

# Hacking the fetal brain: Confessions of EEG and ECG

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[FraschLab.org](http://FraschLab.org)

# Conflicts of interest

1. Maternal abdominal electrocardiogram (aECG) to record fetal ECG and analyze HRV: two patents pending
2. Fetal EEG monitor: US 9,215,999

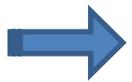
# Overview of the talk

- Intro: why, what and how
- Intrapartum monitoring of hypoxia/acidemia using EEG and ECG - comparisons to ultrasound-derived FHR
- Antepartum monitoring of inflammation and stress using ECG
- Quo vadis?

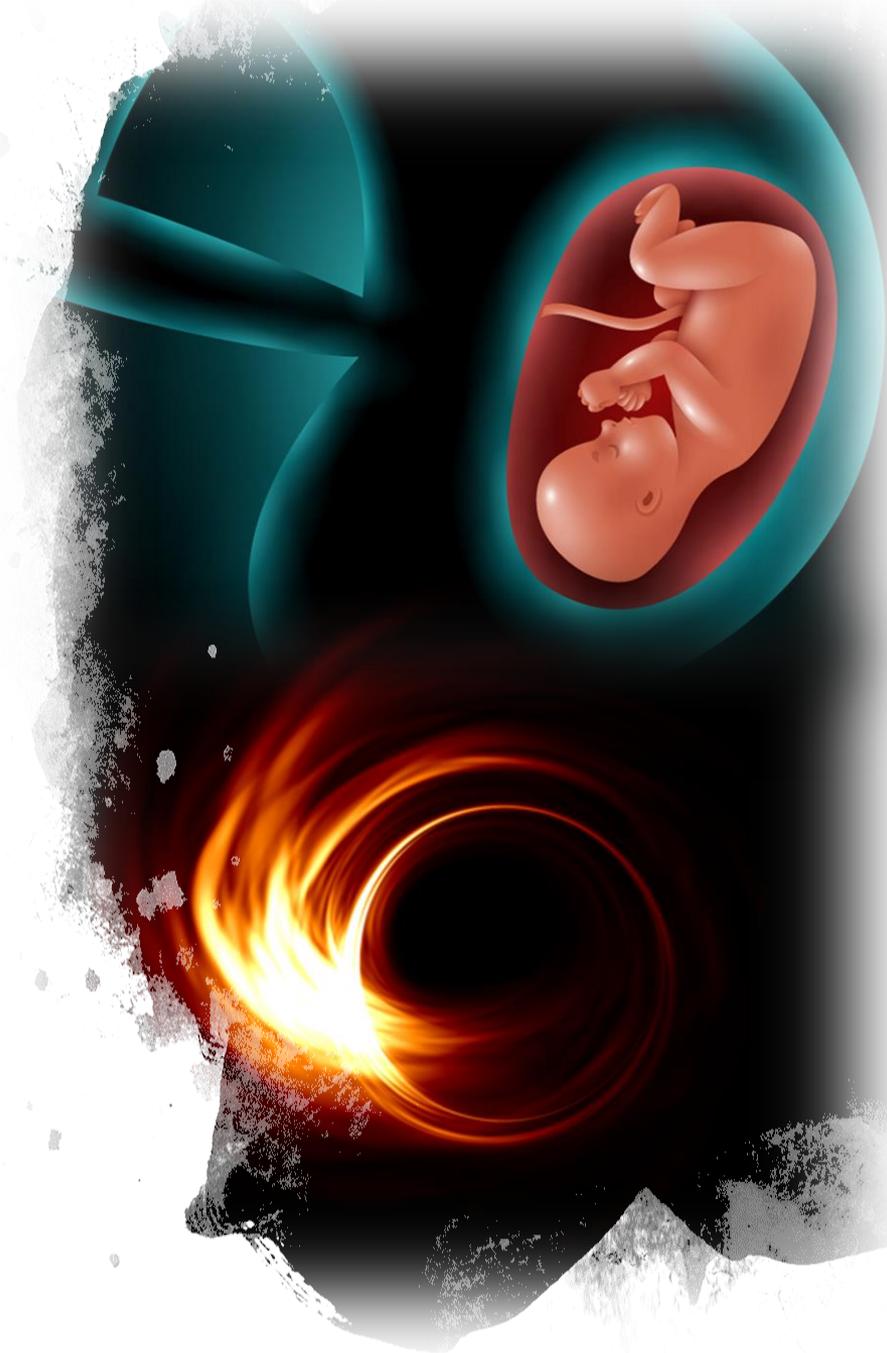
# The problem

**Information about fetal well-being is imprecise, outdated or invasive**

1. Before birth: a black hole
2. During labor: fetal brain injury cannot be detected



*The end result is a series of life long health sequelae*



# Solutions

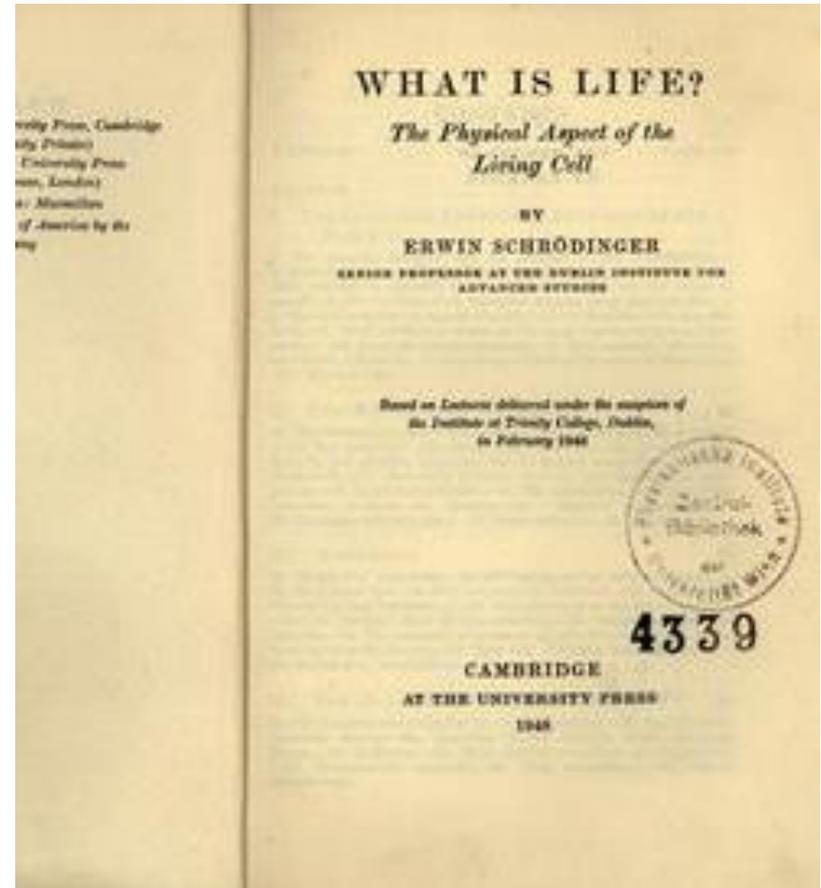
1. Non-invasive monitoring of fetal health via maternal abdominal electrocardiogram (aECG)
2. Fetal EEG monitoring during labor

# Cognitive framework

**“Nature is not economical of structures  
- only of principles”**

Abdus Salam

- Can we discover rules governing brain's complex patterns?
- Until recently, tackling data streams of 1,2 M data points per minute was impossible;
- Advancement in ML techniques;
- Enter the era of bioelectronic medicine



# Bioelectronic medicine



HOME SEARCH

The New York Times Magazine

Magazine

## Can the Nervous System Be Hacked?

By MICHAEL REHAR MAY 23, 2014

### Bioelectronic medicines: a research roadmap

NATURE REVIEWS | DRUG DISCOVERY

VOLUME 13 | JUNE 2014 | 399

*Karen Birmingham, Viviana Gradinaru, Polina Anikeeva, Warren M. Grill, Victor Pikov, Bryan McLaughlin, Pankaj Pasricha, Douglas Weber, Kip Ludwig and Kristoffer Famm*

Realizing the vision of a new class of medicines based on modulating the electrical signalling patterns of the peripheral nervous system needs a firm research foundation. Here, an interdisciplinary community puts forward a research roadmap for the next 5 years.

## HUFFPOST HEALTHY LIVING

June 8, 2015

Edition: U.S.



