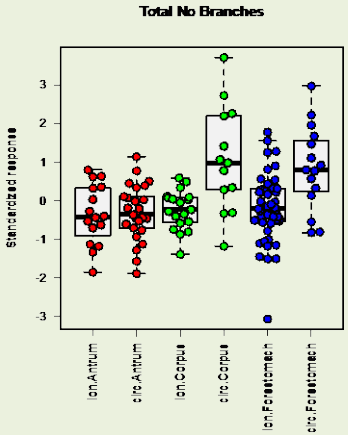


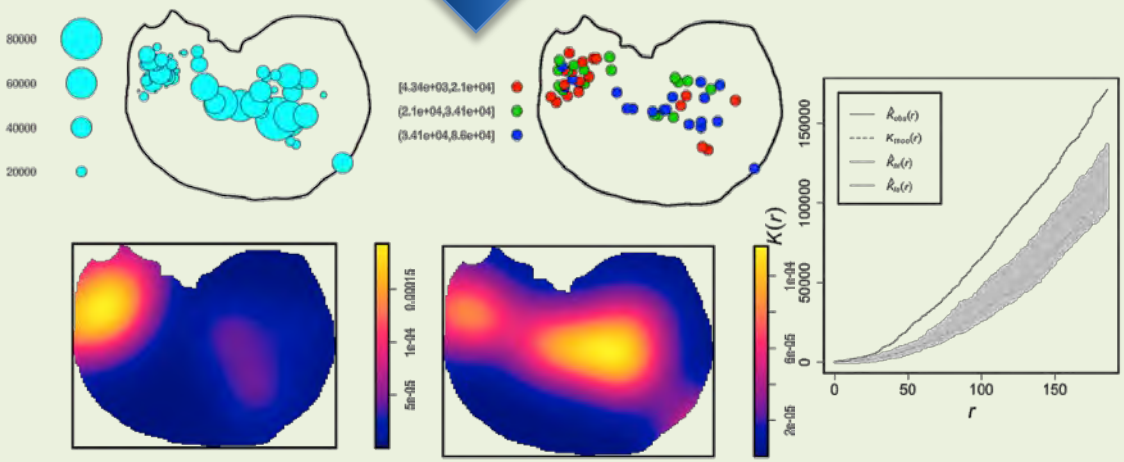
Imaging



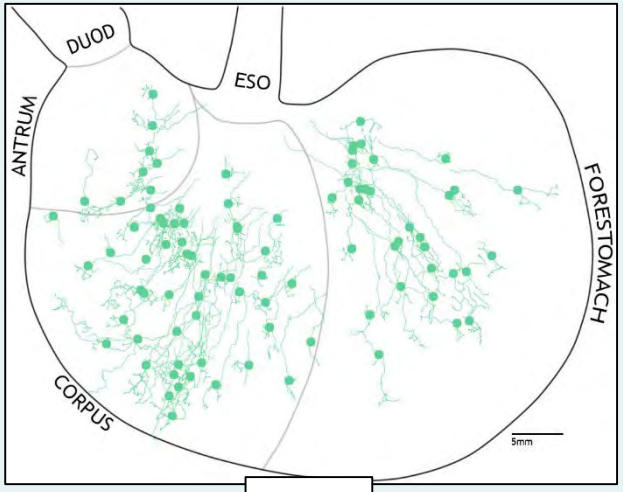
Mapping

Statistical analysis

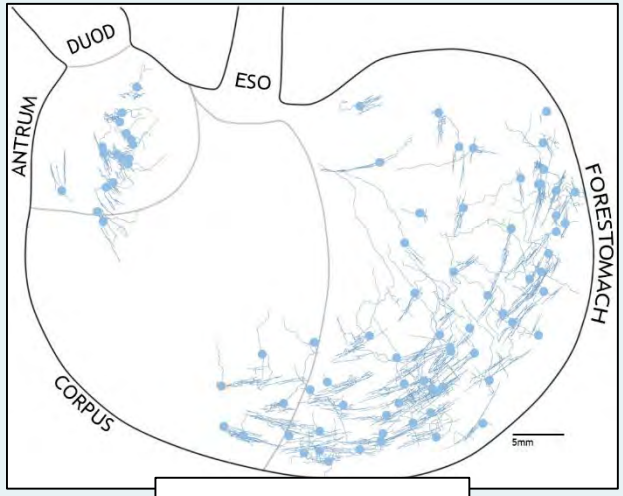




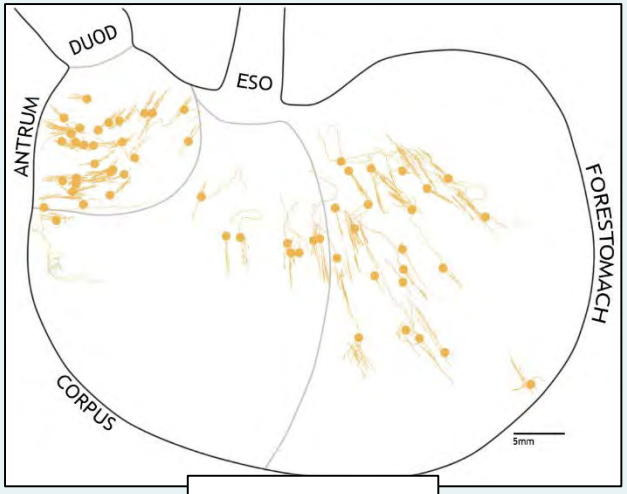
MAPS OF NEURITE ARBOR BRANCHING AND ARBOR ORIGIN DENSITY



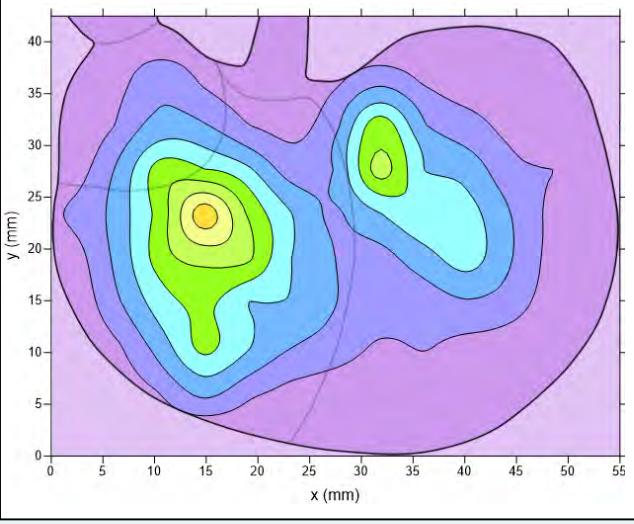
IGLEs

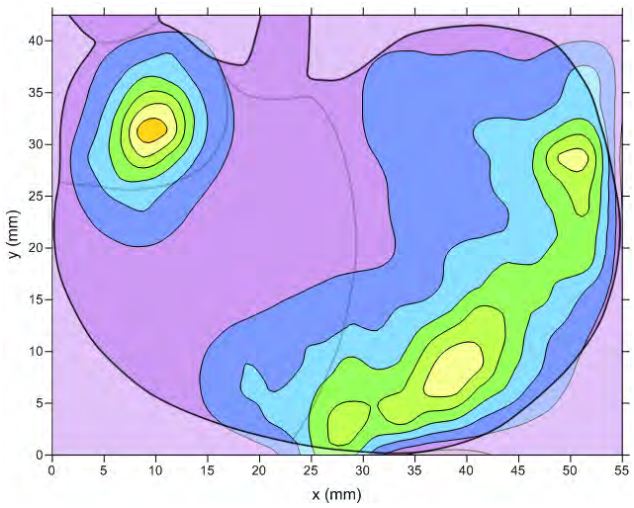


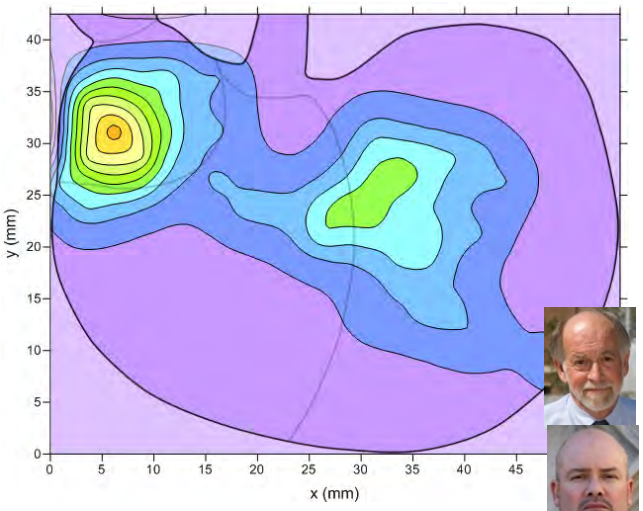
Longitudinal IMAs



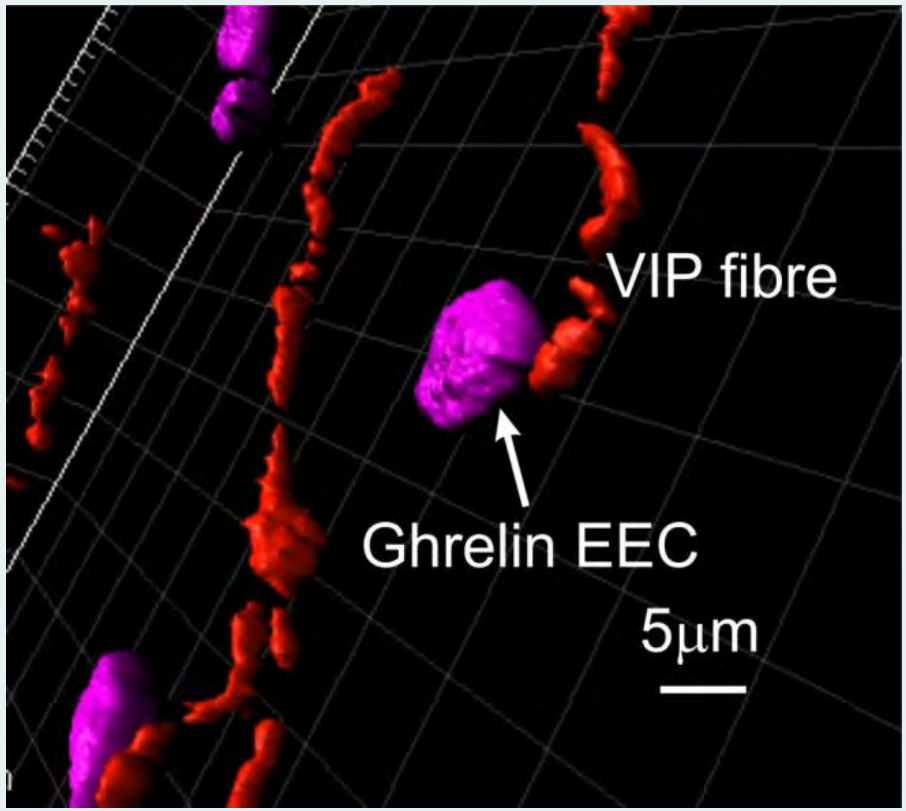
Circular IMAs

