Mathematical properties of fetal heart rate variability: a journey to bedside fetal health monitoring

Université de Montréal | Faculté de médecine vétérinaire CRRA

Centre de Recherche du CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

Université de Montréal

LAWSON HEALTH RESEARCH INSTITUTE

The research institute of London Health Sciences Centre and St. Joseph's Health Care, London.

Martin G. Frasch, MD, PhD

Département d'obstétrique, Centre de Recherche du CHU Ste-Justine, Université de Montréal

http://fraschlab.ca

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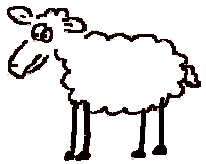

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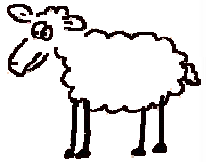
Summary: epistemological view

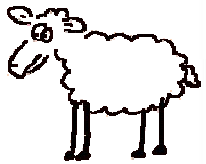
- **“Nature is not economical of structures - only of principles”**

Abdus Salam



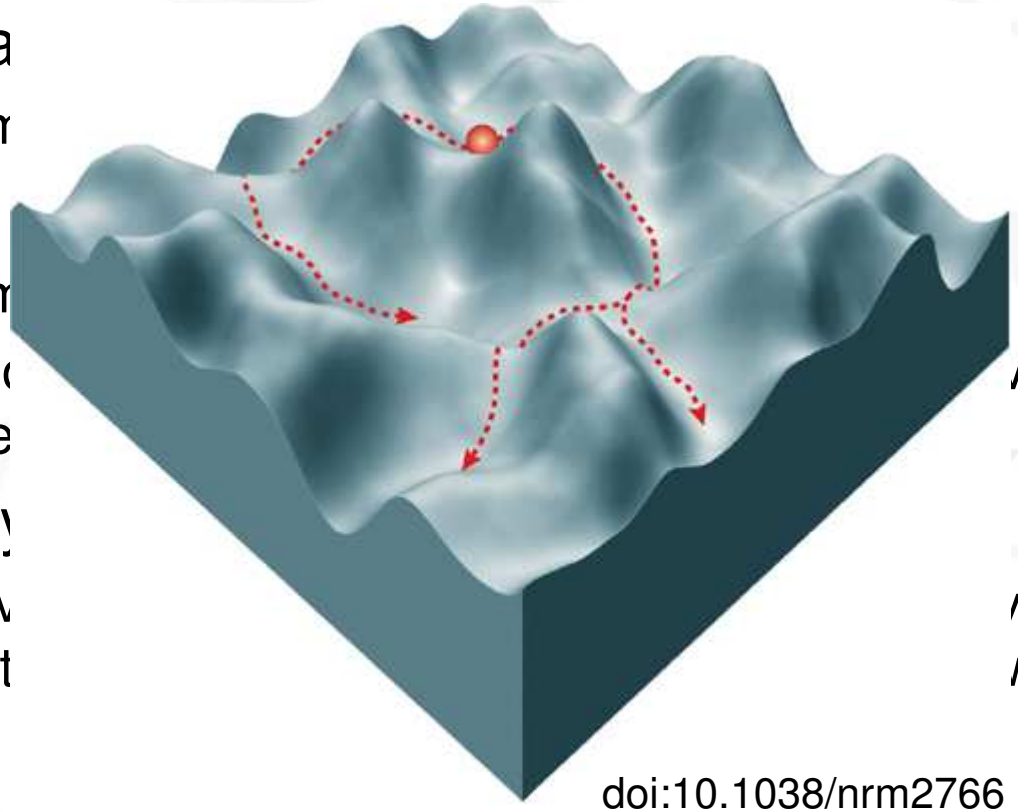
Summary: bed-side view

- Clinical need for improved fetal heart rate (FHR) monitoring of incipient infection and acidemia
- Fetal EEG – an old – new ancillary tool for fetal monitoring
- Fetal cholinergic anti-inflammatory pathway (CAP) and acidemia
- FHRV monitoring promising tool
- Candidates:
  - fHRV: time domain, entropy and complexity measures
  - EEG: amplitude/frequency properties
- Comprehensive (multivariate) approach needed (CIMVA)
- Real life utility: ultrasound-based fHRV/EEG technology



Summary: math view

- Past: “ma
  - Problem
- Still past:
  - Problem
  - Irony: z / or EEG) deploye
- Future: d
  - Hope: M variate descript way



doi:10.1038/nrm2766

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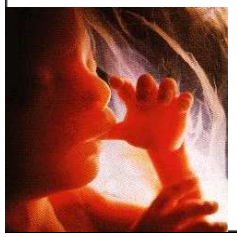