FRONT PAGE WOMEN TASTE GOOD NEWS PARENTS STYLE POST50 RELIGION WEDDINGS HUFFPOST LIVE ALL SECTIONS

Healthy Living • Health And Fitness • GPS for the Soul • Health News • Sleep • Moments Not Milestones • Third Metric • Thrive • Stronger Together • Life Handbook

## Hacking The Nervous System

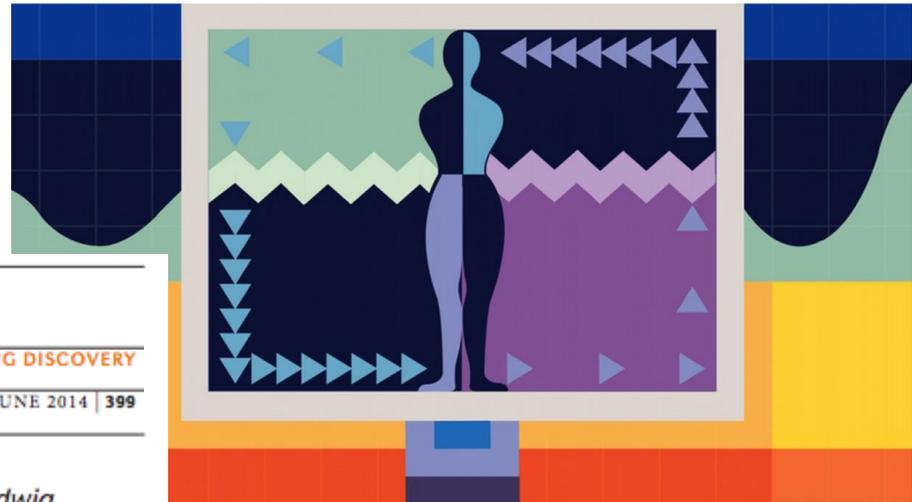
By Gaia Vince | Mosaic

Posted: 05/29/2015 9:39 pm EDT | Updated: 05/30/2015 10:59 pm EDT



116

Pin it



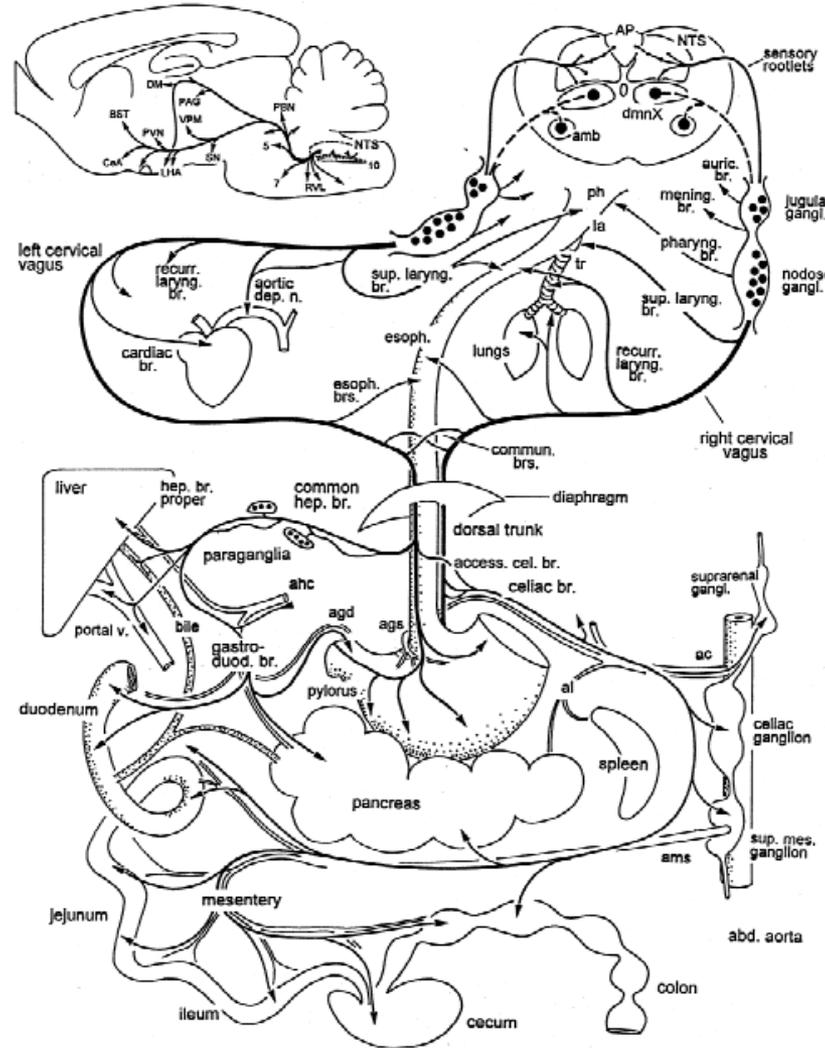
*erve connects your vital organs, sensing and shaping your health. If we learn to  
ol it, the future of medicine will be electric.*

# Vagus nerve information superhighway

**What is innervated by vagus nerve's afferent fibers?**

*(What isn't?)*

- Heart
- Lower airways
- Thymus
- Paraganglia (distributed sensor system in thorax and abdomen)
- Liver, portal vein, bile ducts
- GI tract
- Uterus
- Pancreatic islets
  
- (Spleen)
- (Gall bladder, adipose tissue)



**What is being sensed?**

*Chemoreceptors*

- Nutrients
- Nutrient-related compounds
  - glucose, amino acids, fatty acids, neuropeptides

*Mechanosensors*

- Touch
- Tension
- Serosal

*Temperature*

*Osmosensors*

*Nociception*

**Brain**

**projections**

- Brainstem
- Hypothalamus
- Amygdala
- Insular cortex

# Labor

# Detecting fetal acidemia

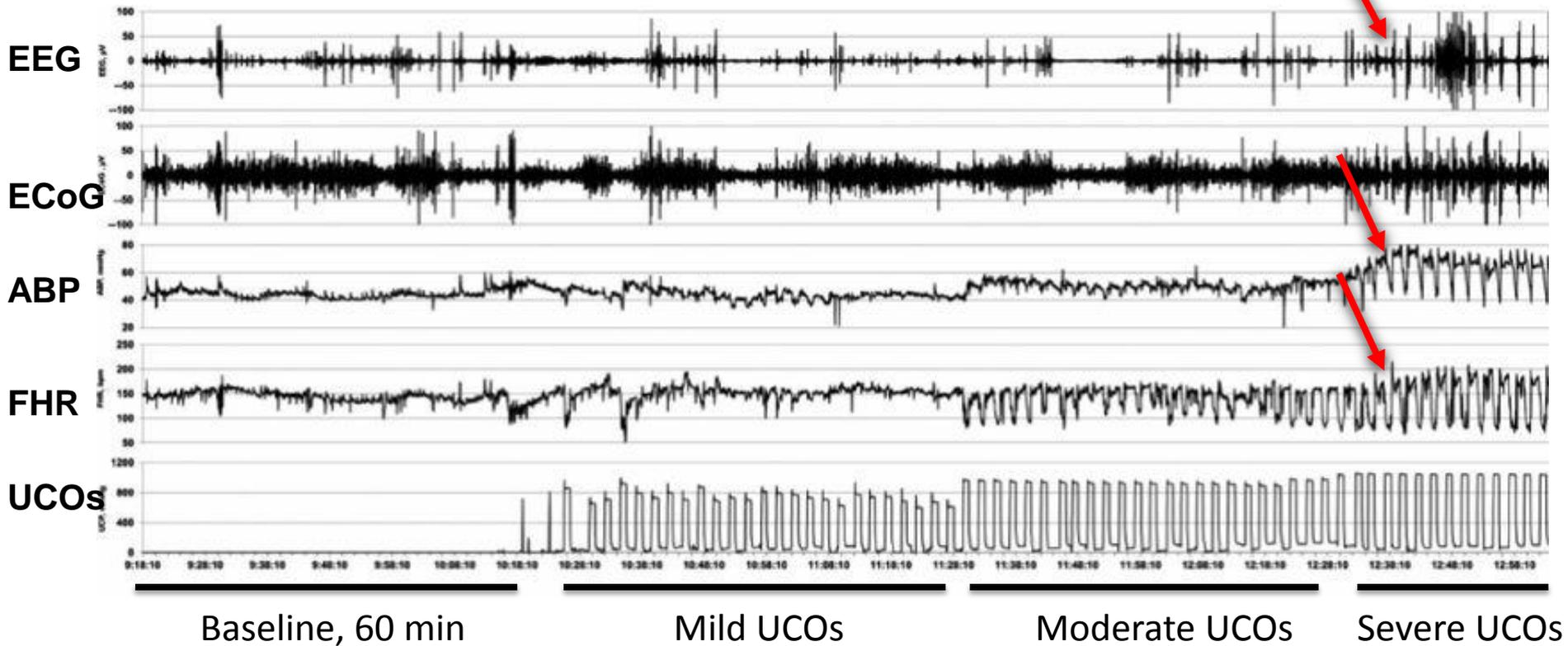
- Positive Predictive Value for fetal acidemia intrapartum 50%