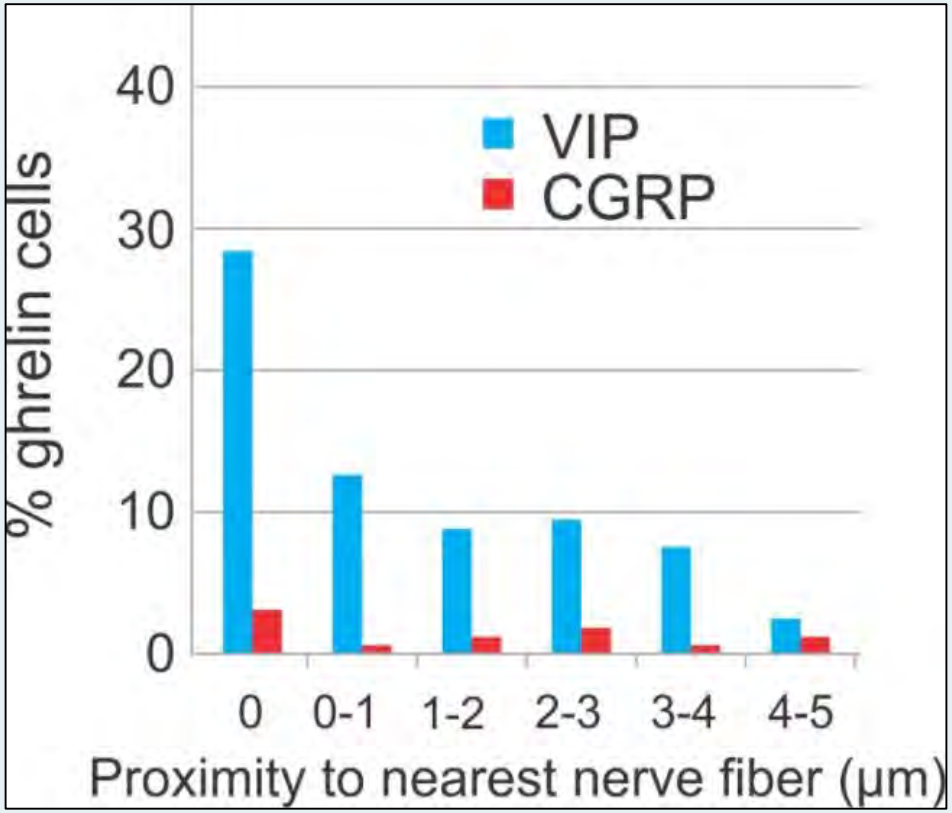






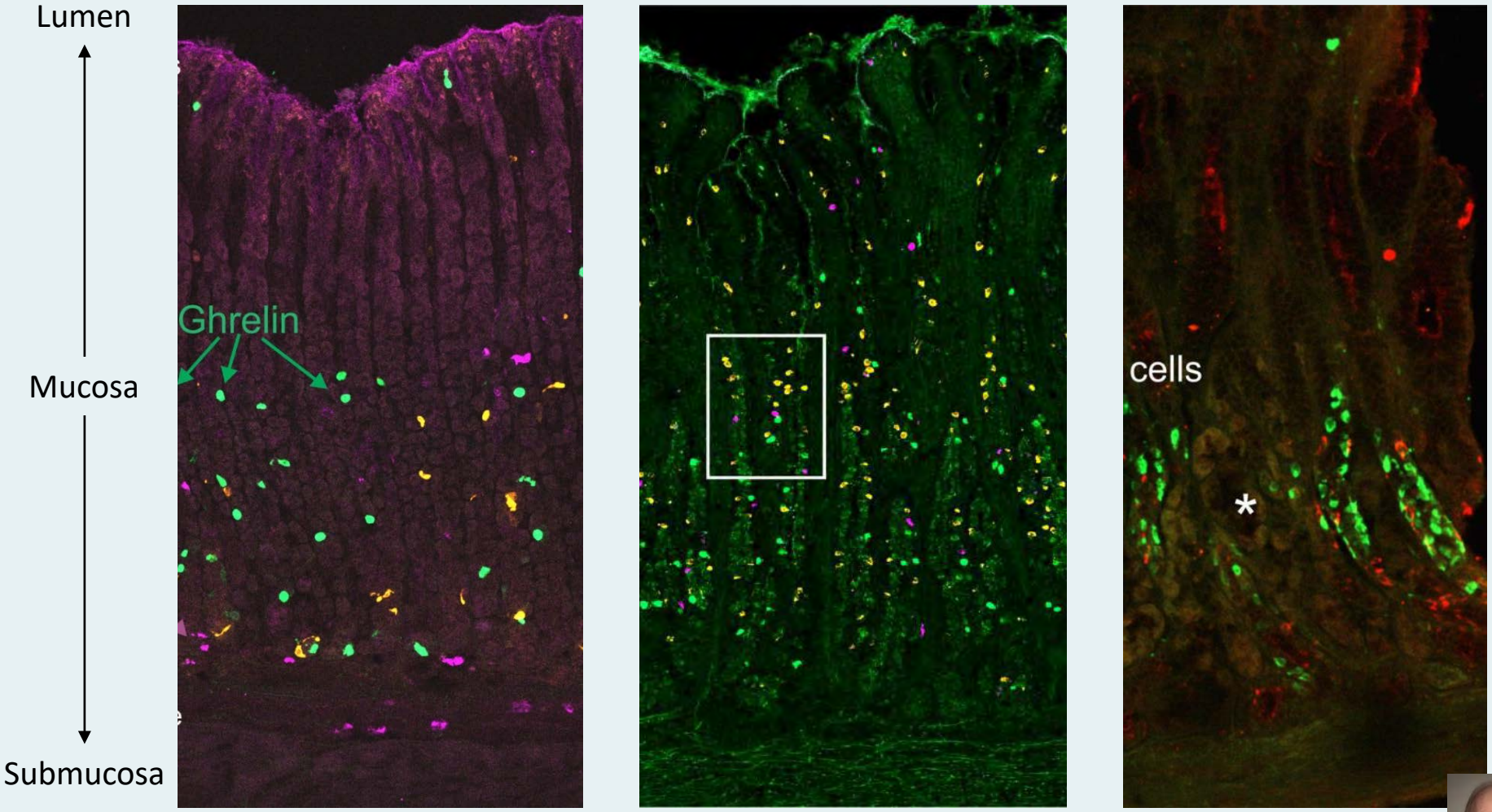
EEC MAPPING AND TRANSLATIONAL STUDIES (FURNESS)



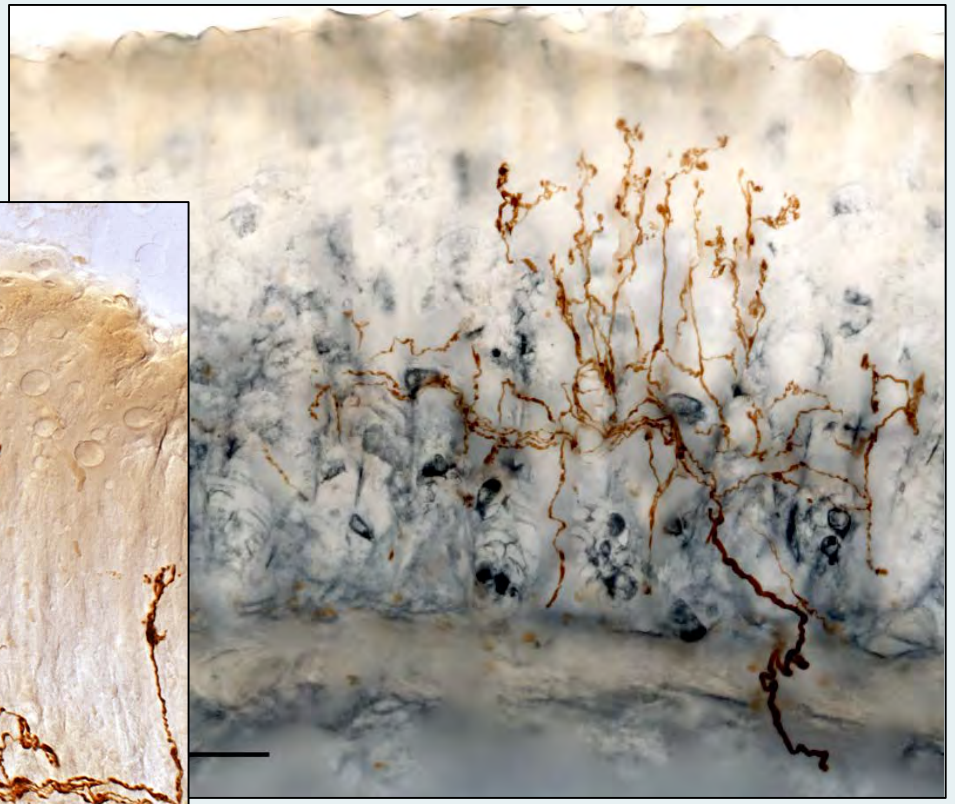


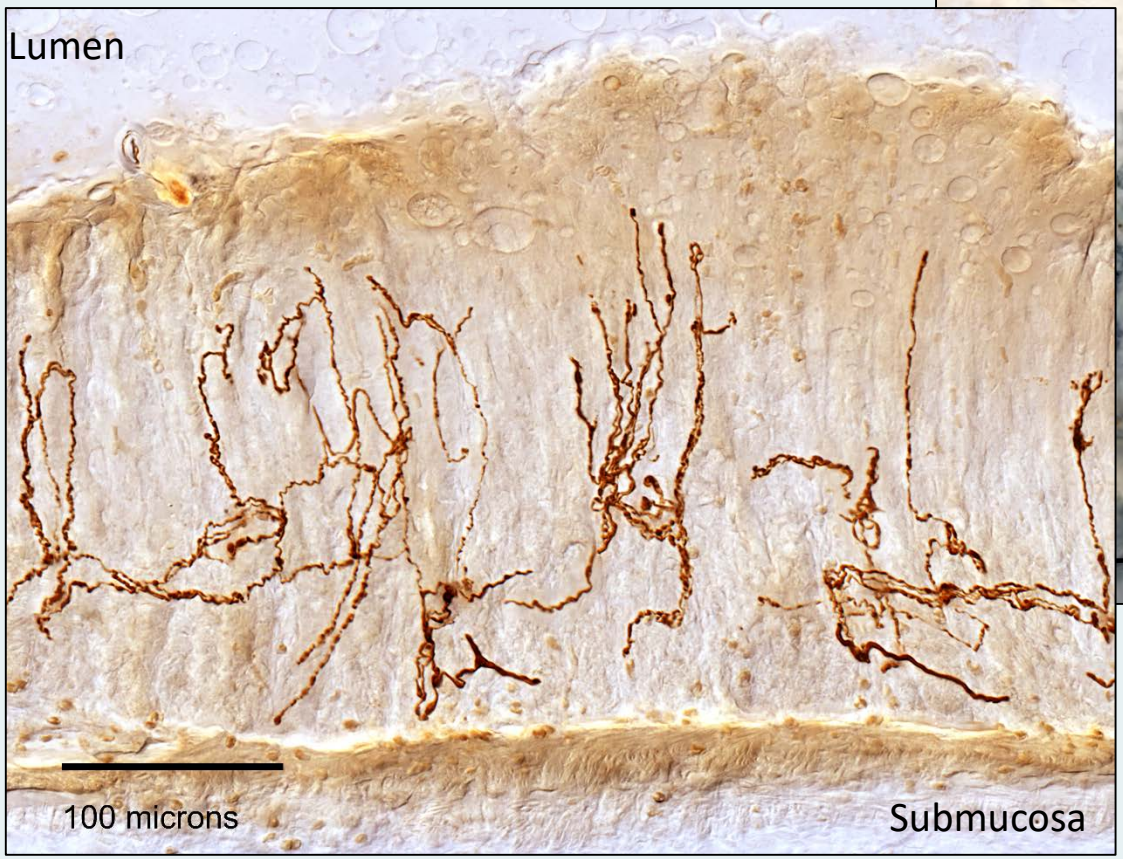
Cells containing ghrelin, a gastric hormone that increases appetite and reduces nausea, are innervated by VIP fibers. Stimulation of ghrelin release may reduce post-prandial satiety and nausea in gastroparesis. 50% of ghrelin cells have a VIP fiber within 2 microns.

EEC MAPPING AND TRANSLATIONAL STUDIES (FURNESS)