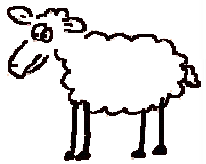

Physiology and Monitoring of fHRV and EEG

- Before birth:
  - Neural autonomic activity matures around 32nd week (æ RMSSD, SDNN, complexity, long-term correlations) and correlates with behavioural states
  - RMSSD is reduced by atropine (vagal blockade) in fetal sheep near-term
  - Higher vagal tone = more efficient homeostasis = multifractal FHR control

  - Non-invasive Doppler (ultrasound) FHR monitoring (heart beat measurement)
    Precision (sampling rate) BUT used in > 90% of North-American hospitals
  - fMCG: non-invasive, precise BUT exotic

  - Brain maturation: behavioural states; accessible via fetal MEG only and hence exotic

- During birth:
  - Fetal scalp ECG, derivation of HRV similar to adult ECG
  - Possibility to validate Doppler versus fetal scalp ECG
  - Fetal EEG can be recorded from the scalp

Hoyer et al. 2009 Early Hum Dev 85(6):379-86.
Frasch et al. 2007. J Physiol, 579(3):893-907.
Lake et al. 2003 Ped Res 53(6): 889-890.
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Rosen & Scibetta. 1969 *Am J Obstet Gynecol* 104:1057-1060.
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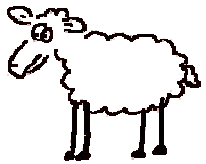

Clinical motivation: Pathophysiology

- Before birth: Hypoxic/asphyxic and inflammatory events impact brain development in late-gestation fetus (fHRV and EEG)

- During birth: Uterine contractions during labour can restrict umbilical blood flow:
  - ˜ fetal oxygenation ˜ adverse neonatal outcome: newborn encephalopathy, cerebral palsy

- After birth: Long-term neurodevelopmental sequelae in children and adults:
  - ˜ Cerebro-cardiovascular, neuroinflammatory and cognitive disorders

Saigal & Doyle 2008 Lancet 371, 261-269.
Gotsch et al. 2007. Clin Obstet Gynecol 50, 652-83.
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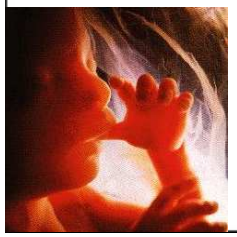

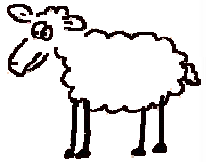

Clinical motivation: Need to detect

- Fetal asphyxia results in early vagal activation (æ RMSSD and adaptive brain shut-down – specific EEG changes)

- Fetal inflammatory response may be controlled by vagal neural activity via cholinergic anti-inflammatory pathway (CAP)

  ~ Non-invasive monitoring per fetal heart rate variability (fHRV)?

  ~ Identify and test candidate markers RMSSD, ApEn, $aAIF_{short}$, multifractal analyses, others?

  ~ Implement comprehensive and real-life applicable fHRV and EEG algorithms (CIMVA)

Frasch et al. 2010 Repro Sci. 16, 137A and 243A.
Prout et al. 2010 Am J Obstet Gynecol 202(1): 82.e1-9.
Ahmad *et al.* 2009 *PLoS One* 4, e6642
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Frasch et al. 2009 Am J Physiol Regul Integr Comp Physiol 296, R702-7
Frank et al. 2006 Biomed Tech (Berl) 51(4): 233-6.
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Tracey 2007 J Clin Invest, 117(2):289-296.
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Li et al. 2005 Acta Obstet Gynecol Scand, 84 (9):837-843
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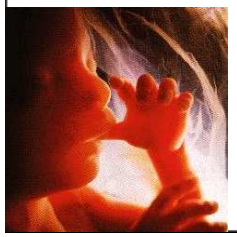
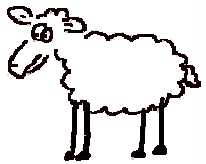