- FHR monitoring inconsistently detects fetal acidemia
- Reasons for FHR monitoring inconsistencies:
  - Non-specificity of FHR decelerations
  - Variation in observers and methods interpretation of FHR patterns
  - Uncertainty about which fetal heart rate variability measures to use

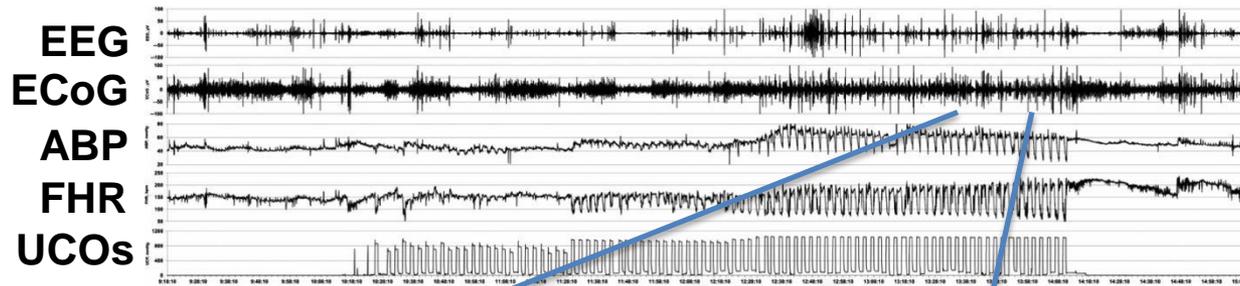
Electronic fetal heart rate monitoring: research guidelines for interpretation. 1997. Am J Obstet Gynecol 177:1385-1390; Parer, J.T. 2003. Obstet Gynecol Surv 58:561-563)

# Labor simulation with EEG monitoring



Synchronized EEG – FHR pattern at  $\sim\text{pH}=7.2$  and  $\sim 60$  min prior to pH drop to less than 7.00. EEG, electroencephalogram, uV; ECoG, electrocorticogram, uV; ABP, fetal systemic arterial blood pressure, mmHg; FHR, fetal heart rate, bpm; UCOs, umbilical cord occlusions, mmHg (rise in pressure corresponds to a UCO; note the increase in strength of the UCOs corresponding to mild, moderate and severe UCOs).

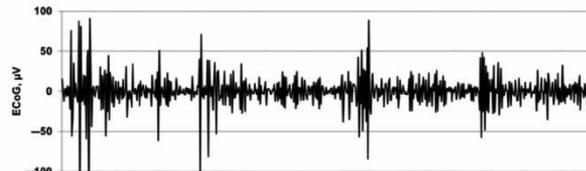
# Labor simulation with EEG monitoring



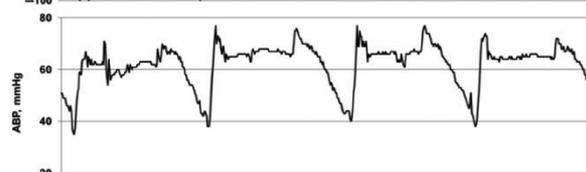
EEG



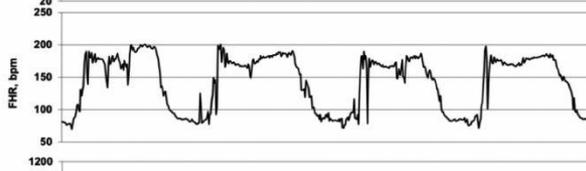
ECoG



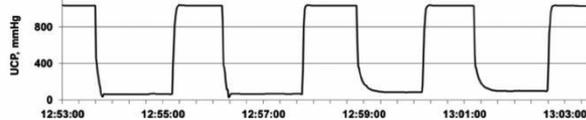
ABP



FHR



UCOs

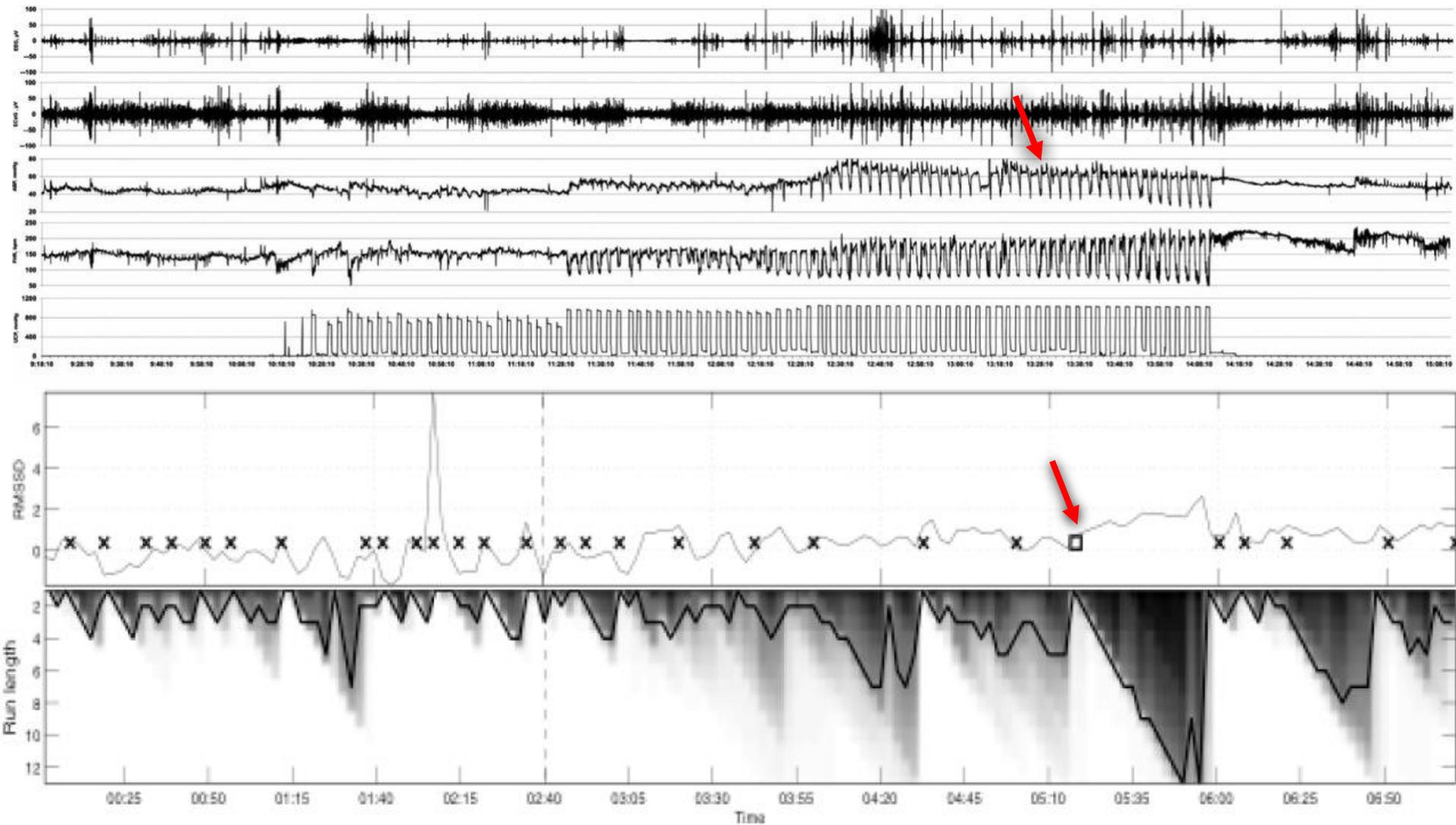


## Objectives:

- Feasibility to record spontaneous fetal EEG
- Detection of incipient acidemia

Recruiting for one year or until five acidemia cases observed

# Change point detection in fHRV during labour



# Online detection of fetal acidemia in EEG-FHR during labour

- Fetal EEG – HR monitoring allows for an automated early detection of worsening hypoxic-acidemia with good accuracy.