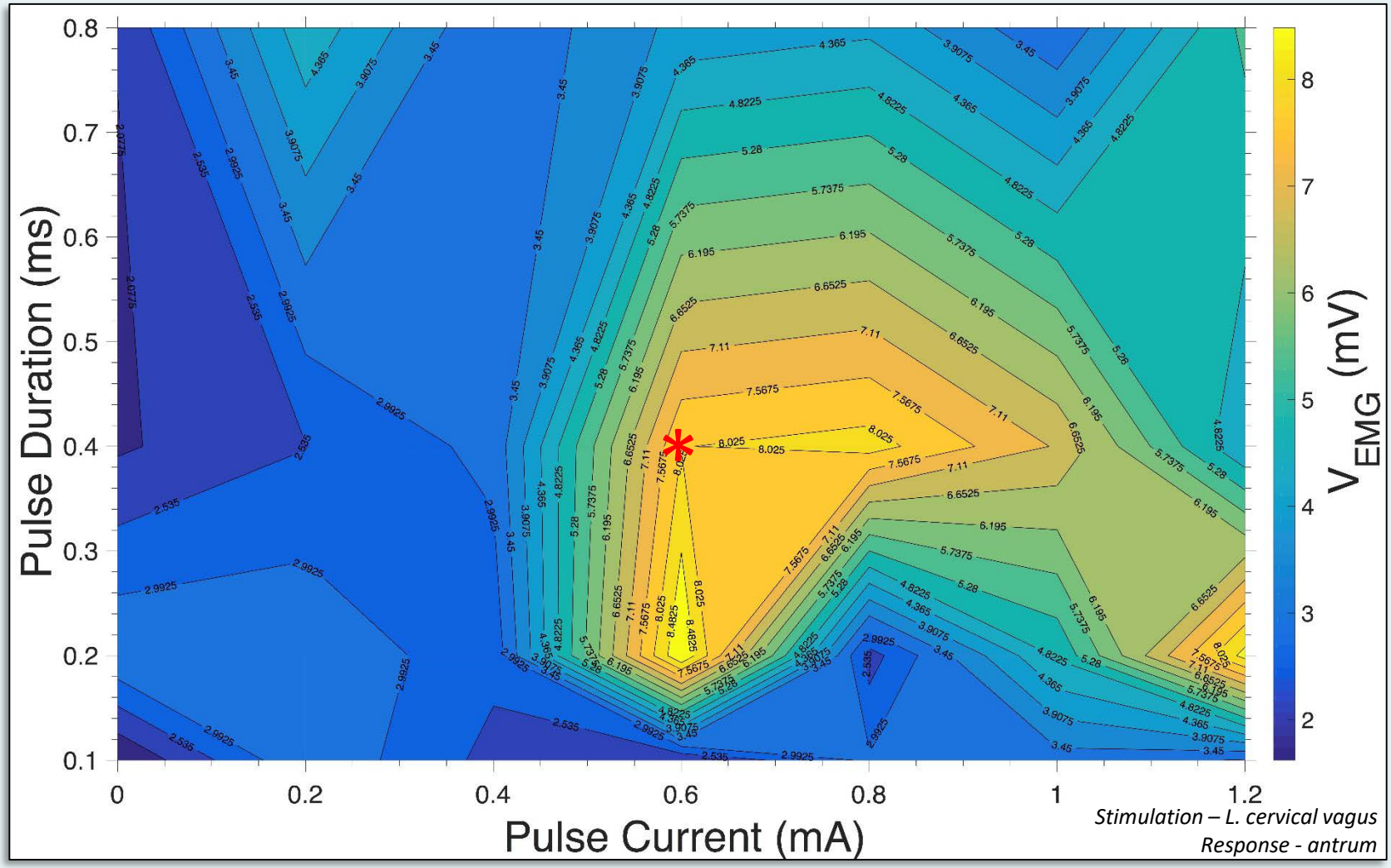


GASTRIC MUCOSA WITH AND WITHOUT GASTRIN DOUBLE LABELING



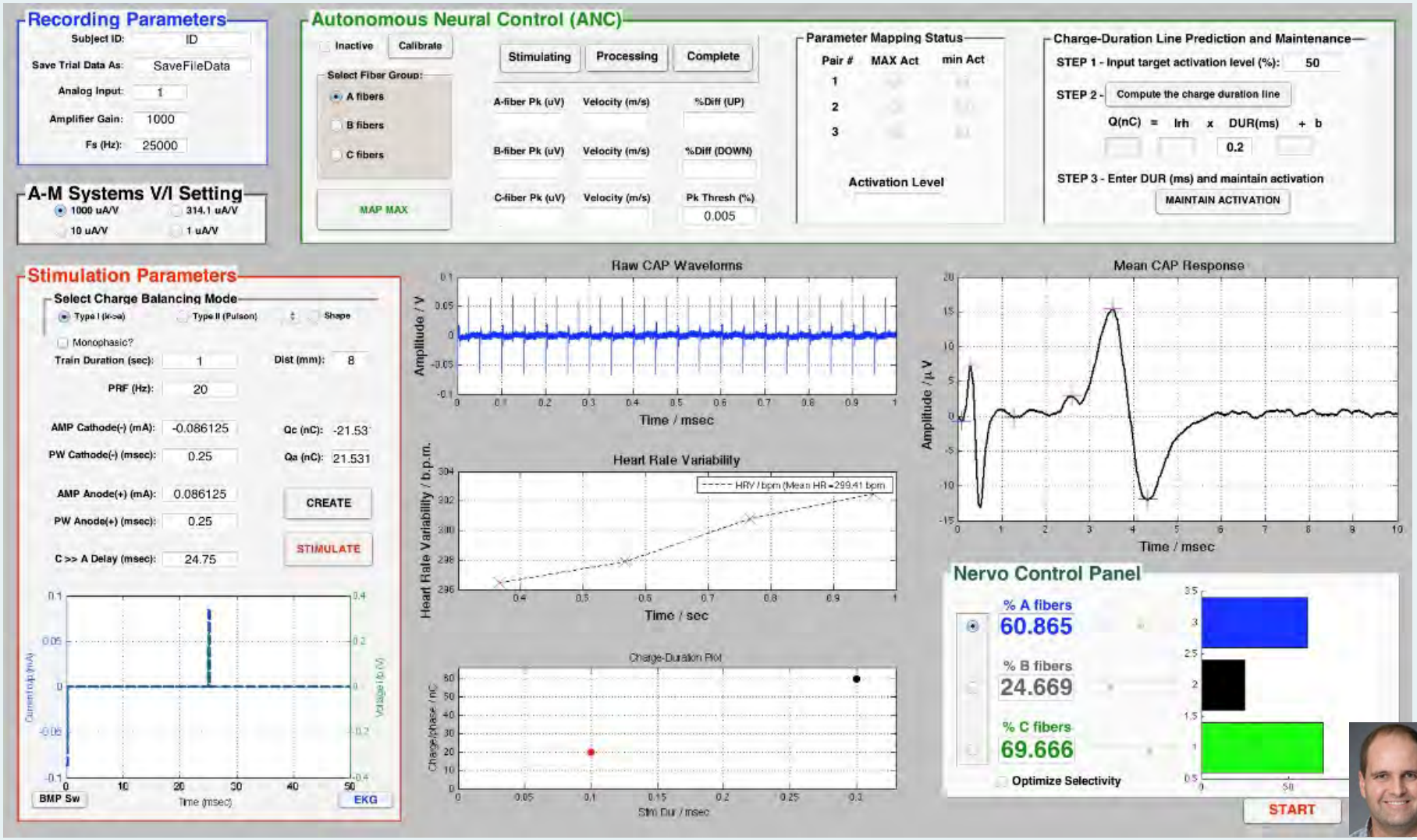


STIMULUS RESPONSE SURFACE (MATT WARD)



Stimulation – L. cervical vagus
Response - antrum

AUTONOMOUS NEURAL CONTROL GUI (MATT WARD)

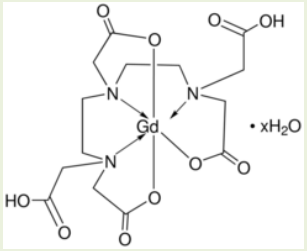


CONTRAST-ENHANCED GASTRIC MRI (ZHONGMING LIU)

Fast

Feed

Gd-DTPA



\+

DietGel

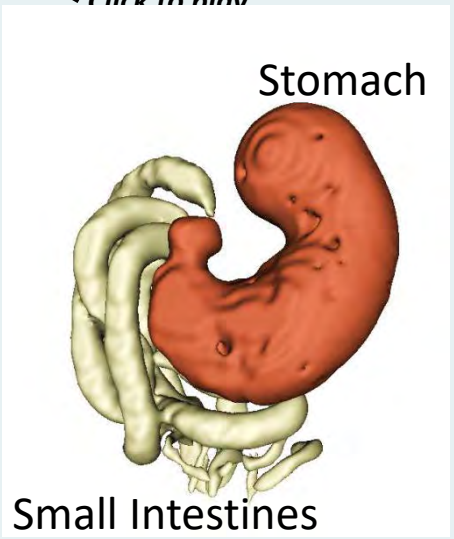
Scan

Lu et al., (2017) IEEE Trans. Biomed. Engr.

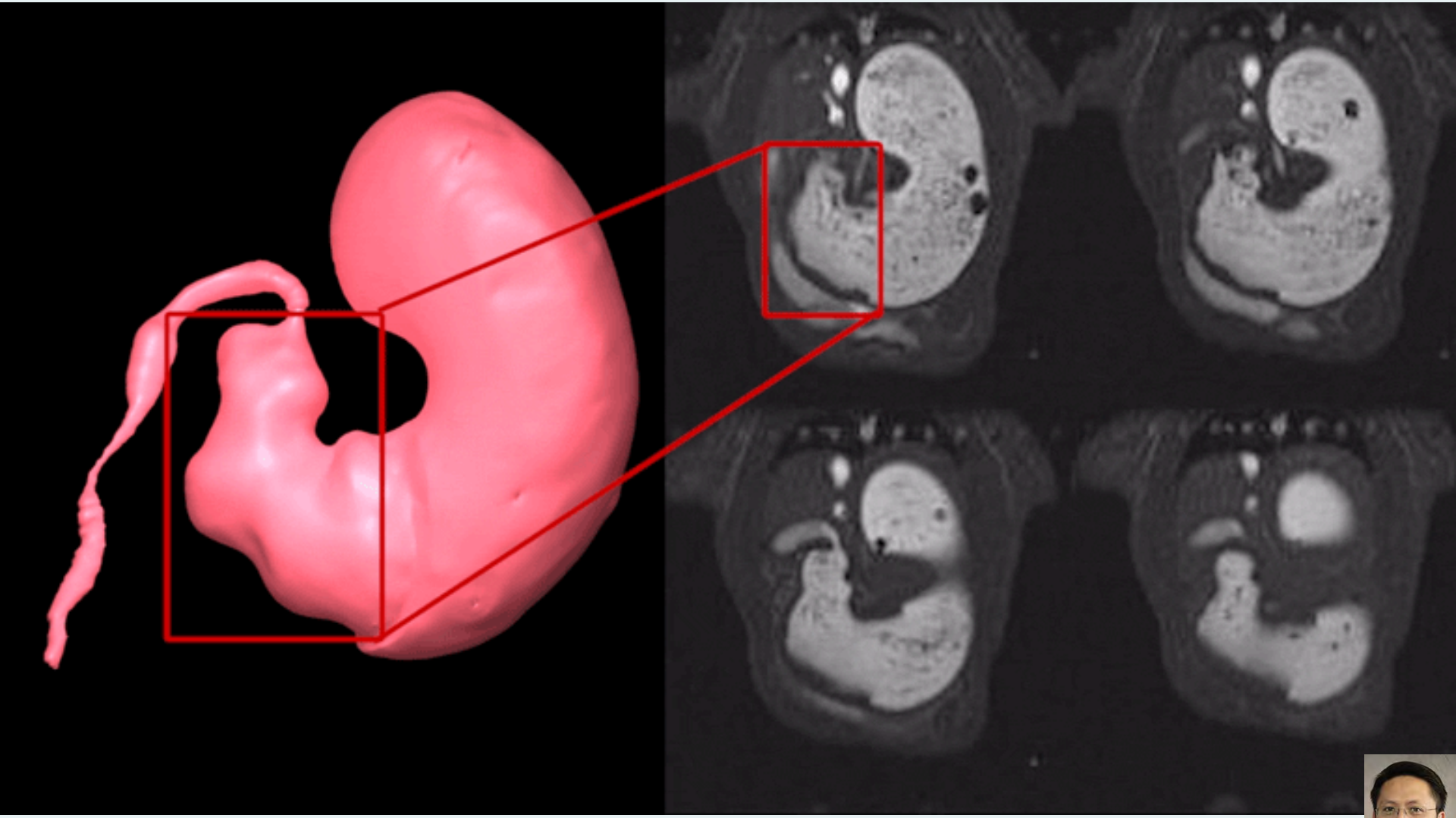
High-resolution Gastric MRI

Click to play

Click to play

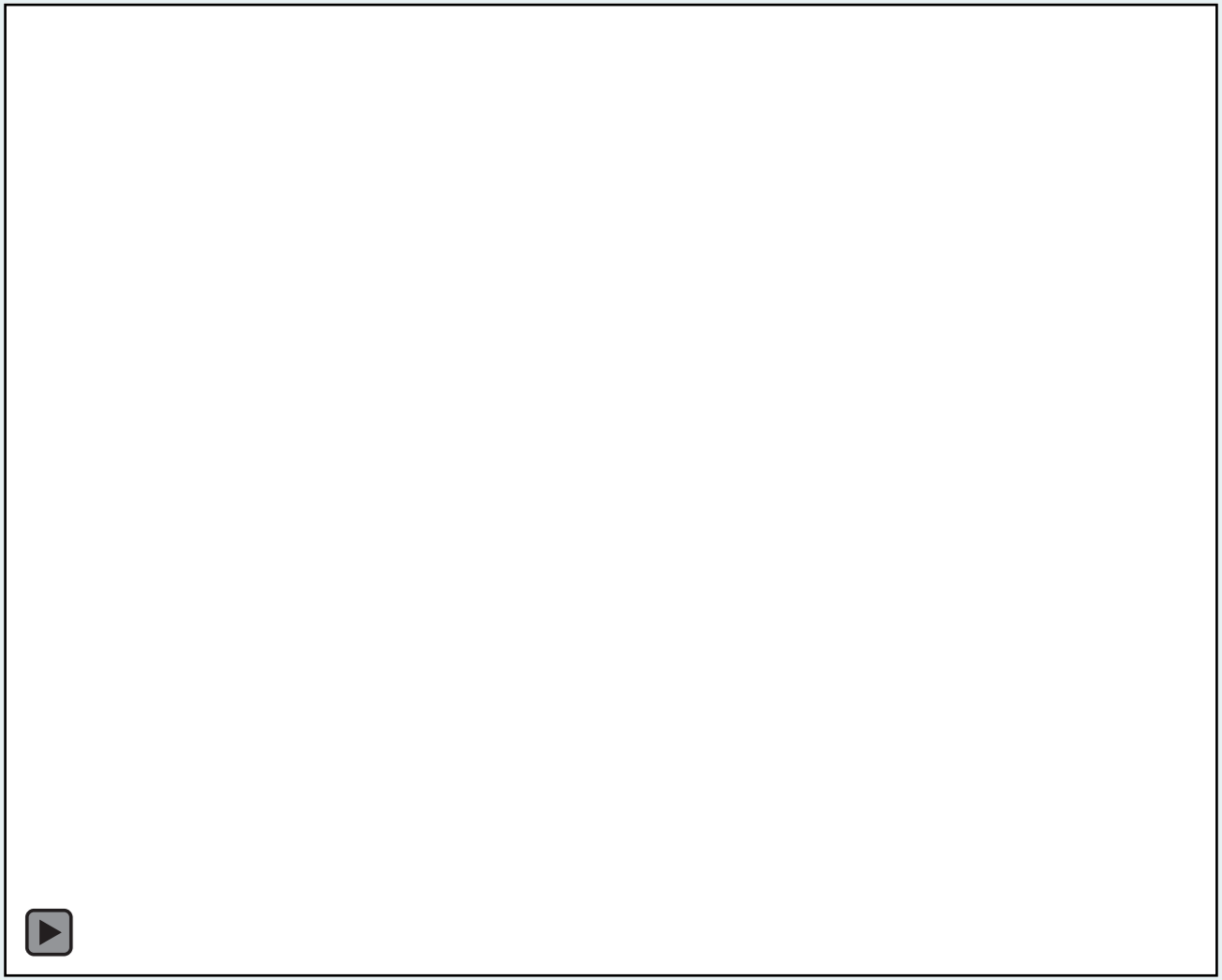


SPARC at Purdue



Lu et al., (2017) IEEE Trans. Biomed. Engr.