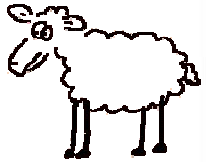


Next slides …

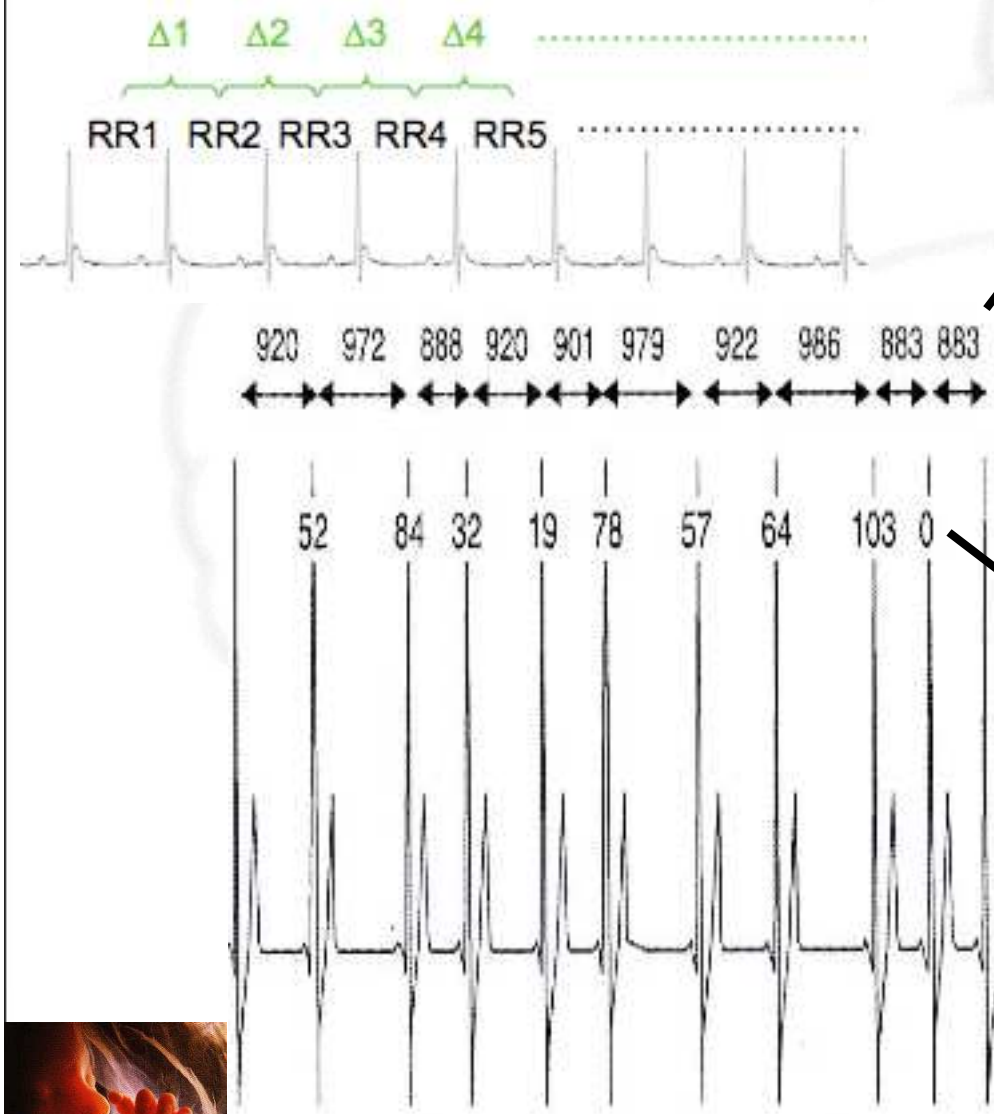
I. Focus on fHRV

II. Focus on fetal EEG

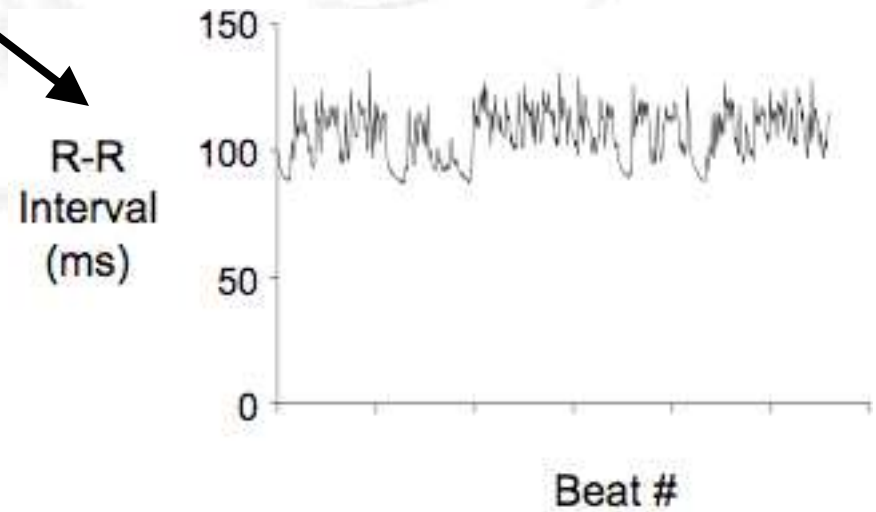
III. Synthesis: A mathematical problem