OPEN ACCESS Freely available online

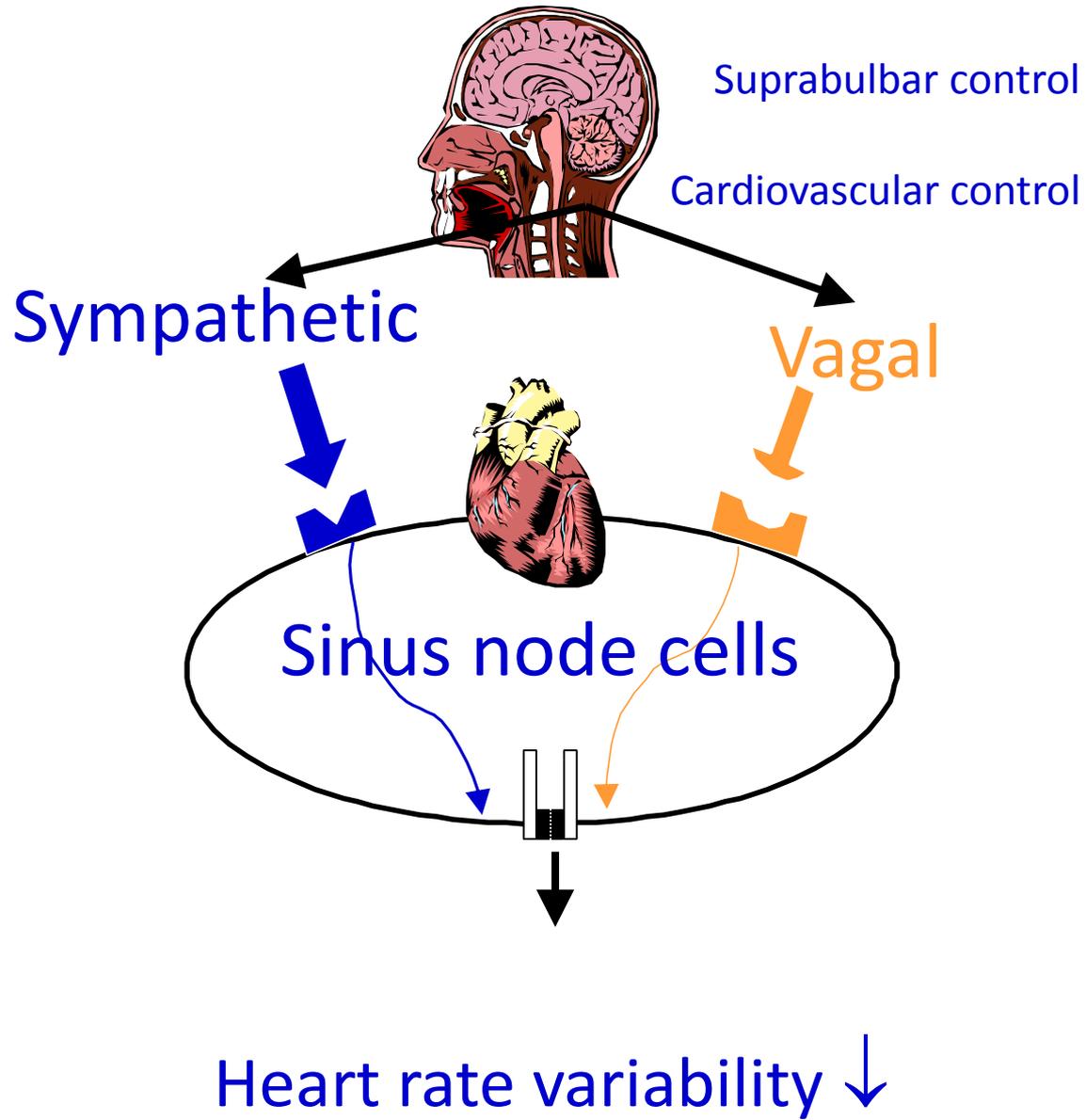
 PLOS ONE

## Online Detection of Fetal Acidemia during Labour by Testing Synchronization of EEG and Heart Rate: A Prospective Study in Fetal Sheep

Xiaogang Wang<sup>1</sup>, L. Daniel Durosier<sup>2</sup>, Michael G. Ross<sup>3</sup>, Bryan S. Richardson<sup>4</sup>, Martin G. Frasch<sup>2,5\*</sup>

<sup>1</sup> Department of Mathematics and Statistics, York University, Toronto, Ontario, Canada, <sup>2</sup> Department of Obstetrics and Gynecology and Department of Neurosciences, CHU Sainte-Justine Research Centre, Université de Montréal, Montreal, Quebec, Canada, <sup>3</sup> Department of Obstetrics & Gynecology, LA BioMed at Harbor-UCLA Med. Ctr., Torrance, California, United States of America, <sup>4</sup> Department of Obstetrics and Gynecology, Univ. Western Ontario, London, Ontario, Canada, <sup>5</sup> Animal Reproduction Research Centre (CRRA), Faculty of Veterinary Medicine, Université de Montréal, Montréal, QC, Canada

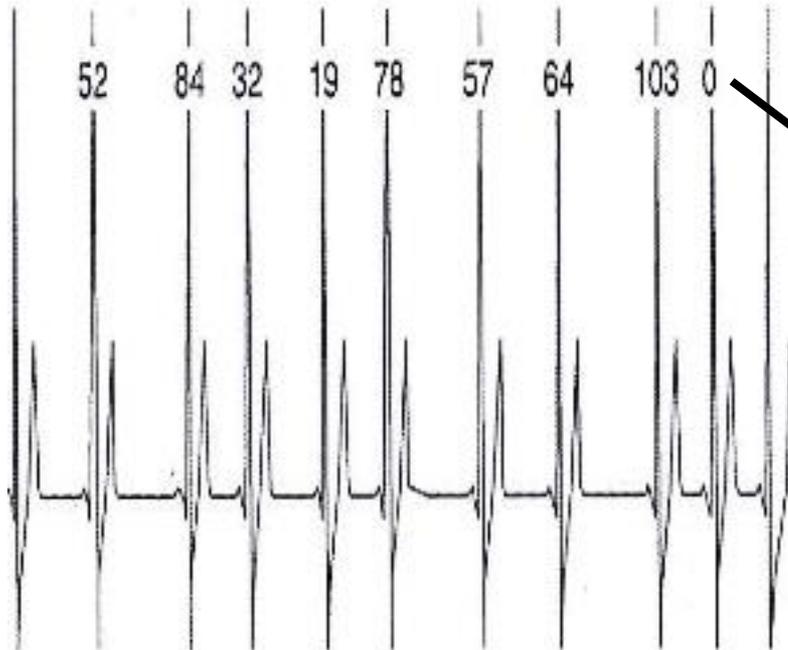
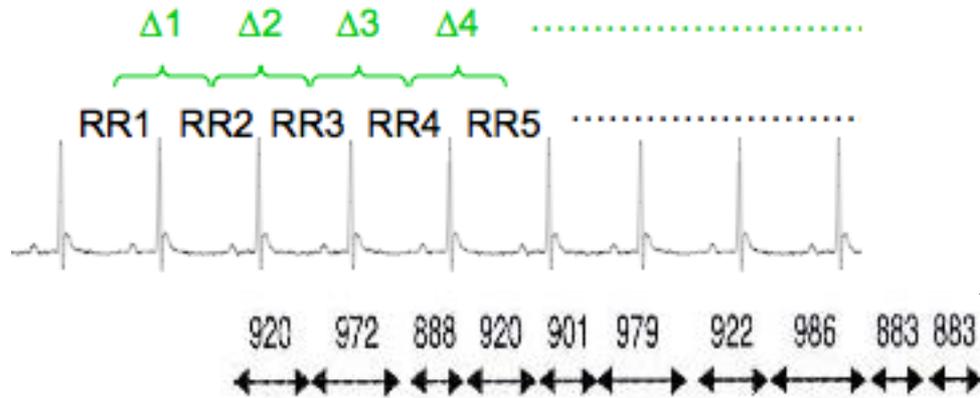
From mathematics to  
physiology



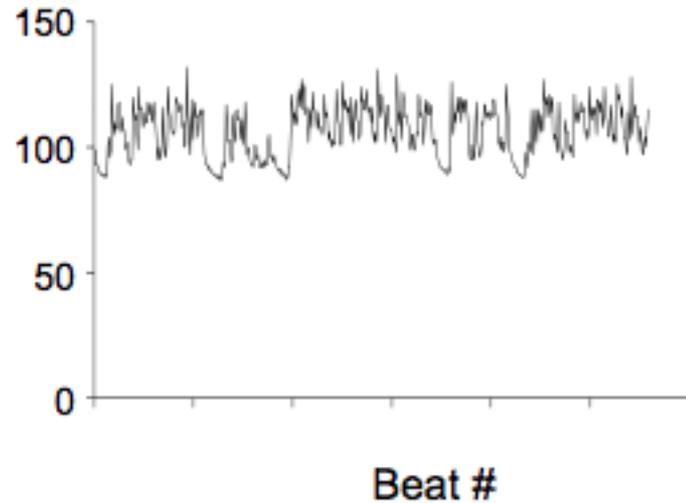
↑ RMSSD

# RMSSD

RMSSD, Root Mean Square of Successive Differences in R-R intervals (estimate of short-term components of HRV)



R-R Interval (ms)