HUMAN GASTRIC MRI

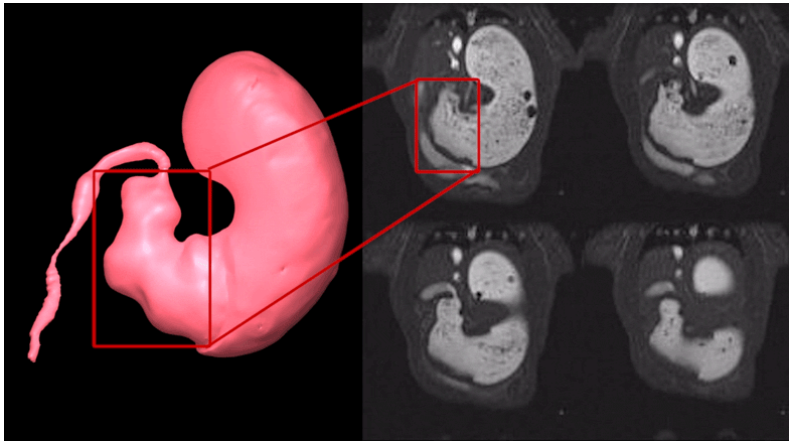


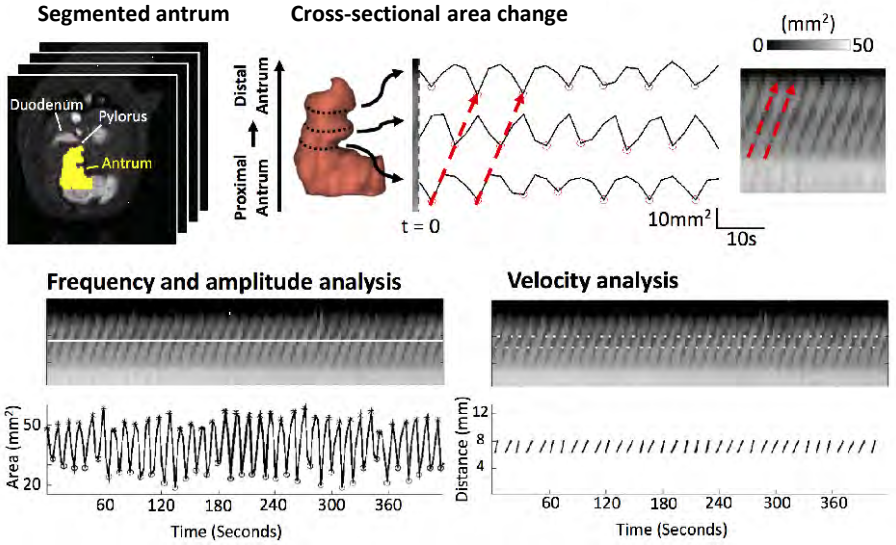
Napadow and Kuo, Harvard/MGH

SPARC at Purdue

Rat

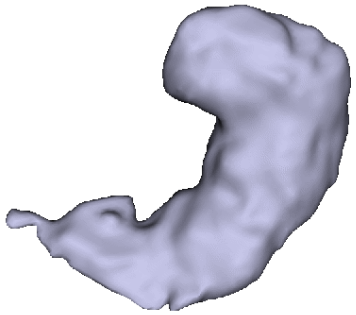
Gastric MRI



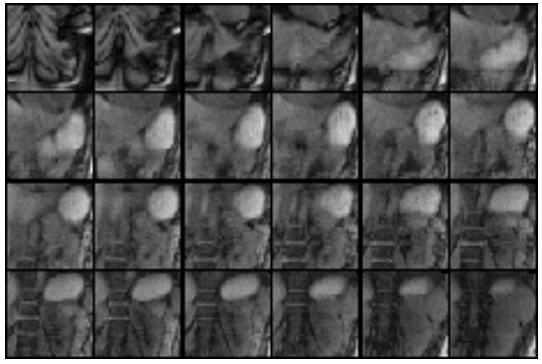


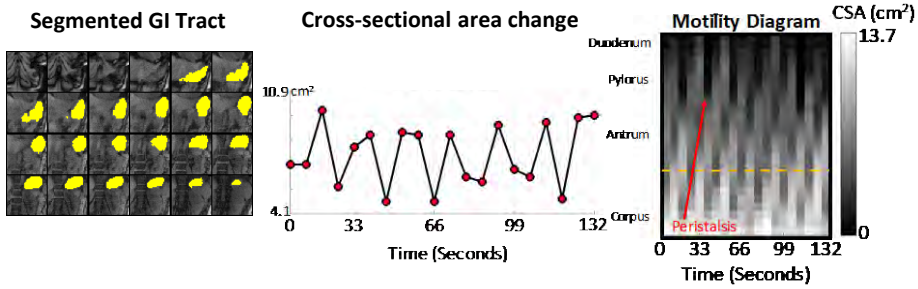
Human

3D-rendered Stomach



Gastric MRI



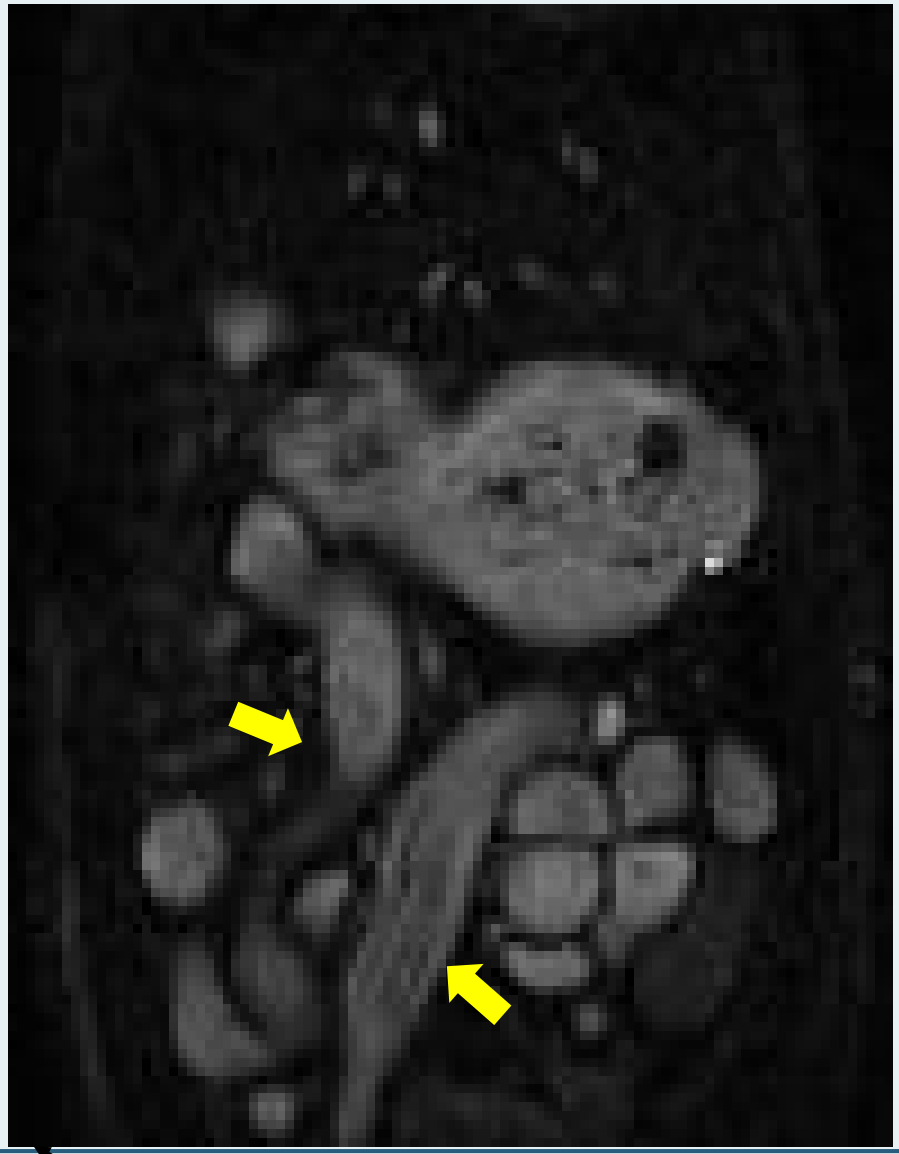


Human Gastric MRI: collaborators Napadow and Kuo at Harvard/MGH -- SPARC/Purdue collaborators

Segmentation, Analysis and Rendering of Human Gastric MRI: Lu and Liu

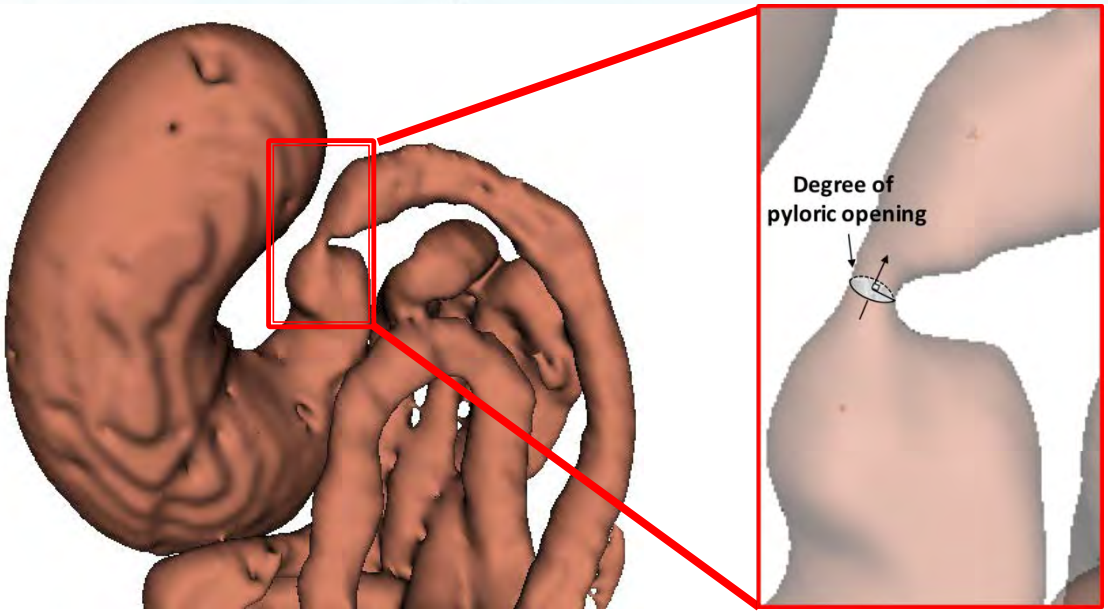
Translational gastric imaging and analysis protocols. **Left:** Rat gastric MRI. **Right:** Human gastric MRI.