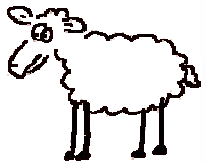


RMSSD

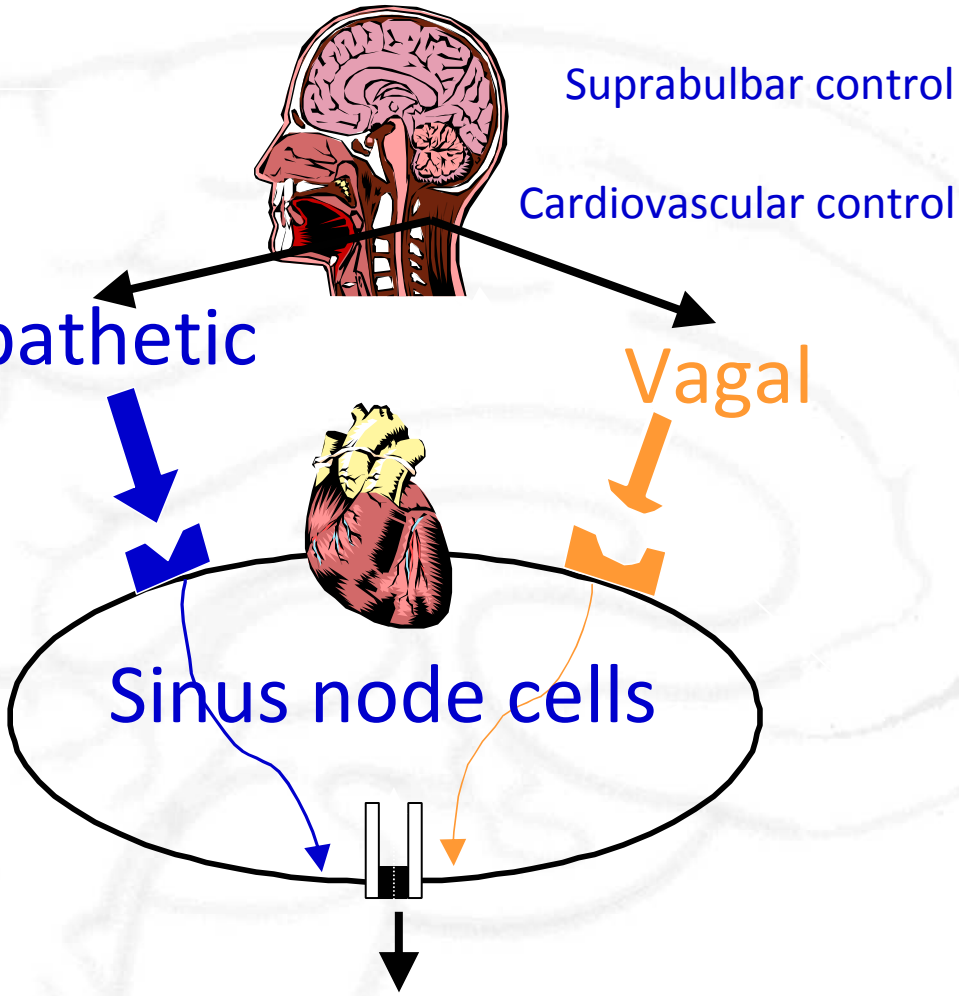


RMSSD, Root Mean Square of Successive Differences in R-R intervals (estimate of short-term components of HRV)