# Fetal HRV monitoring alerts to incipient fetal acidemia: FHR sampling rate matters



## Sampling rate of heart rate variability impacts the ability to detect acidemia in ovine fetuses near-term

**L. Daniel Durosier<sup>1</sup>, Geoffrey Green<sup>2</sup>, Izmail Batkin<sup>2</sup>, Andrew J. Seely<sup>2</sup>, Michael G. Ross<sup>3</sup>, Bryan S. Richardson<sup>4</sup> and Martin G. Frasch<sup>1,5</sup>\***

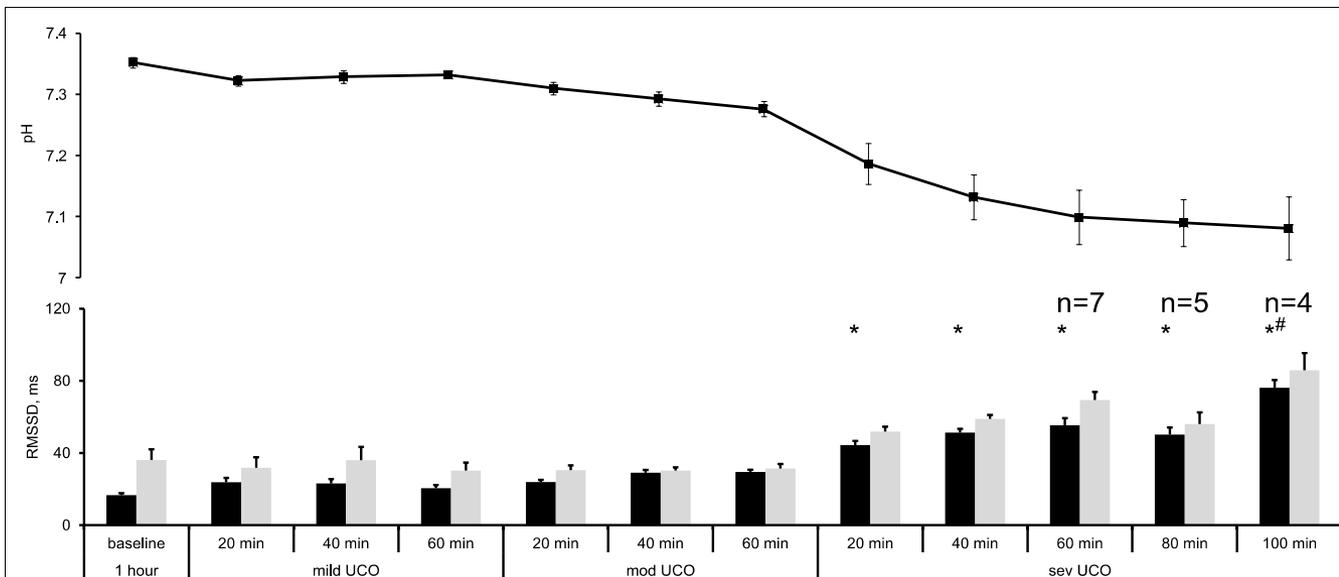
<sup>1</sup> Department of Obstetrics and Gynecology, CHU Ste-Justine Research Center, Université de Montréal, Montréal, QC, Canada

<sup>2</sup> Dynamical Analysis Laboratory, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

<sup>3</sup> Department of Obstetrics and Gynecology, LA BioMed at Harbor-UCLA Medical Center, Torrance, CA, USA

<sup>4</sup> Department of Obstetrics and Gynecology, University of Western Ontario, London, ON, Canada

<sup>5</sup> Faculty of Veterinary Medicine, Animal Reproduction Research Centre (CRRA), Université de Montréal, St-Hyacinthe, QC, Canada



**FIGURE 2 | FHRV analysis of RMSSD changes during worsening acidemia (black) at 1000 Hz and (gray) 4 Hz sampling rates.** Animals reached pH nadir <7.00 between the time points “severe UCO 40 min” and “severe UCO

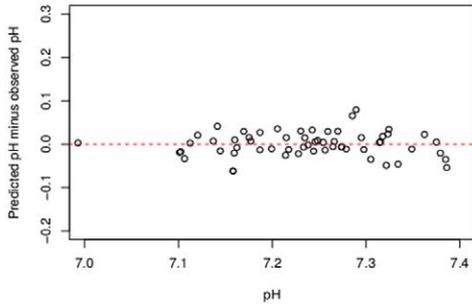
100 min.” Accordingly, sample sizes of these time points were lower where indicated. For other time points,  $N = 9$ . Mean  $\pm$  SEM. \*  $p < 0.05$  versus baseline for 1000 Hz sampled fHRV; # versus baseline for 4 Hz sampled fHRV.

Fast Track Communication

### Correlating multidimensional fetal heart rate variability analysis with acid-base balance at birth

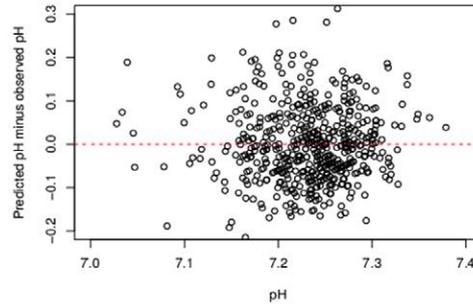
Martin G Frasch<sup>1</sup>, Yawen Xu<sup>1</sup>, Tamara Stampalija<sup>1</sup>,  
Lucien D Durosier<sup>1</sup>, Christophe Herry<sup>1</sup>, Xiaogang Wang<sup>2</sup>,  
Daniela Casati<sup>3</sup>, Andrew J E Seely<sup>4</sup>, Zarko Alfrevic<sup>5</sup>,  
Xin Gao<sup>1</sup> and Enrico Ferrazzi<sup>1</sup>

t-a fECG 900 Hz FHR cohort



RMSE = 0.09

CTG 4 Hz FHR cohort



RMSE = 0.03

Fast Track Communication

### Sampling frequency of fetal heart rate impacts the ability to predict pH and BE at birth: a retrospective multi-cohort study

Xuan Li<sup>1</sup>, Yawen Xu<sup>1</sup>, Christophe Herry<sup>2</sup>, L Daniel Durosier<sup>6</sup>,  
Daniela Casati<sup>1</sup>, Tamara Stampalija<sup>1</sup>, Emeline Maisonneuve<sup>4</sup>,  
Andrew J E Seely<sup>2,3,5</sup>, Francois Audibert<sup>6</sup>, Zarko Alfrevic<sup>7</sup>,  
Enrico Ferrazzi<sup>1</sup>, Xiaogang Wang<sup>1</sup> and Martin G Frasch<sup>6,7</sup>

If information is encoded in the HRV signal, it must be sampled correctly for true representation to contain predictive information

- Novel bioinformatics approach to fHRV derived from maternal abdominal ECG during labour predicted well acid-base status at birth. Further refinement and validation in larger cohorts are needed.
- Potential to predict fetal cardiovascular decompensation during labour and acid-base status at birth.