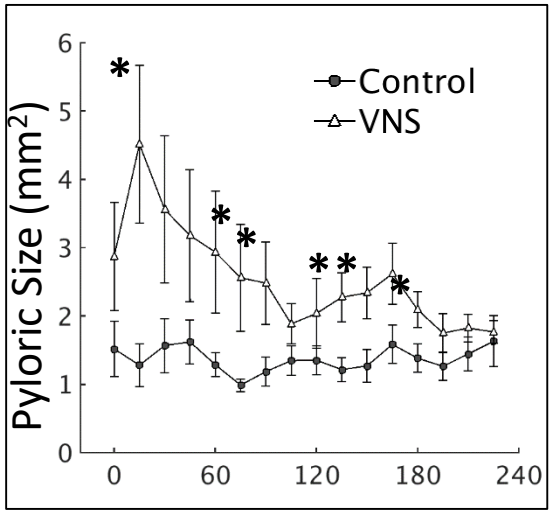
Small Intestinal Motility



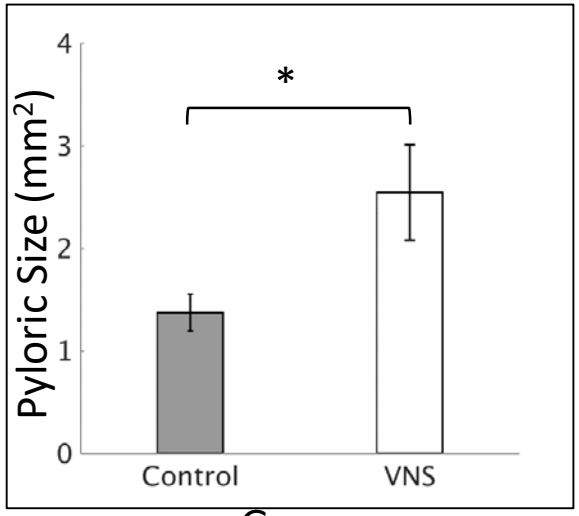
Click to play

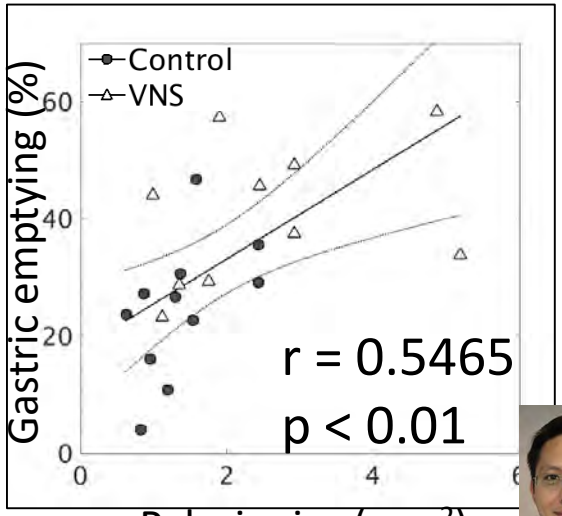
SPARC at Purdue



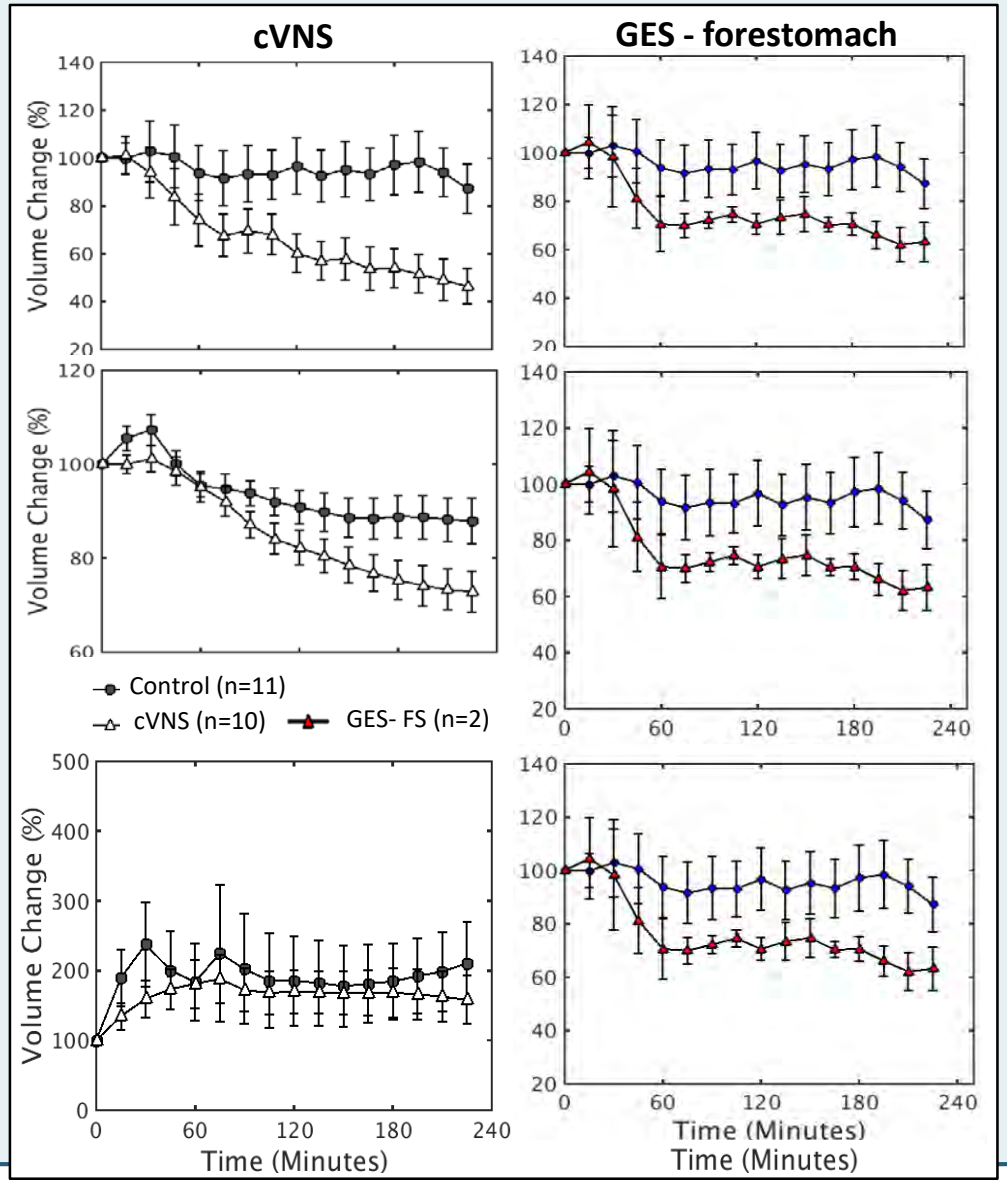


VNS promotes stomach emptying by increasing pyloric opening

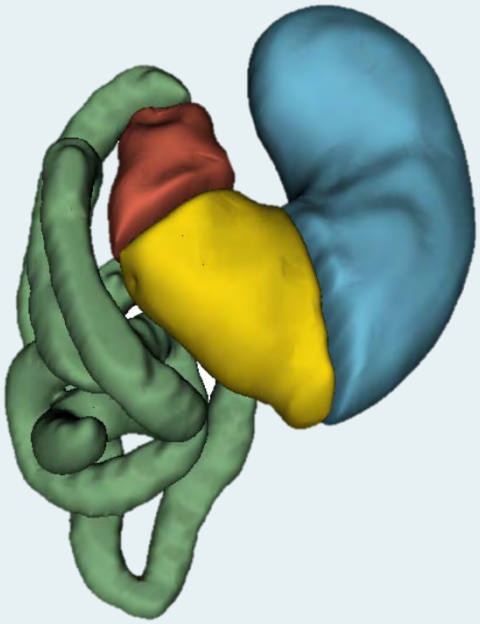




SPARC at Purdue



cVNS *vs.* GES

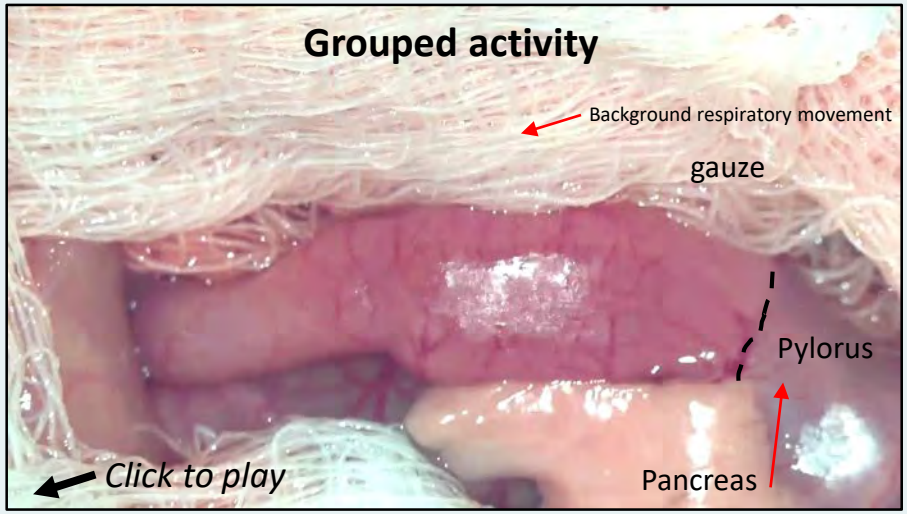


cVNS may promote
- ↑ Gastric emptying
- ~ Intestinal absorption

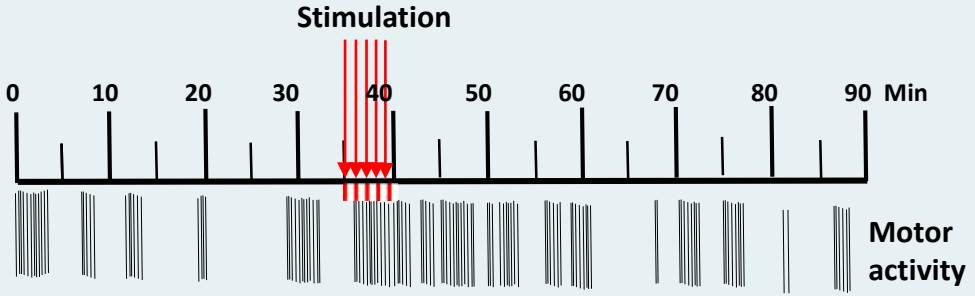
GES-FS may promote
- ↑ Gastric emptying
- ↑↑ Intestinal absorption

DUODENAL MOTILITY (TAN, WARD, ZHANG, POWLEY)

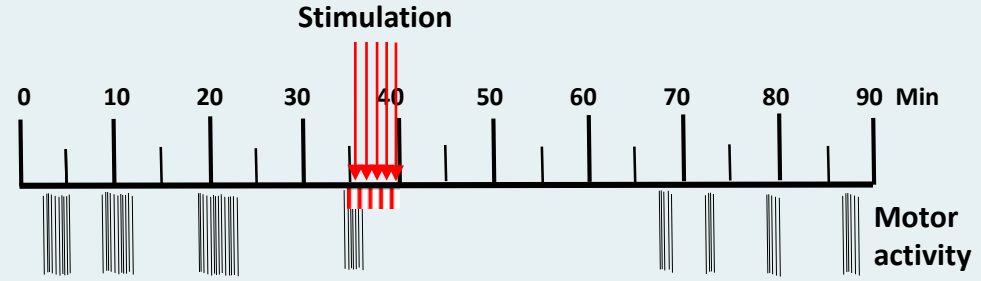
PERISTALSIS

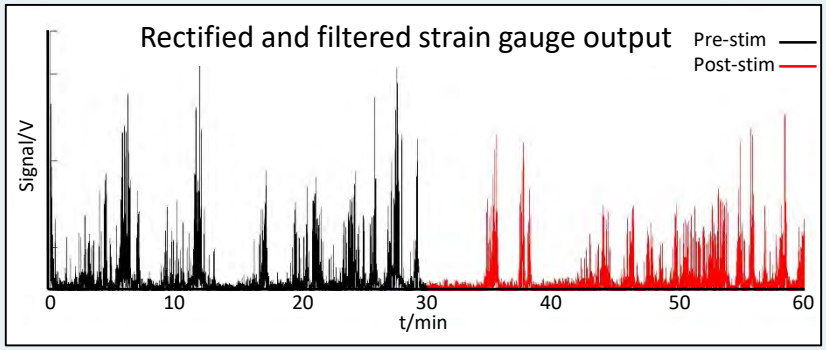


Electrode located in forestomach area of concentration of **longitudinal IMA "hotspot"**:



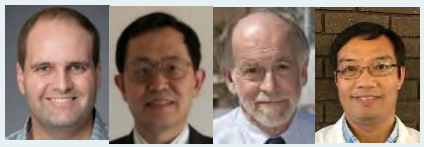
Electrode located close to limiting ridge i.e. affecting **corpus** and not on "stretch" receptor concentration:



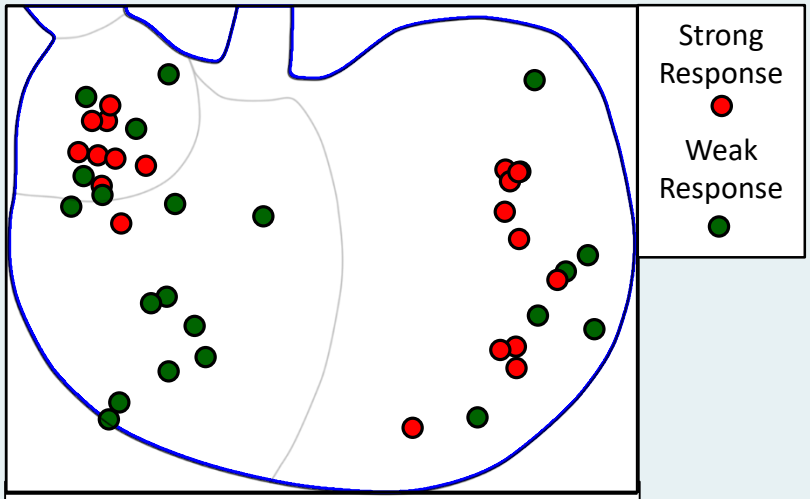


Visual observation

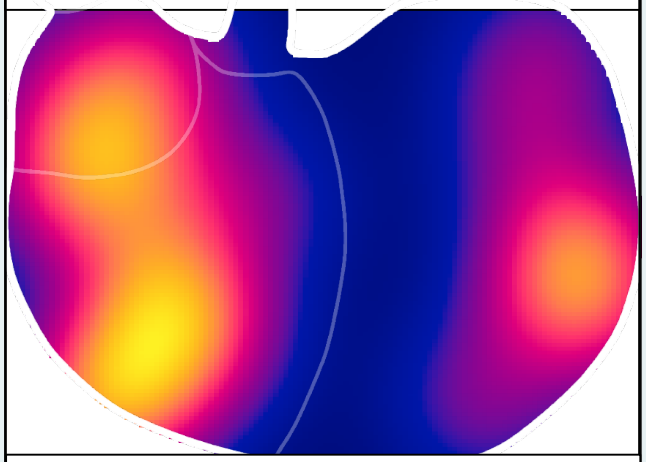
Strain gauge quantification



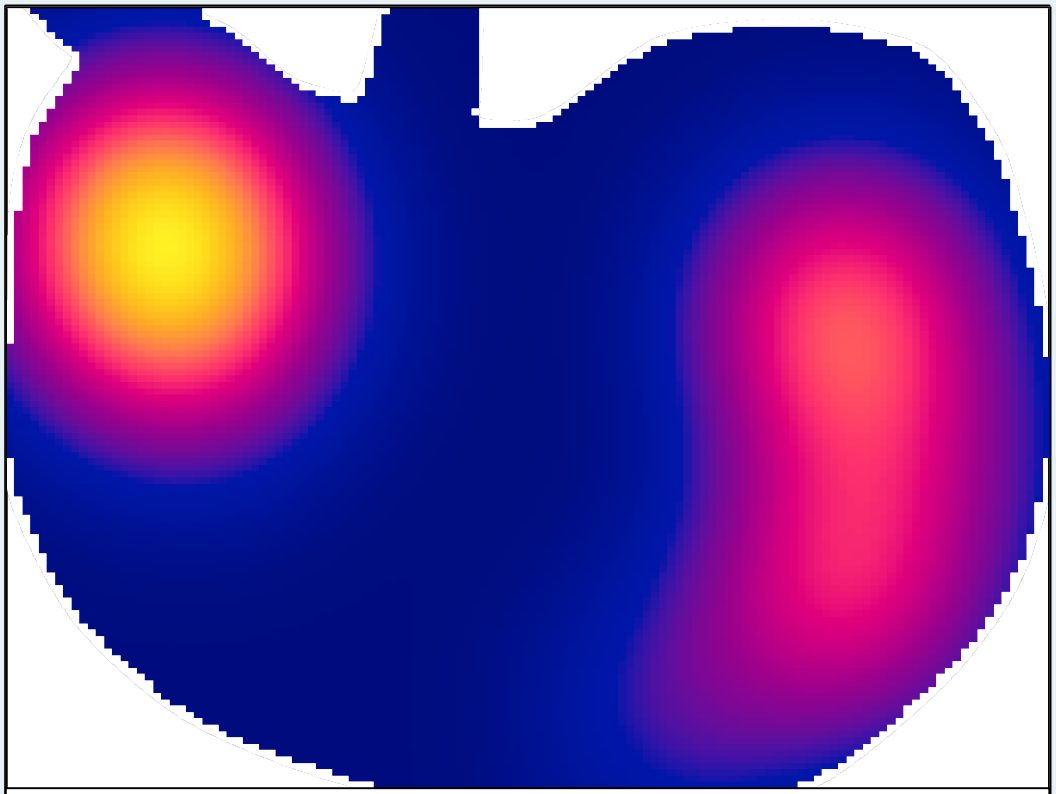
DUODENAL MOTILITY RESPONSE DEPENDS ON STIMULATION LOCATION



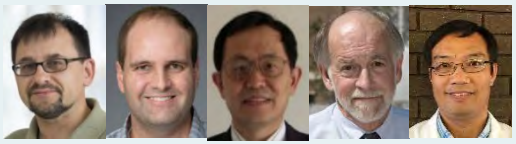
Distribution of stimulation locations to date