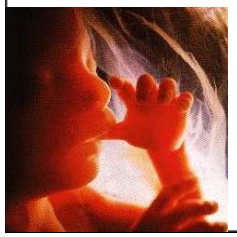


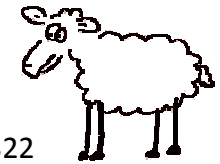
From mathematics to physiology



Heart rate variability ↓↑

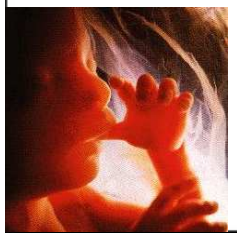
∅ RMSSD

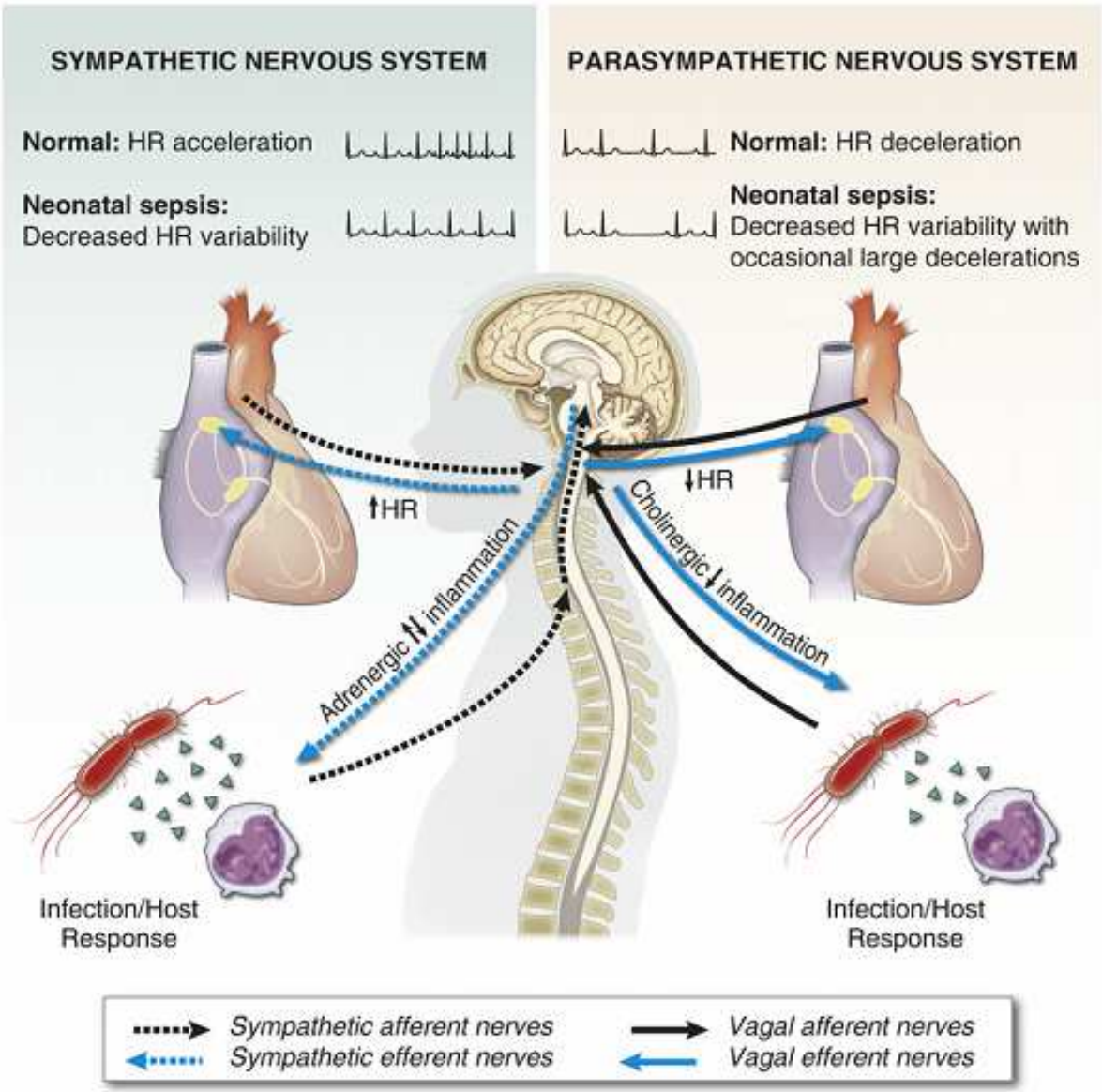


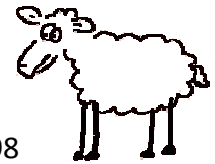


Schmidt et al. 2001. Curr Opin Crit Care 7:314-322

From mathematics to physiology







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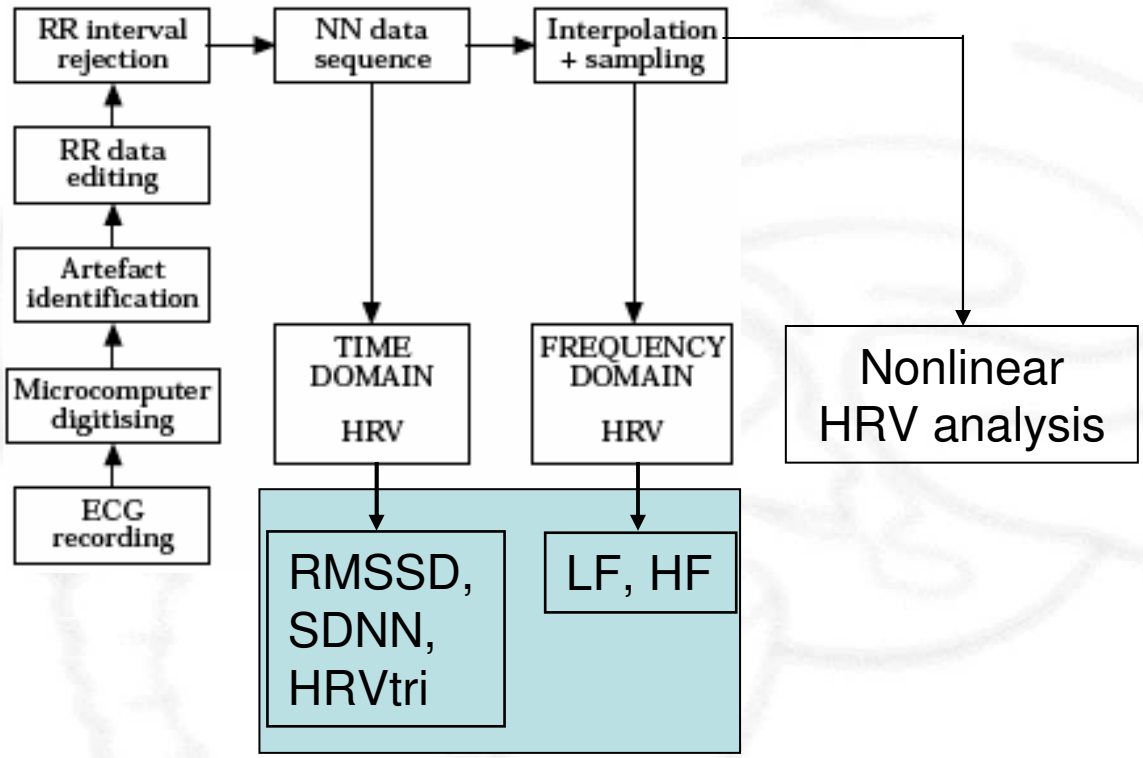
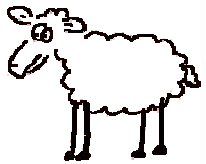
Acquisition & Analysis of HRV