# Intrapartum monitoring: Progress to date

Animal studies  
completed

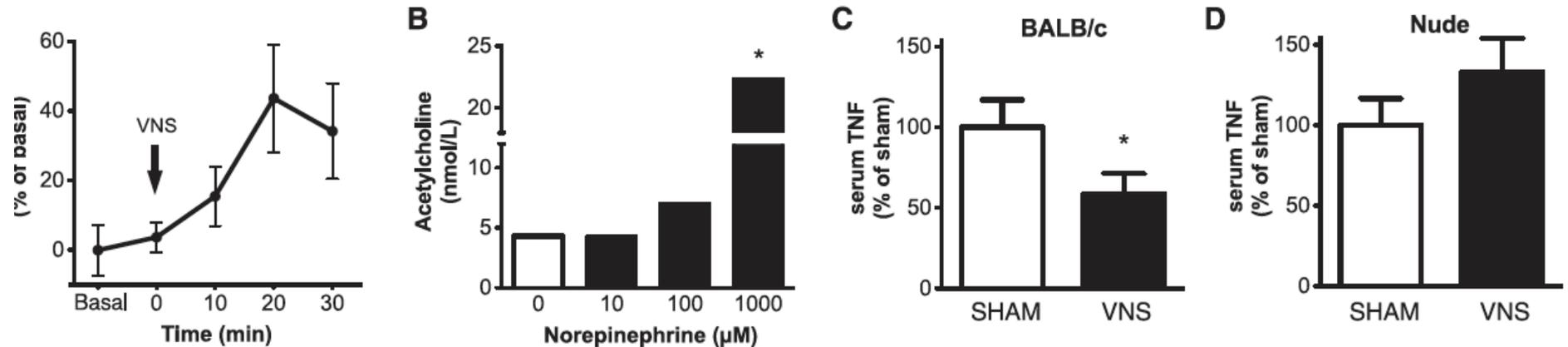
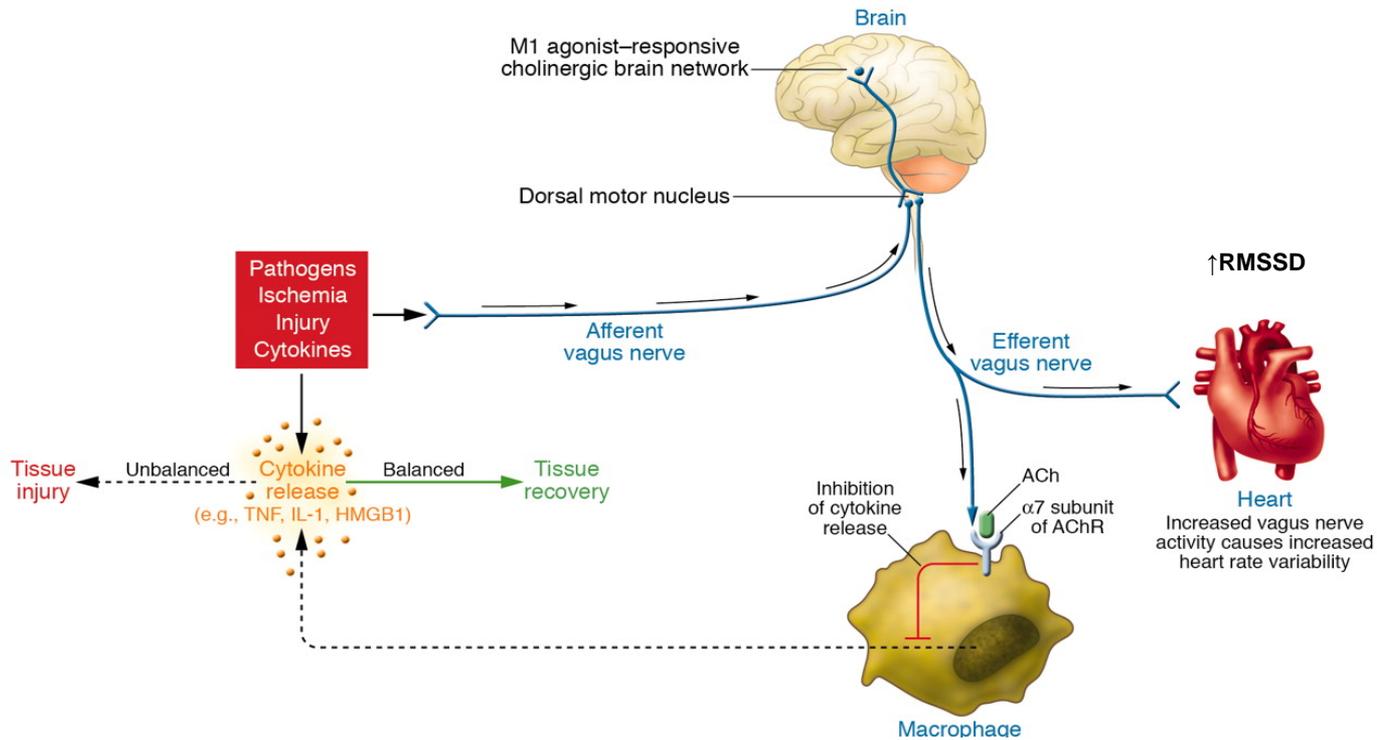
- Fetal EEG proof-of-principle studies show early detection of fetal acidemia
- Fetal EEG device prototype

Clinical study at  
UW is in progress

- **ClinicalTrials.gov Identifier:**  
NCT03013569
- Fetal scalp electrode
- Labor EEG as evoked response

# Pregnancy

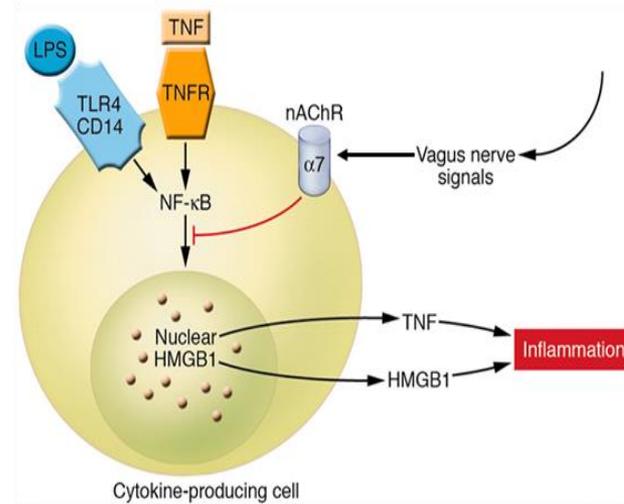
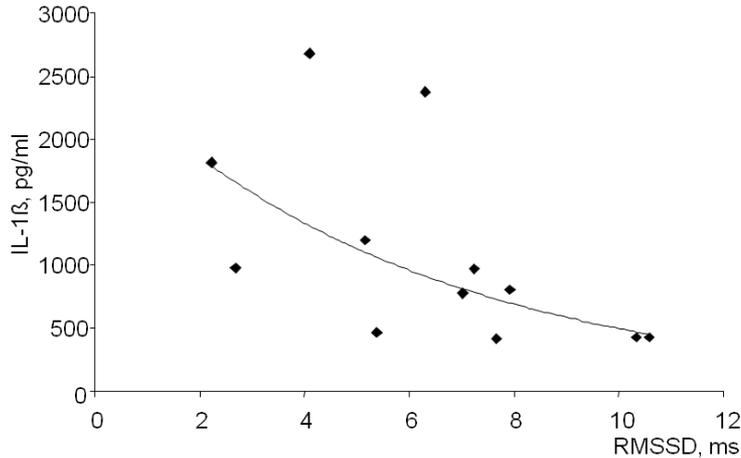
# Cholinergic anti-inflammatory pathway (CAP)



Vagus nerve stimulation increases acetylcholine levels in the spleen and requires T lymphocytes to attenuate TNF-α in endotoxemia. Rosas-Ballina et al, Science 2011.

# Cholinergic anti-inflammatory pathway (CAP)

## Spontaneous fetal CAP activity



Frasch et al. *Journal of Neuroinflammation* (2016) 13:103  
DOI 10.1186/s12974-016-0567-x

Journal of Neuroinflammation

**BRAIN INTEGRATION?**  
**Neuroimmunological**  
**homunculus?**  
**Plasticity? Recovery potential?**  
**Biomodulation?**

RESEARCH

Open Access



Decreased neuroinflammation correlates to higher vagus nerve activity fluctuations in near-term ovine fetuses: a case for the afferent cholinergic anti-inflammatory pathway?

M. G. Frasch<sup>1,2,3,4,8\*</sup>, M. Szykaruk<sup>4</sup>, A. P. Prout<sup>4</sup>, K. Nygard<sup>5</sup>, M. Cao<sup>1,2</sup>, R. Veldhuizen<sup>6</sup>, R. Hammond<sup>7</sup> and B. S. Richardson<sup>4,6</sup>

Tracey 2007 *J Clin Invest*, 117(2):289-296.

Pavlov & Tracey *Nat Neuro* 2017: 20(2)

Frasch et al. 2009 *Reprod Sci*. 16(3) (Suppl):137A.

# The multi-talented vagabond: how does it talk and can we talk back?

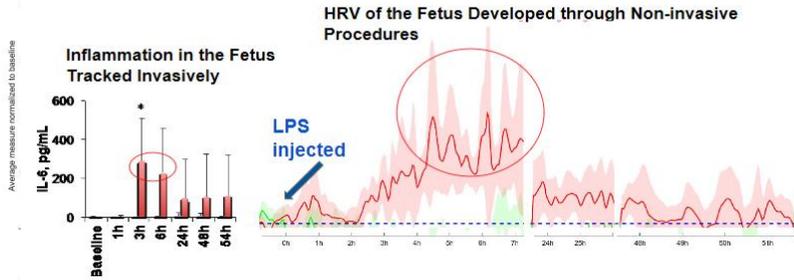
- Direct study of VENG / Vagotomy (Vx) / VNS
- Indirect analysis of multi-dimensional HRV properties in relation to outcome measures
- HRV / Vx / VNS / VENG studies yielded first insights into existence of vagus code and its amenability to manipulation
- Vagus signaling in fetus impacts
  - brain regional and gut blood flow
  - systemic glucose levels
  - peripheral (gut) and central (neuro) inflammation levels
  - microglial and astrocytes' phenotype
  - the response patterns differ dramatically from those in adult organisms
- How does vagus nerve communicate? How is this information organized in the brain? (Immunological homunculus) Is this information reflected in HRV code?

# The inverse and direct problems

M.G. Frasch et al.