Distribution of weak response results



Distribution of strong response results

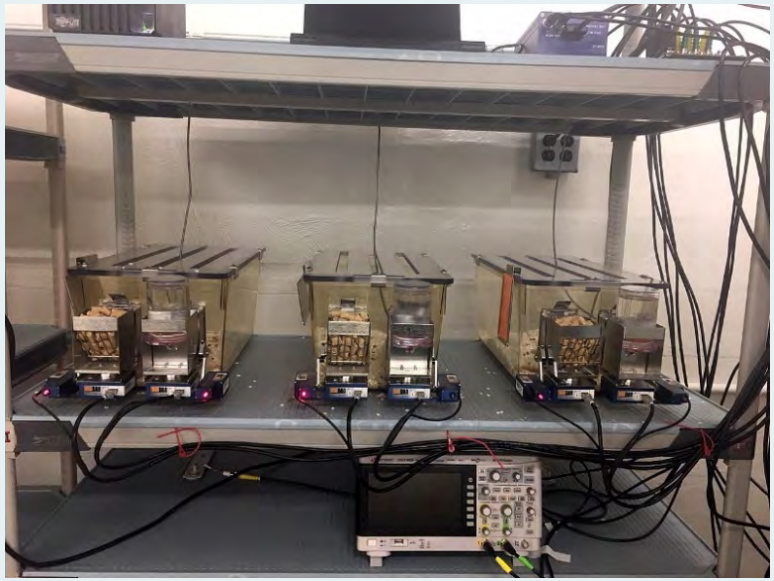


ONGOING CHRONIC FEEDING STUDY (PHILLIPS)

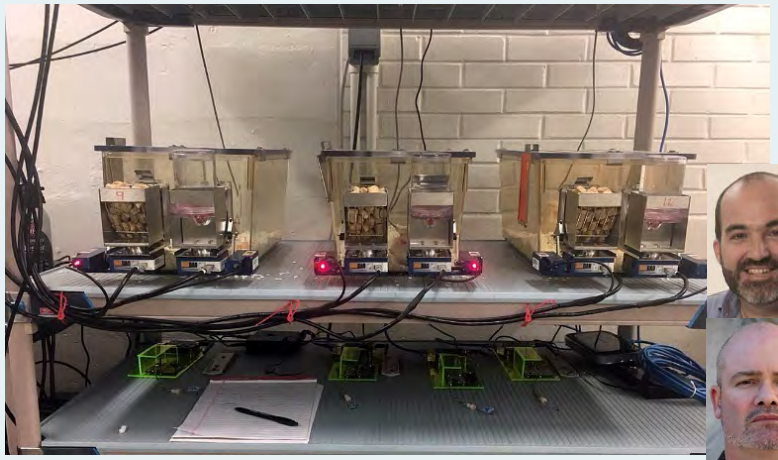
- Twelve rats with implanted improved patch electrodes are currently housed in home cages outfitted with BioDAQ feeders; Panel A.
- All 12 rats are tethered to overhead commutators and are receiving 12-hours of stimulation (6 pm to 6 am) using either a PlexStim electrical stimulator controlled by PlexStim software (Plexon Systems) or Bionode stimulators; Panels B and C, respectively.
- All 12 rats are habituated to the feeding system, behavioral paradigm, and stimulation protocol as validated by stable nightly food and water intake.

A

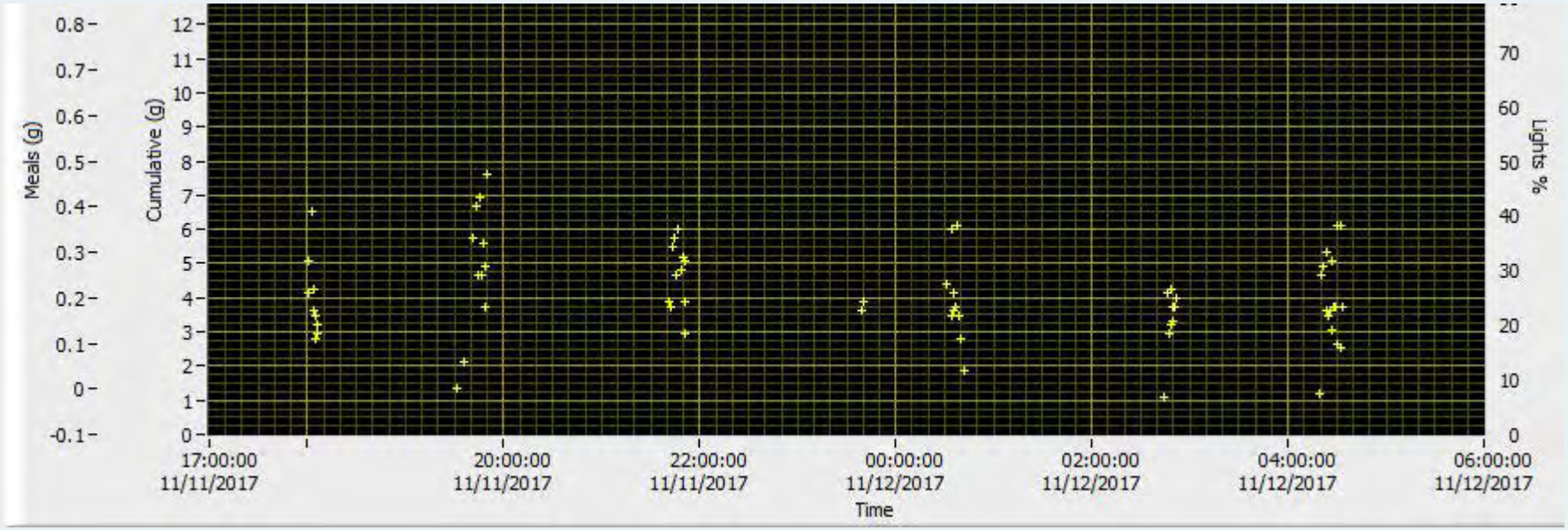
B



C



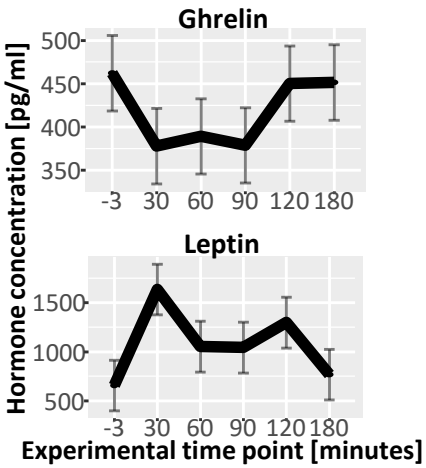
MICROSTRUCTURAL ANALYSIS OF FOOD INTAKE (PHILLIPS)



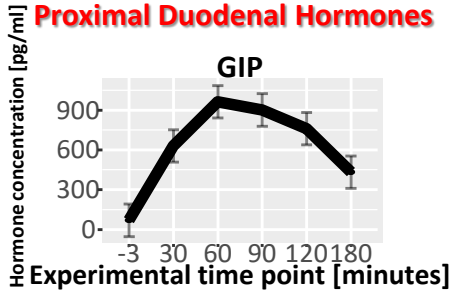
- Size of a Meal = Satiation — 2.21 grams
- Time Between Meals = Satiety — 78 minutes
- Number of Meals — 7 meals
- Total Daily Intake — 15.47 grams