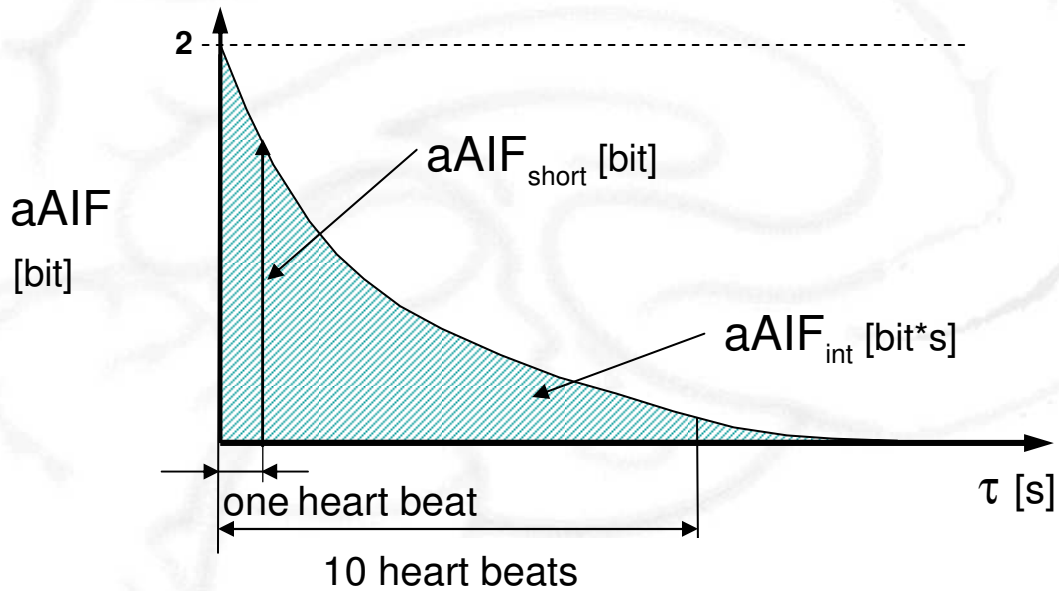


- Fractal dimension
- Entropy (complexity)
- Lyapunov exponent
- Non-linear prediction
- Comparison with surrogate data

HRV Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996. Circulation.
Mansier, P., J. Clairambault, et al. 1996. Cardiovasc Res 31(3): 371-9.