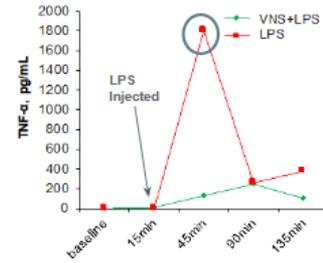
Neuroscience and Biobehavioral Reviews xxx (xxxx) xxx-xxxx

## A HRV indices track Fetal Infection

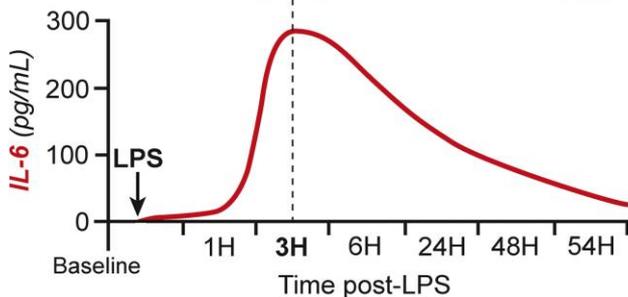
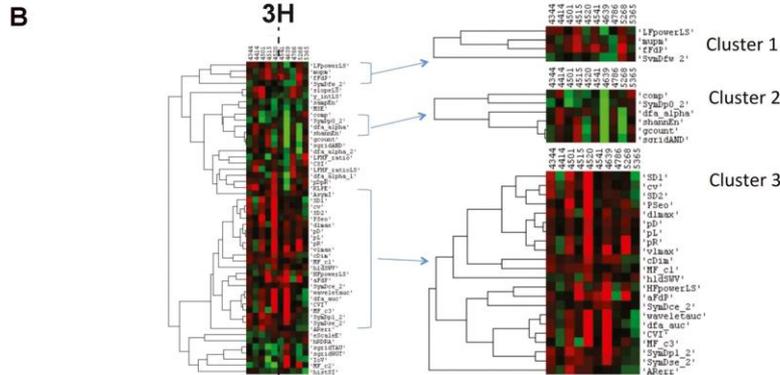
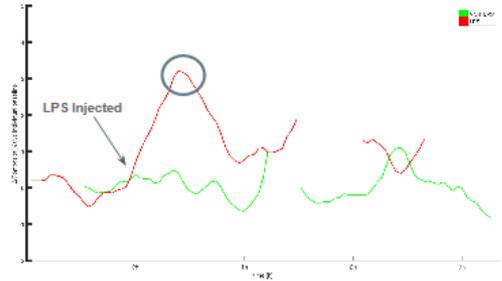


## HRV indices track Neonatal Sepsis and VNS effects

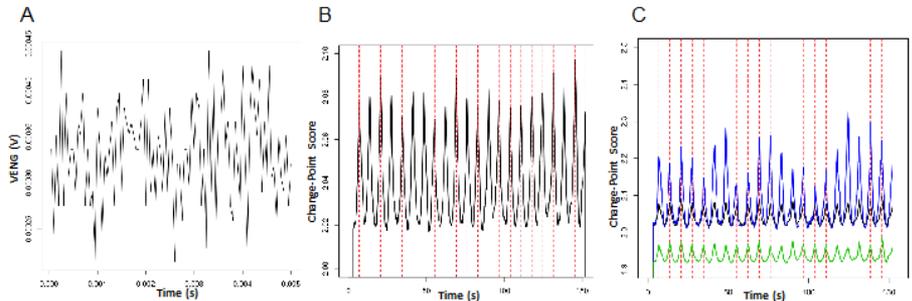
### Inflammation in the Piglet Tracked Invasively



### HRV of the Piglet Developed through Non-invasive Procedures



## Change-Point Analysis Uncovers Two Underlying States in the Vagus Nerve



Frasch et al. SRI 2018 (manuscript in preparation)

Hemphill, J. C. et al. (2011) Multimodal monitoring and neurocritical care bioinformatics *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2011.101

Durosier et al. 2015  
Herry C. et al. 2016

## Can Monitoring Fetal Intestinal Inflammation Using Heart Rate Variability Analysis Signal Incipient Necrotizing Enterocolitis of the Neonate?

Liu, Hai Lun BSc; Garzoni, Luca MD; Herry, Christophe PhD; Durosier, Lucien Daniel MD, MSc; Cao, Mingju PhD; Burns, Patrick BVSc; Fecteau, Gilles DMV; Desrochers, André DMV, MSc; Patey, Natalie MD, PhD; Seely, Andrew J. E. MD, PhD; Faure, Christophe MD; Frasch, Martin G. MD, PhD

Pediatric Critical Care Medicine: April 2016 - Volume 17 - Issue 4 - p e165–e176  
doi: 10.1097/PCC.0000000000000643  
Online Laboratory Investigations

SDC

Abstract

Author Information

Objective: Necrotizing enterocolitis of the neonate is an acute inflammatory intestinal disease that can cause necrosis and sepsis. Chorioamnionitis is a risk factor of necrotizing enterocolitis. The gut represents the biggest vagus-innervated organ. Vagal activity can be measured via fetal heart rate variability. We hypothesized that fetal heart rate variability can detect fetuses with incipient gut inflammation.

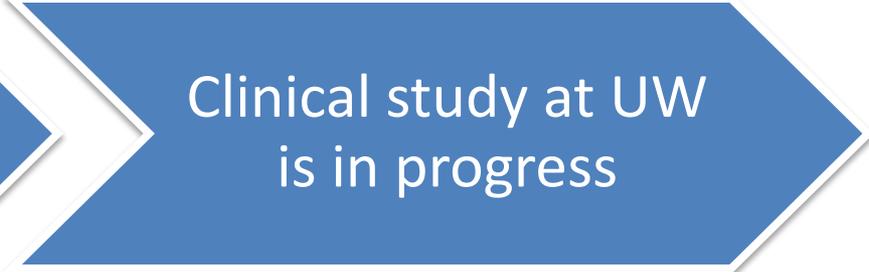
Within gut and brain, no fHRV measure correlated to several markers of inflammation at the same time; that is, there were no overlapping correlations of the fHRV measures.

# Antepartum monitoring: Progress to date



Animal studies  
completed

- Heart rate variability (HRV) permits early detection of fetal infection and acidemia
- aECG is the pre-requisite for precise and continuous acquisition of HRV



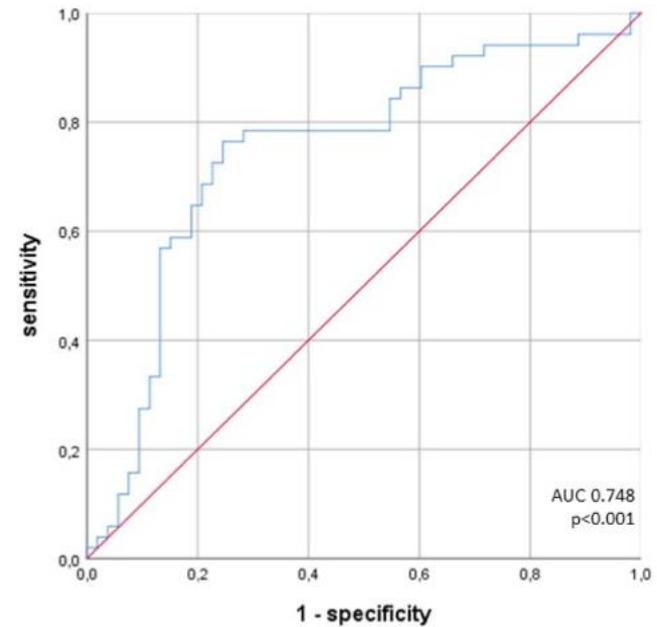
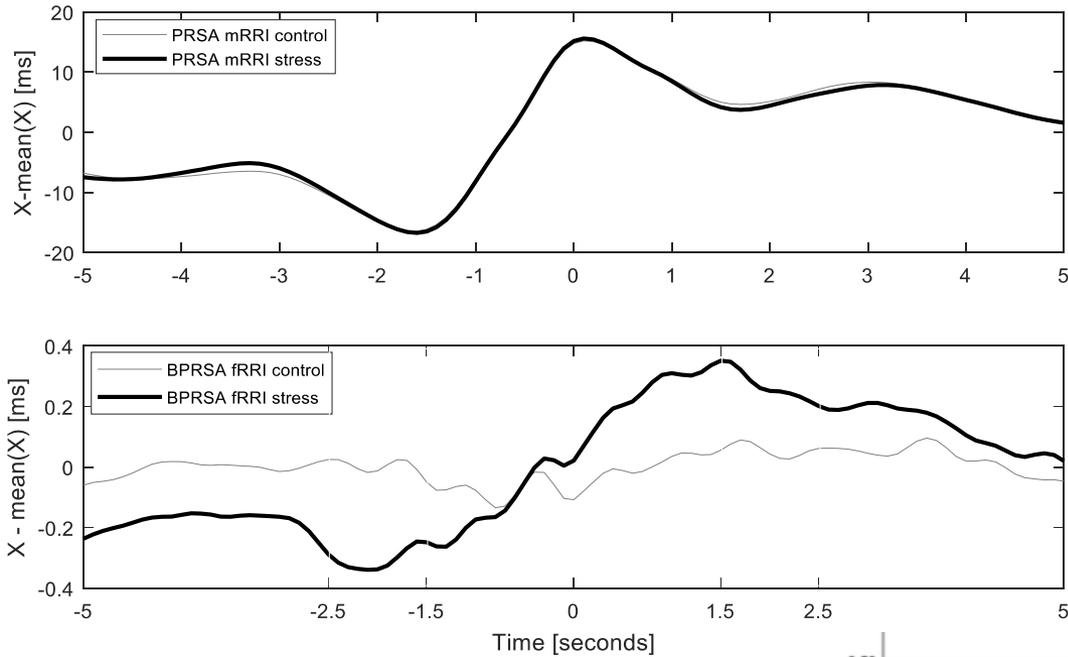
Clinical study at UW  
is in progress