FEEDING EXPERIMENT

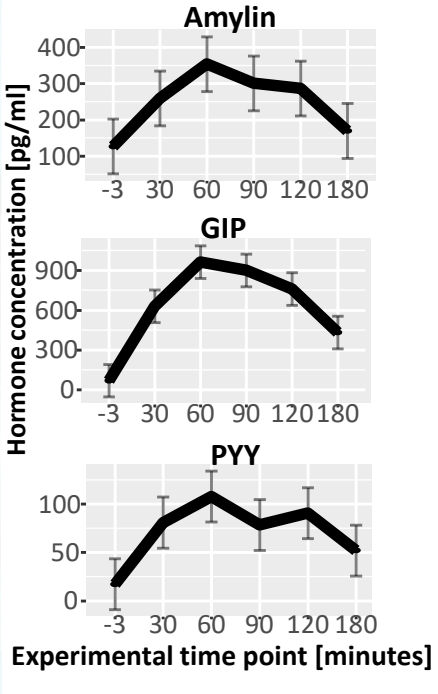
Stomach Hormones



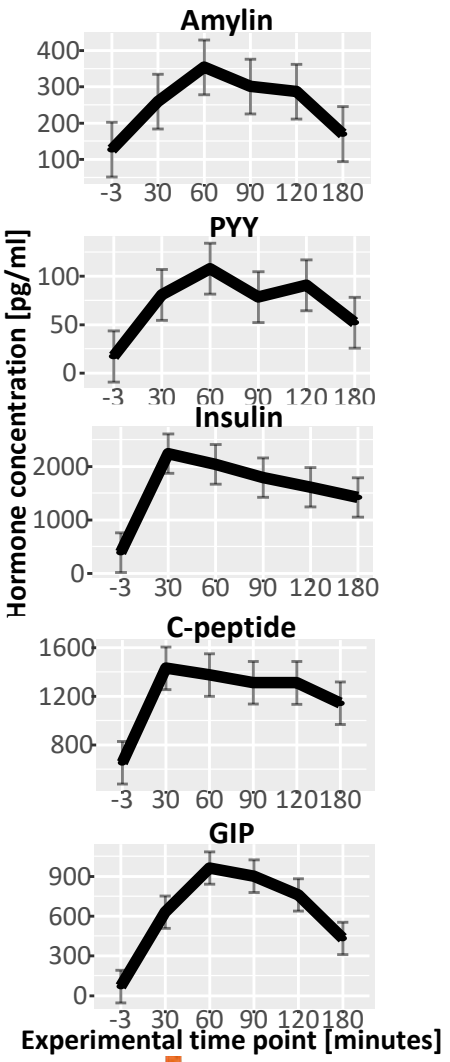
Proximal Duodenal Hormones



Inhibiting Gastric Emptying

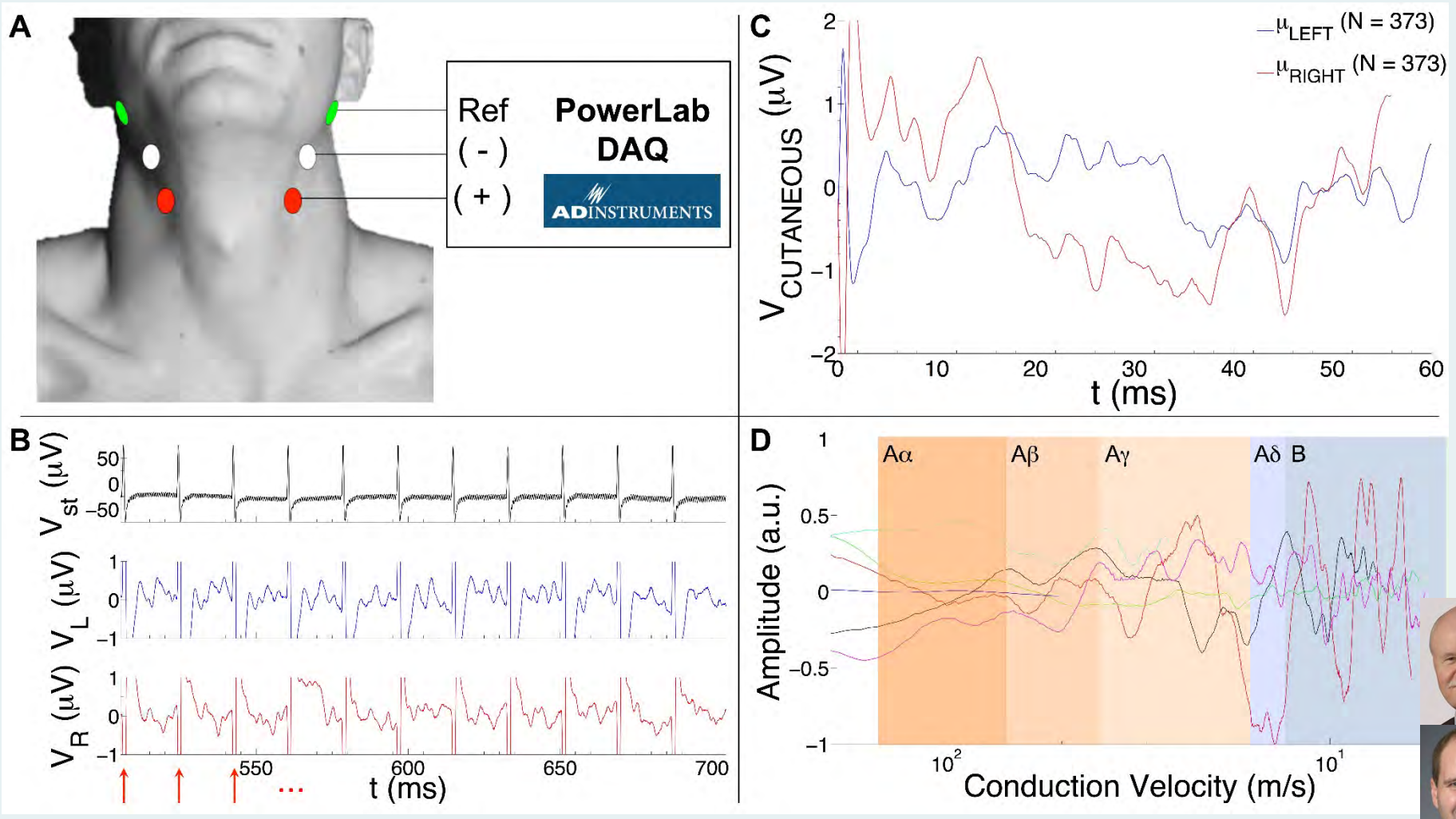


Pancreas / Carbohydrate Homeostasis



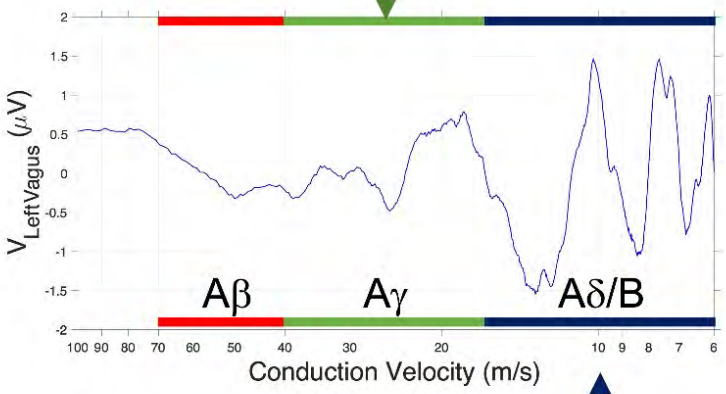
- As illustrated by the pattern seen in the accompanying graphs, a small high-carbohydrate "meal" elicits an apparent transient drop in gastric ghrelin release and a short spike in gastric release of leptin. As the meal reaches the duodenum, GIP release is triggered. As absorption of the carbohydrate load progresses, a multifactorial battery of blood glucose regulatory adjustments, including the release of insulin and C-peptide in the parallel and proportionate patterns expected, as well as the release of amylin and PYY in addition to GIP, each of which potentiates pancreatic insulinogenic control of carbohydrate and simultaneously delays further gastric emptying.

SUMMARY OF VAGAL SIGNAL PROCESSING AND FEATURE IDENTIFICATION



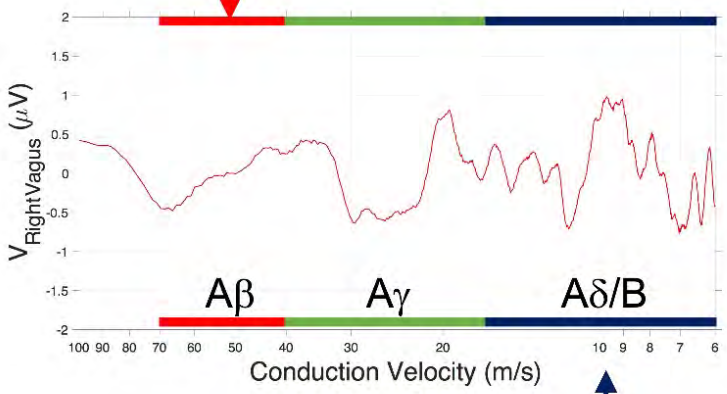
PRIMARY FINDINGS OF OUR YEAR 1 OBSERVATIONAL STUDY

Left vagal Ag fiber volley:
- Predicts reduced nausea, vomiting, early satiety and bloating ($p<0.05$)
- Predicts reduced epigastric pain, epigastric burn, cardiac pain and cardiac burn ($p<0.01$)

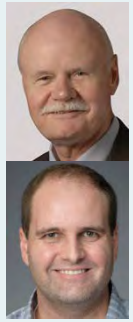


Left vagal Ad/B fiber volley:
- Predicts reduced fullness ($p<0.05$)

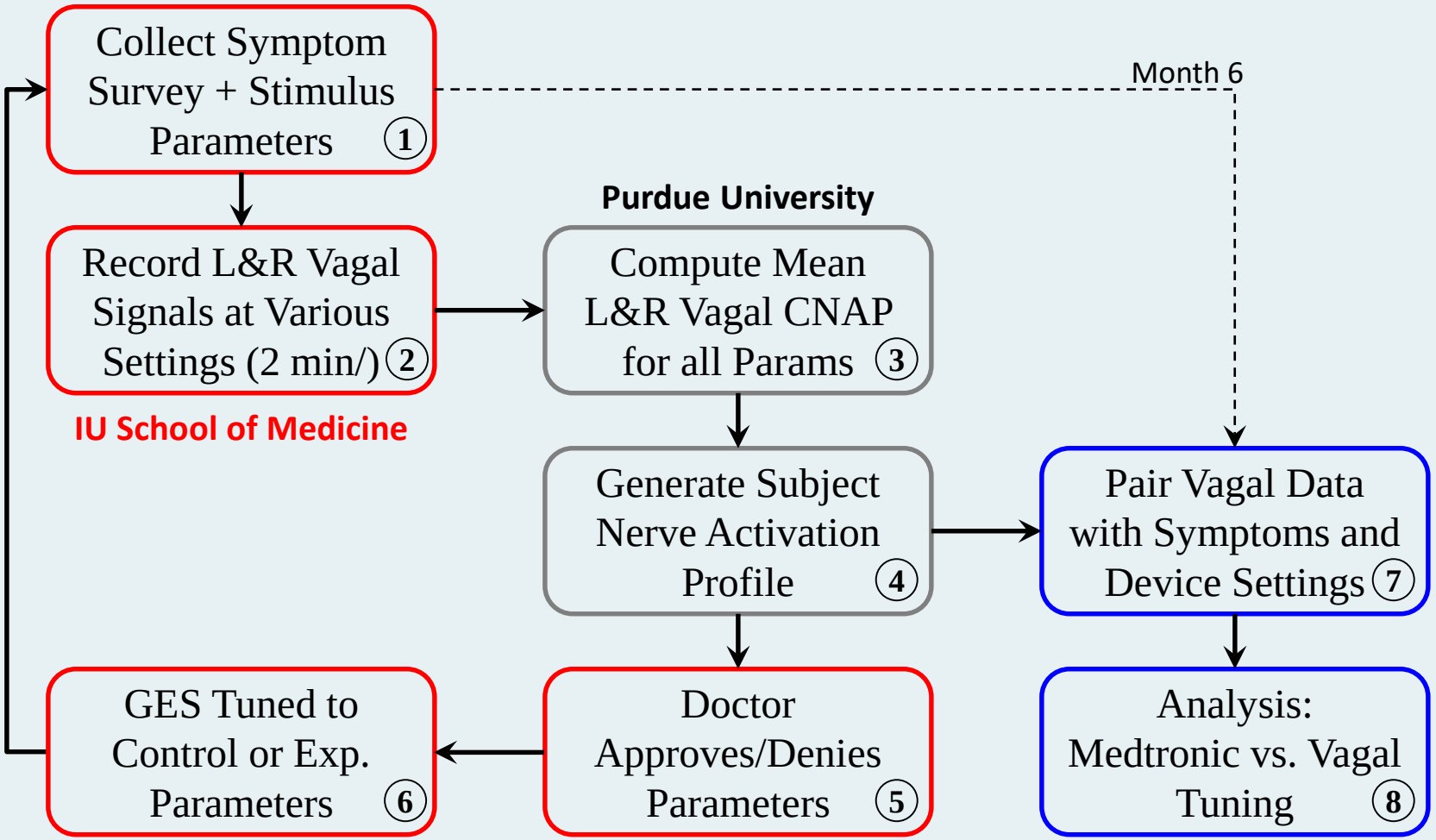
Right vagal Ab fiber volley:
- Predicts reduced epigastric pain severity and cardiac burn ($p<0.05$)
- Predicts reduced epigastric pain frequency ($p<0.01$)



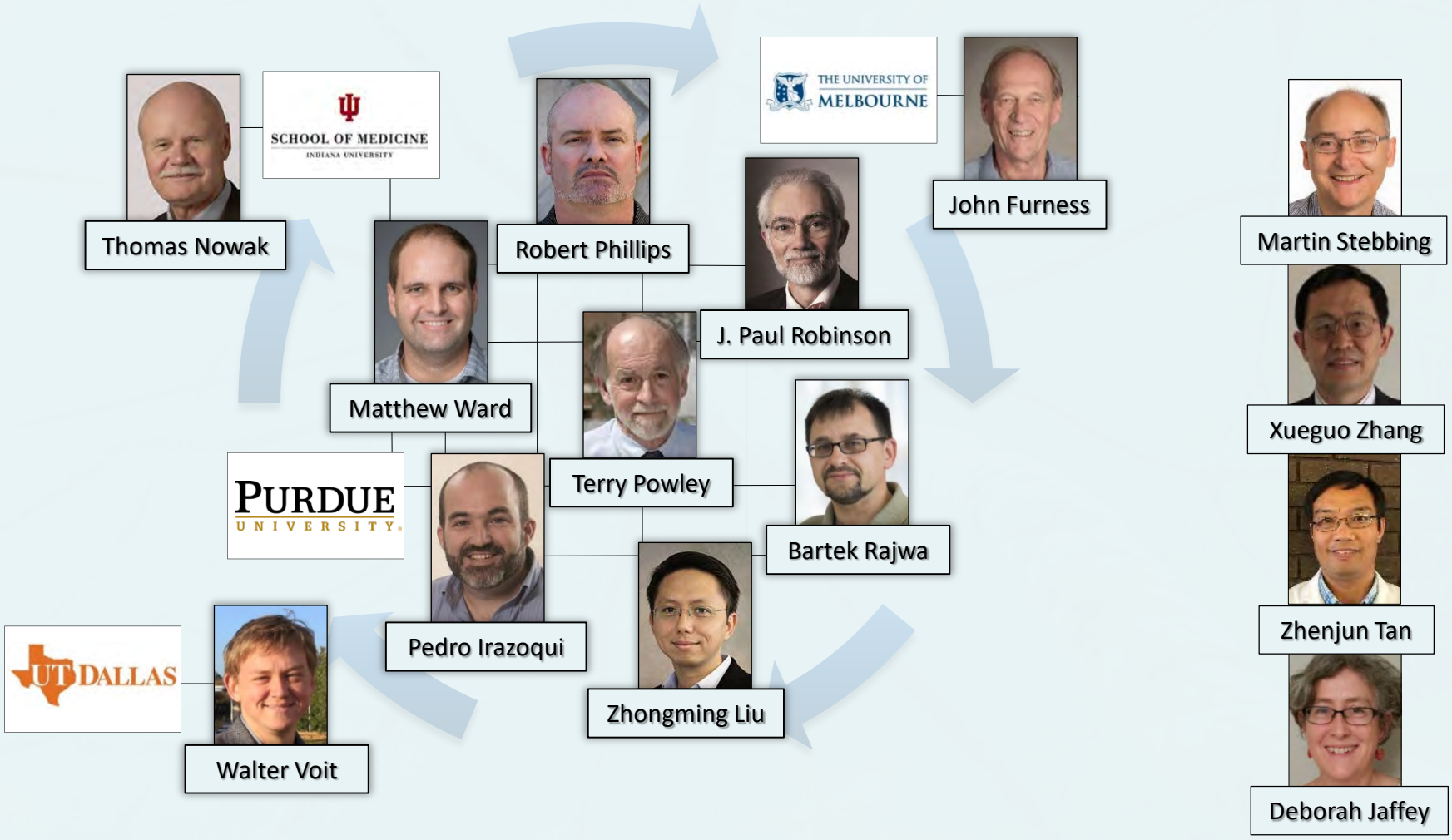
Right vagal Ad/B fiber volley:
- Predicts reduced vomiting frequency, early satiety severity, epigastric burn severity, cardiac burn and anxiety ($p<0.05$)