fHRV measures: aAIF



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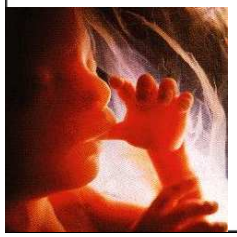
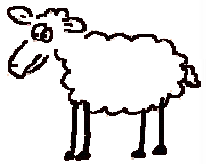
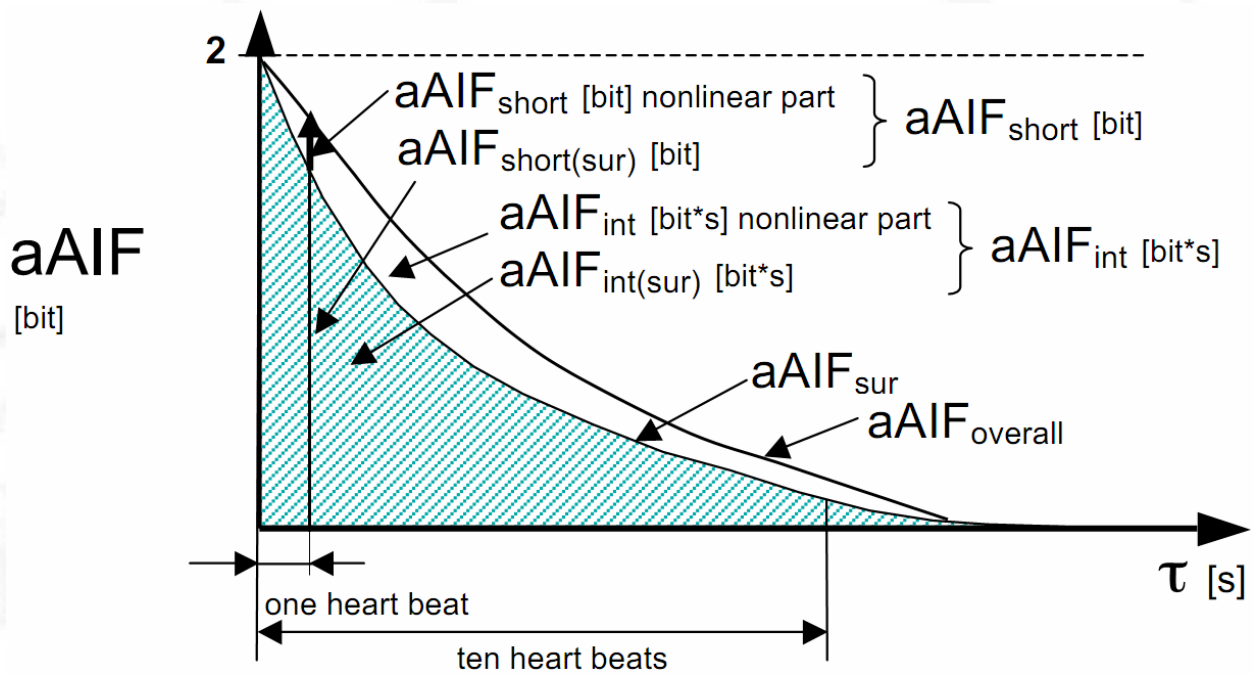




fHRV measures: aAIF zoomed in



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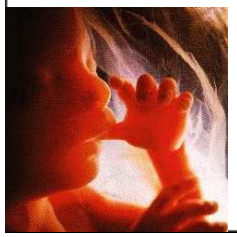
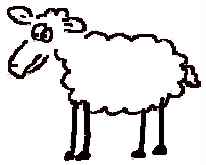
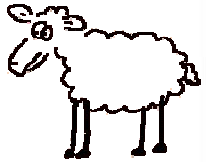