- **ClinicalTrials.gov**  
**Identifier:**  
NCT03111173

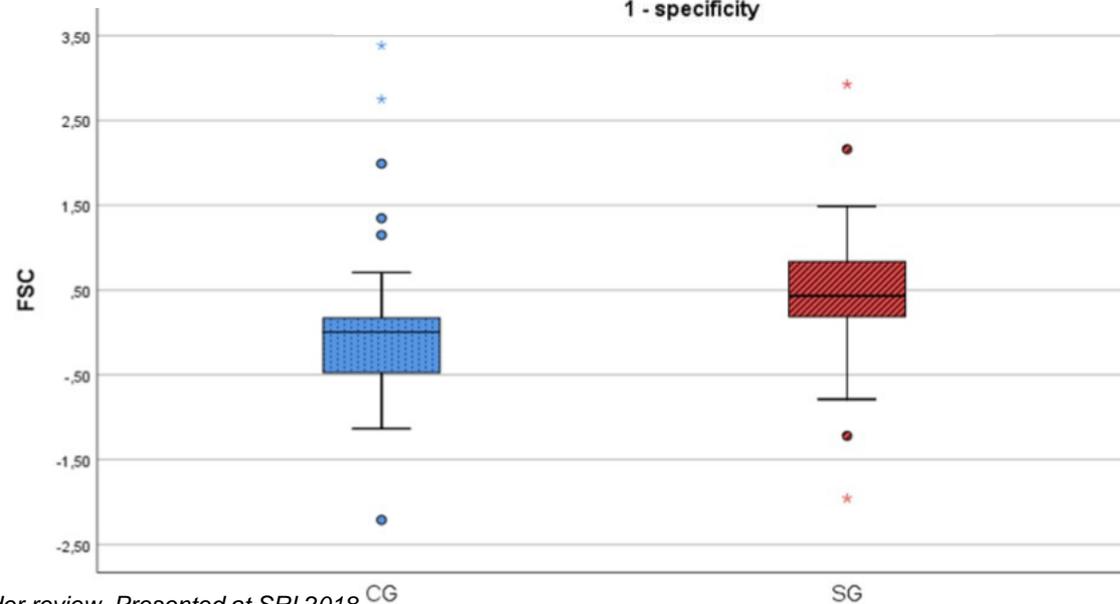
# Outlook

- Is there future for fetal EEG monitoring intrapartum?
  - Long history
  - New medical device ancillary to current FHR monitors
  - Recruitment scale
- How can we make fetal ECG technologies more acceptable?
  - Price
  - Validation
  - Future uses at home and in clinic, antepartum and intrapartum
  - Joint mother-fetus monitoring

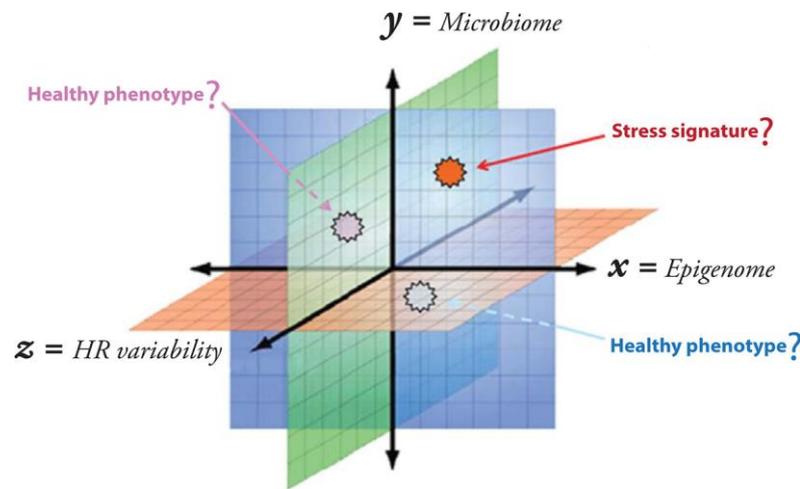
# Maternal-fetal stress memory



- Maternal prenatal stress impacts the fetal heart rate reactivity to maternal heart rate.
- Joint m/f ECG monitoring!
- This impact can be detected non-invasively from maternal transabdominal ECG.



# Multi-scale phenotype



**A complex multi-scale phenotype of the healthy or prenatally stressed individual.**

- Can the rapidly advancing machine learning techniques help distinguish individual phenotypes based on all its features across the scales of observations, from microbiome, over to epigenetic landscape to the heart rate (HR) time series?

# From Bioelectronics to Electroceutics



## THE TARGET

Molecular biologists identify 'targets' of disease or health



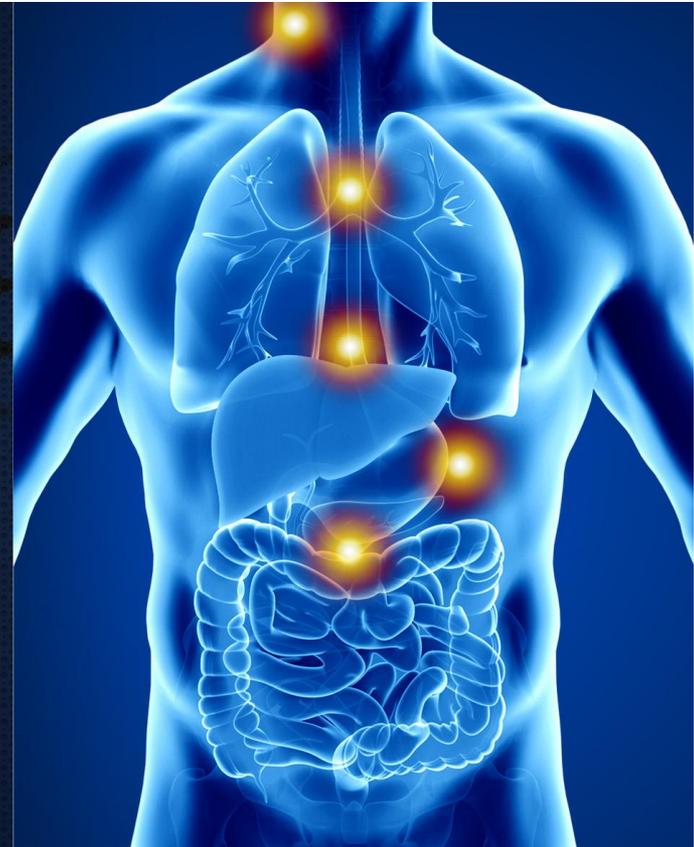
## THE SIGNAL

Neuroscientists identify the neural pathway to manipulate the target



## THE DEVICE

Engineers and computer scientists design a device to modulate the appropriate pathway



Magazine

# Can the Nervous System Be Hacked?

By MICHAEL BEHAR MAY 23, 2014



[http://www.nytimes.com/2014/05/25/magazine/can-the-nervous-system-be-hacked.html?\\_r=0](http://www.nytimes.com/2014/05/25/magazine/can-the-nervous-system-be-hacked.html?_r=0)

# Acknowledgements

- Wu lab, *Duke University*
- Dept. of OBGYN, *University of Washington, Seattle*
- Faculté médecine vétérinaire team, *Université de Montréal*
  - Andrew Seely lab, *Ottawa University, ON*
  - Enrico Ferrazzi team, *University of Milan, Italy*
  - Dept. of Math/Stat team, *York University, ON*
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## **Funding:**

- Molly Towell Perinatal Research Foundation
  - CIHR
  - FRQS
- QTNPR (CIHR)
- NeuroDevNet
- MITACS

# Thank ewe!