METHODS SUMMARY: PROSPECTIVE STUDY



INTERDISCIPLINARY SYNERGY



BEGINNING COLLABORATIVE EXTENSIONS

John Wo, Ch. A. Kubal

Leif Havton

Warren Grill, Nikki Pelot

Thomas Nowak

Robert Phillips

Matthew Ward

Terry Powley

Pedro Irazoqui

Zhongming Liu

Walter Voit

John Furness

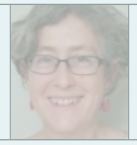
Paul Robinson

Bartek Rajwa

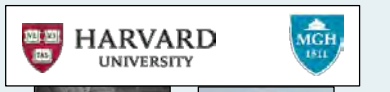
Martin Stebbing

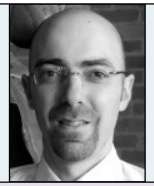
Xueguo Zhang

Zhenjun Tan



Deborah Jaffey



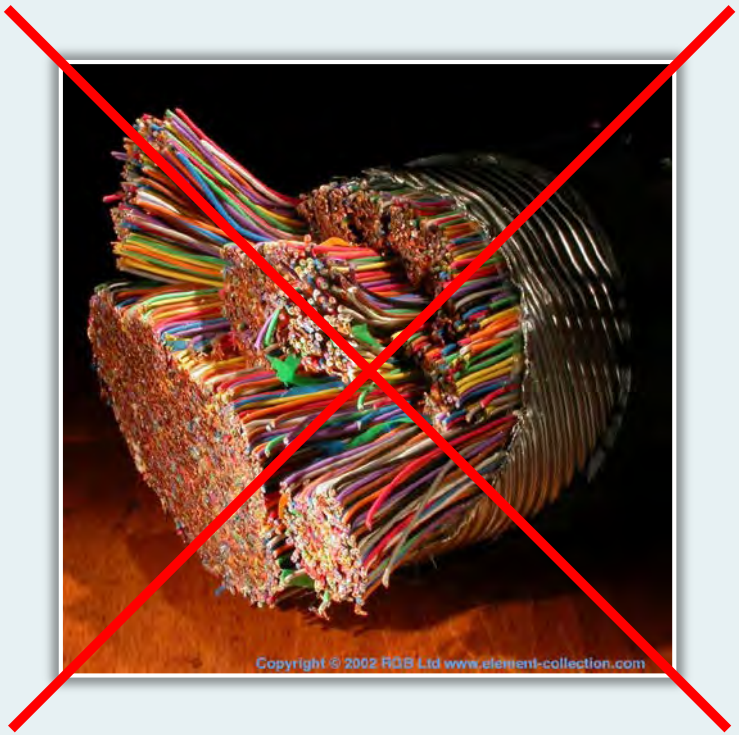


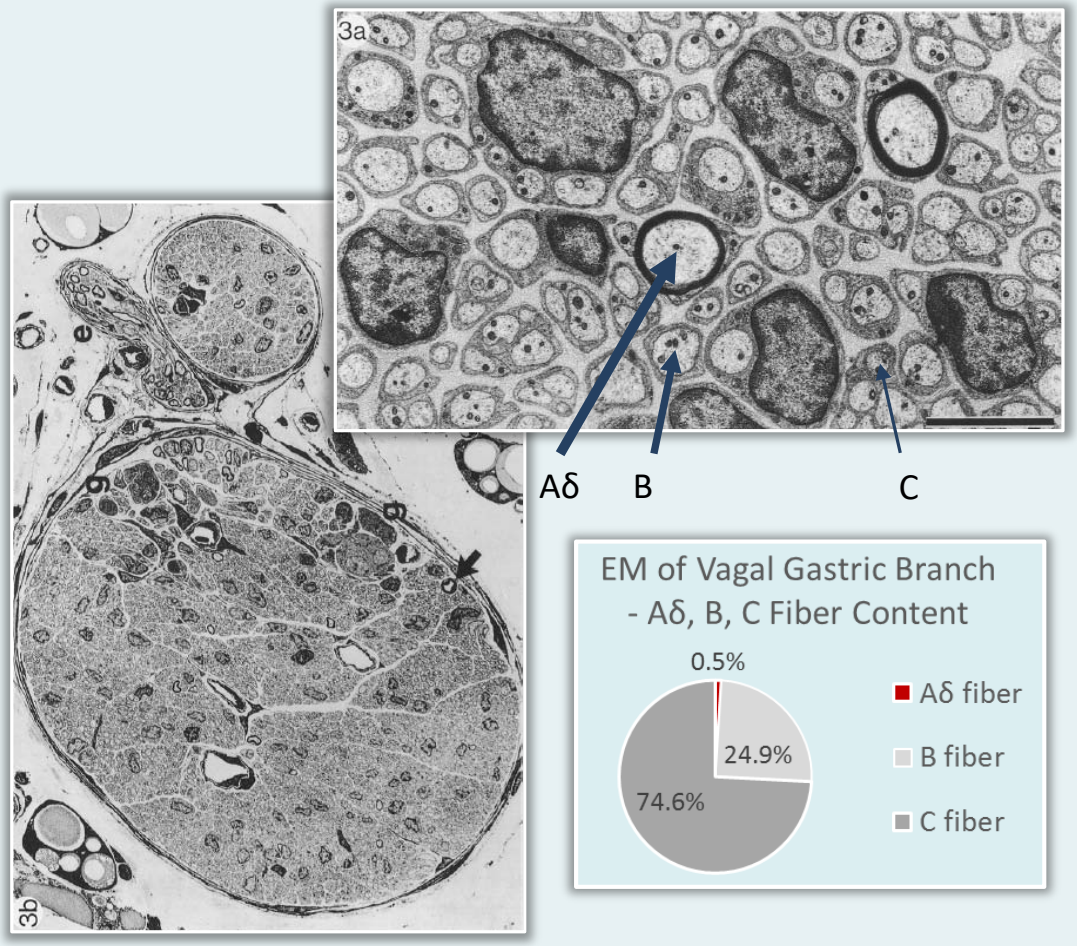
Vitaly Napadow, Braden Kuo

Peter Hunter

Susan Tappan

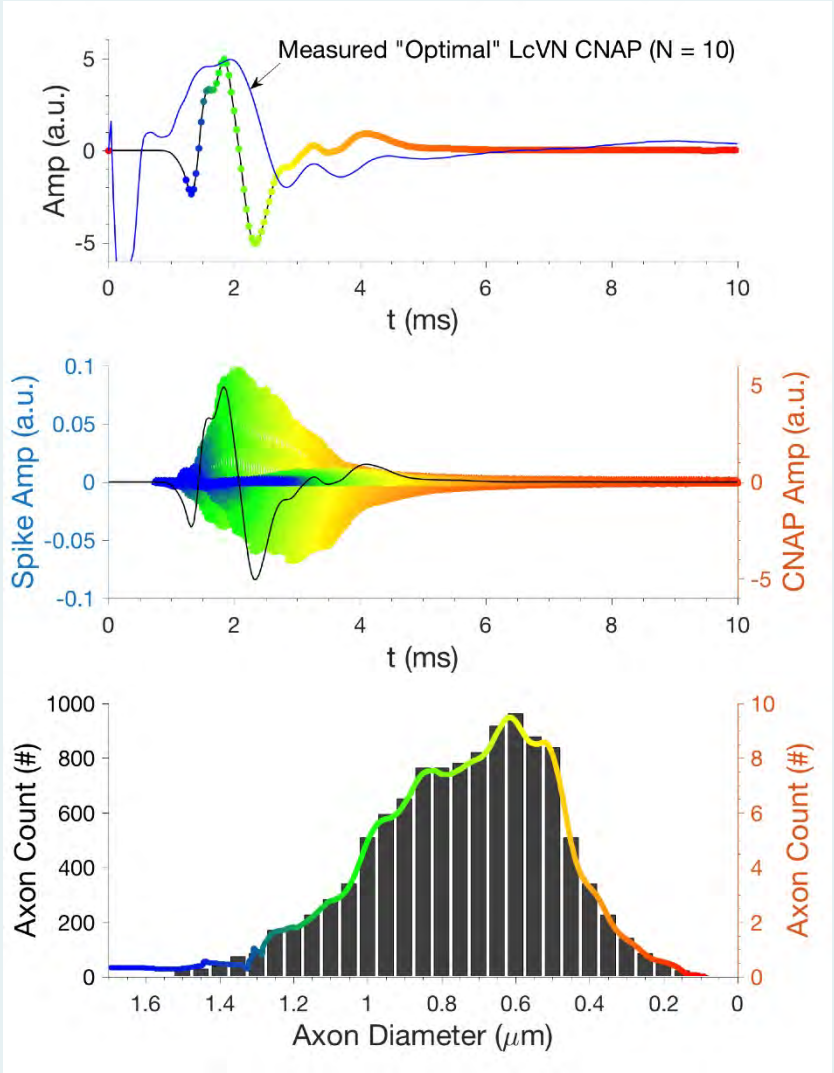
1ST GENERATION'S CABLE MODEL *vs.* REALITY





Prechtl and Powley, Anat. Em. 1990

PERFORMANCE ASSESSMENT: MEASURED VS. MODELED CNAP FROM VNS



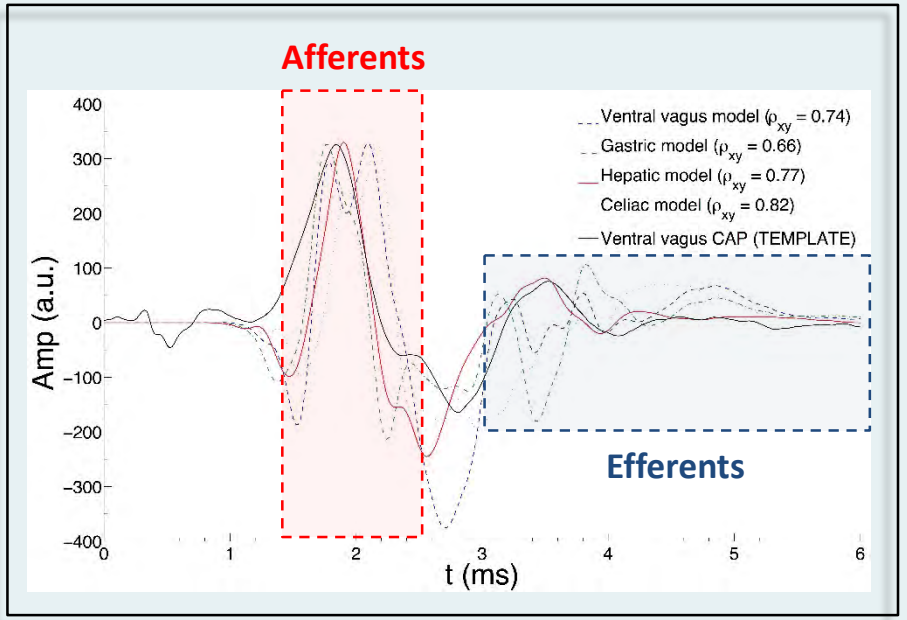
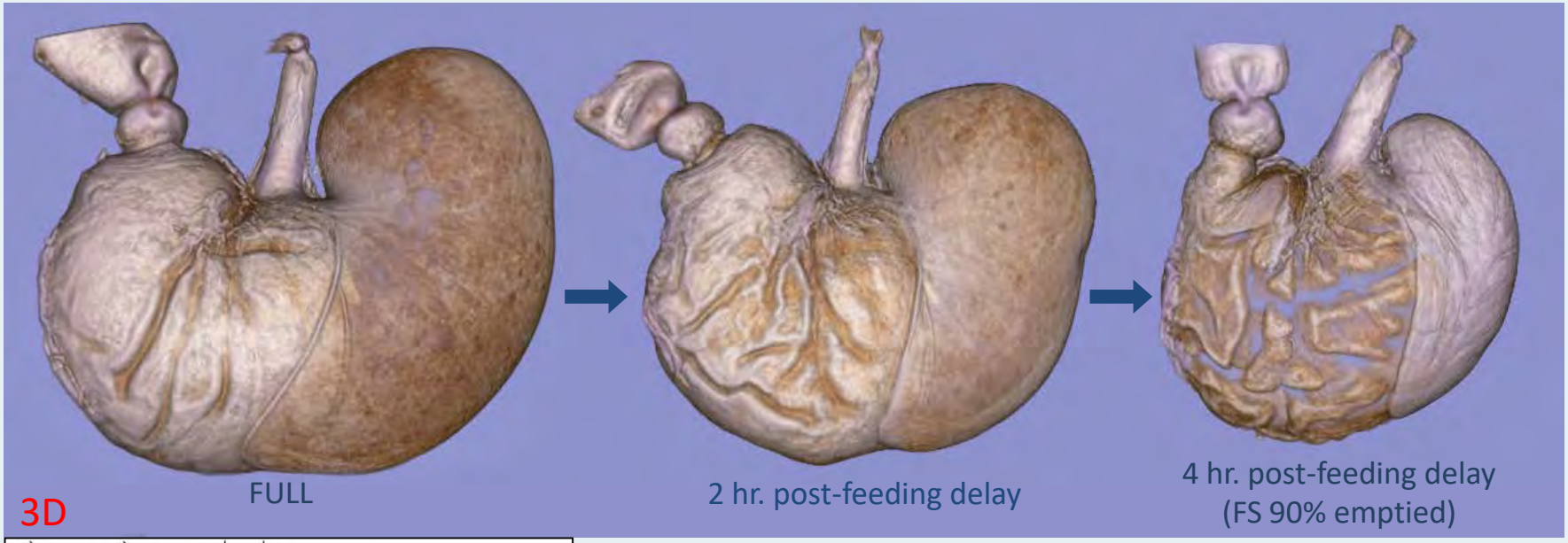
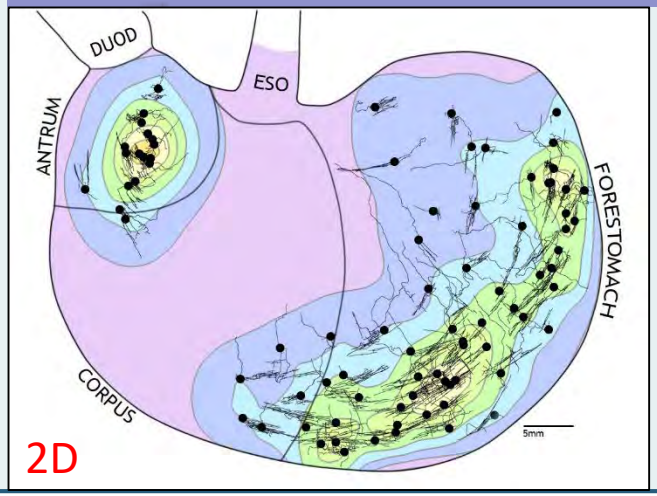


Fig. 4. Quantitative comparison of modeled maximal CNAP response from the ventral vagal trunk and branches to a measured CNAP response from the cervical vagus nerve in rat (8.0 mm conduction distance; 1.0 mm electrode spacing).

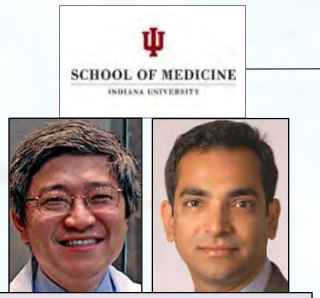
MicroCT CHARACTERIZATION OF MEAL EMPTYING





Integration of neurite maps and changing 4D stomach morphology scaffold

BEGINNING COLLABORATIVE EXTENSIONS



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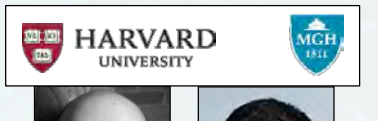

Vitaly Napadow, Braden Kuo

Peter Hunter

Susan Tappan

If we don't know
what, where, how
to stimulate,
we don't know what
we are doing.