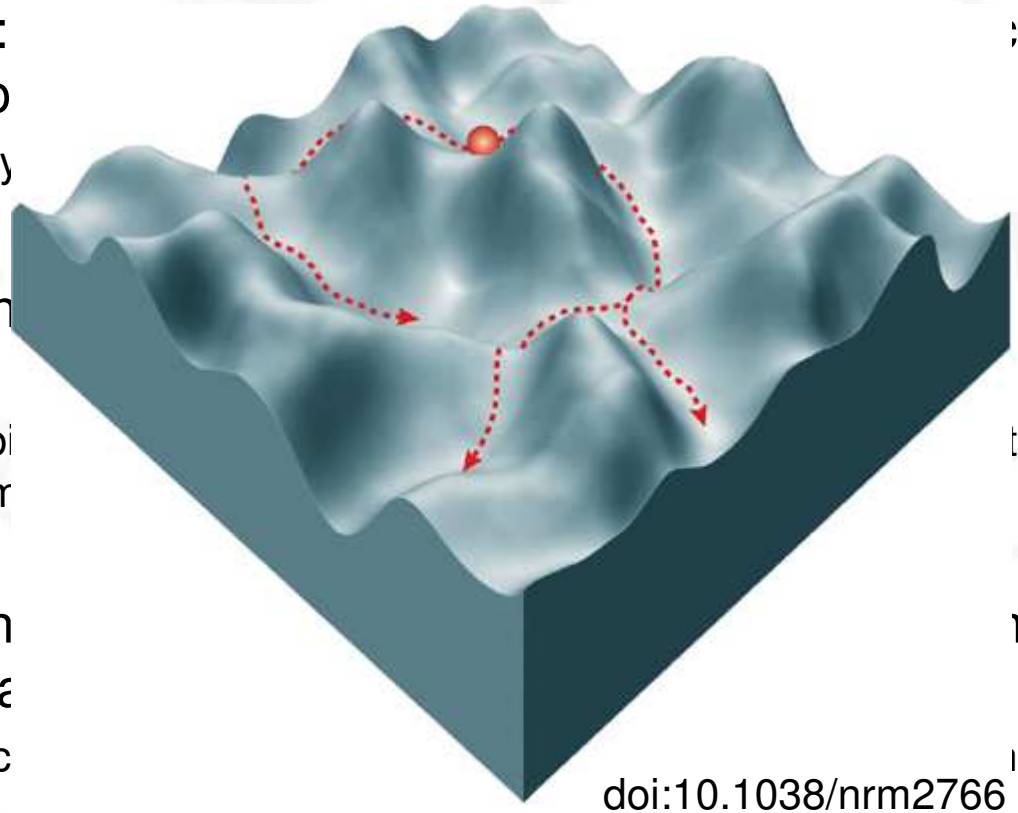
Methods: fetal sheep model

- Late gestation fetal sheep are chronically prepared with arterial catheters, ECG electrodes and vagal nerve stimulation electrodes
- 3 days post-op recovery and data recording
- Experiment: 3-30 consecutive days of recording ABP, ECG.
- Fetal arterial blood sampled for blood gases/pH, metabolites, cytokines levels measured by ELISA.
- RMSSD calculated from ECG-derived FHRV.
- Brain immunohistochemistry: molecular components of CAP in microglia, astrocytes, neurons



Outlook (1): clinical studies – fHRV monitoring

- Pilot study: alp ECG during labo
  - Feasibility
- Subsequen the last trimester
  - to test abi tal infection (chorioam
- Suggestion ne scale fHRV for noisier a
  - No magic ndscape



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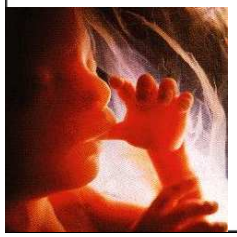
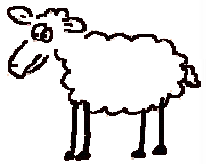
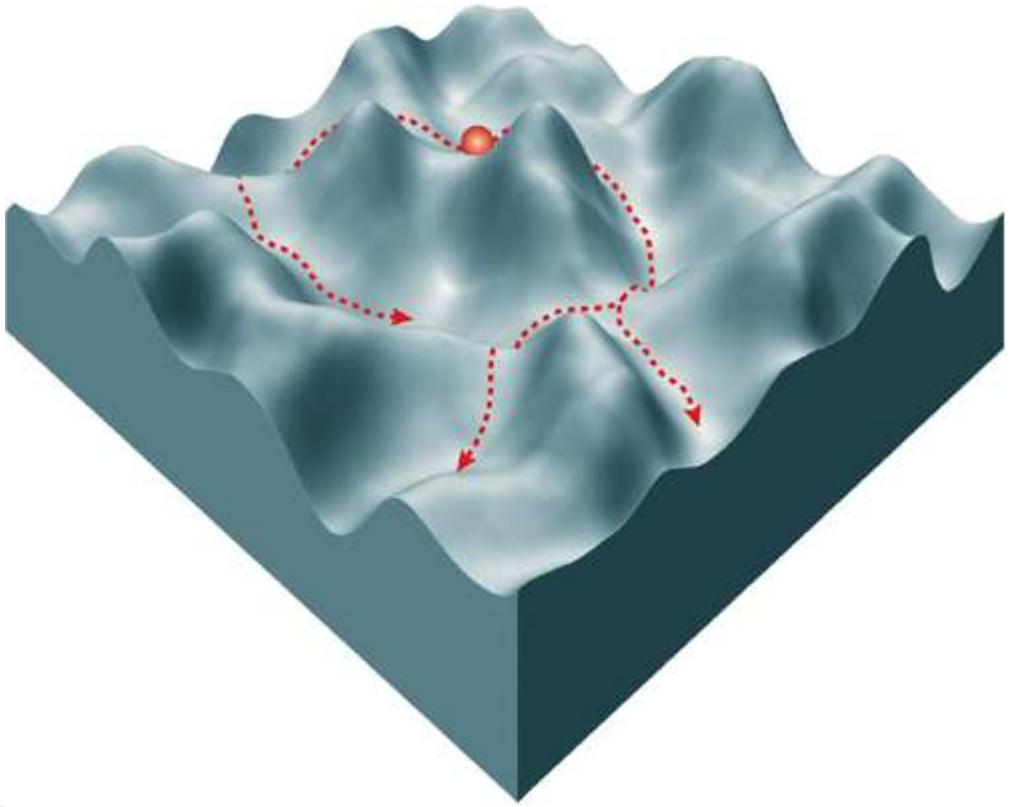


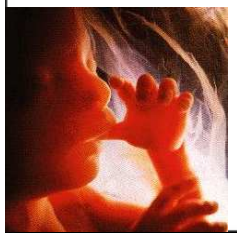
Peters *et al*. 2004 *Physiol Meas* 25, 585-593



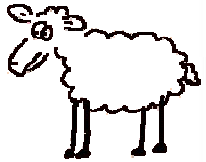
Outlook (3): multivariate fetal monitoring



“Surface complexity arises out of deep simplicity”



Murray Gellmann



Thank ewe!