Brain, Respiration, and Cardiac Causalities in Anæsthesia

Origins, basis, rationale and science

Peter V. E. McClintock[1], Martin Hasler[2], Juergen Kurths[3], Per Kvandal[4], Svein Landsverk[4], Dmitri G. Luchinsky[1], Milan Paluš[5], Arkady Pikovsky[3], Zvezdan Pirtošek[6], Johan C. Ræder[4], Samo Ribaric[7], Michael Rosenblum[3], Andrew F. Smith[8], Aneta Stefanovska[1,9], and Niels Wessel[3]

[1]Lancaster, [2]Lausanne, [3]Potsdam, [4]Oslo, [5]Prague, [6]Ljubljana UMC, [7]Ljubljana FM, [8]Lancaster RLI, [9]Llubljana FEE

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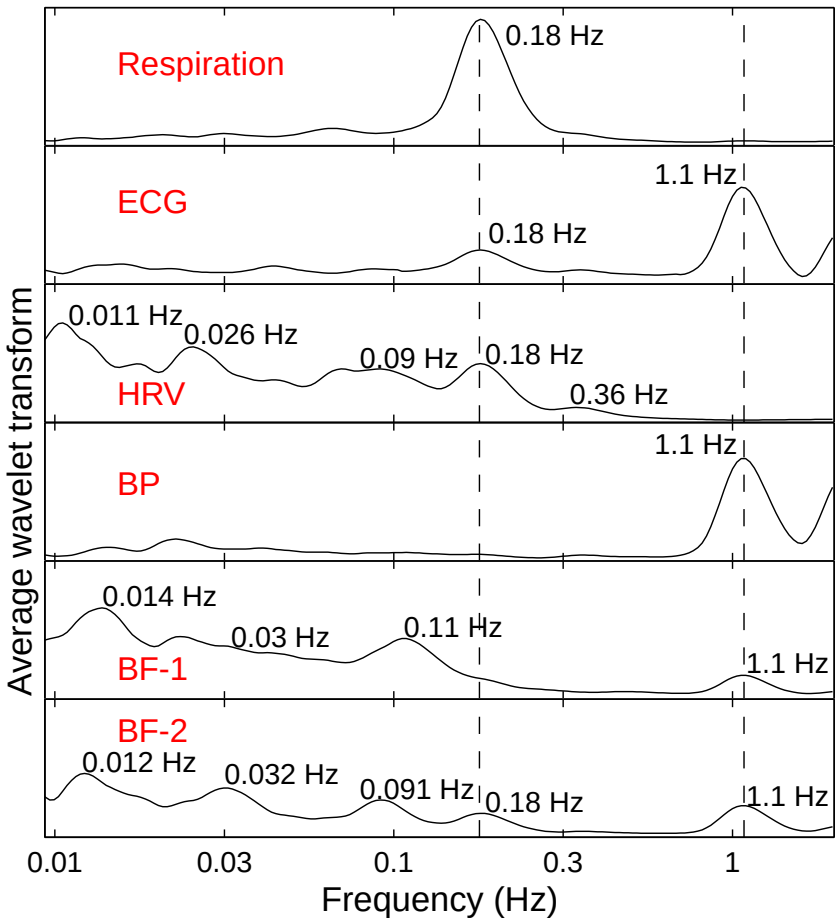
Outline

1. Introduction
   - Physiological oscilllations
   - Anæsthesia
   - Data analysis methods
2. The BRACCIA enterprise
   - Consortium
   - Research programme
3. Conclusion
   - Summary

How do the oscillations and their couplings change in anæsthesia? Might these changes provide a novel basis for measuring depth of anæsthesia?

Averaged wavelet spectra



Note –

- Log frequency resolution
- Same spectral peaks in all data?
- Peaks are broadened by their time-variations.

The body is “humming” with rhythms! But where do they come from?

Physiological origins of the rhythms?

∼Hz	Process
1.0	Heart – obvious
0.2	Respiration – obvious?
0.1	Myogenic activity of smooth muscle – same *in vitro*
0.04	Neurogenic activity – absent after denervation
0.01	Endothelial vasodilation – NO-dependent
0.007	Endothelial vasodilation – endothelin-dependent

Our interest centres especially on –

- Relative amplitudes
- Couplings

between respiratory, cardiac, and cortical (EEG) oscillations, which seem to reflect the state of the organism...

Anæsthesia – practice & problems

What is (general) Anæsthesia?

- A chemical perturbation of the organism resulting in a temporary loss of consciousness.
- Mysterious – mind/body relationship etc.
- Certain nervous pathways blocked.
- Important – needed for surgery.

"...the anæsthetist is still unable to measure the depth of anæsthesia in order to prevent inadvertent awakening during anæsthesia."

C.J.D. Pomfrett, *Brit. J. Anæsthesia*, 1999.

Incidence of awareness in anæsthesia

- Too much anæsthetic $\Rightarrow$ bad for patient.
- Too little anæsthetic $\Rightarrow$ awareness.

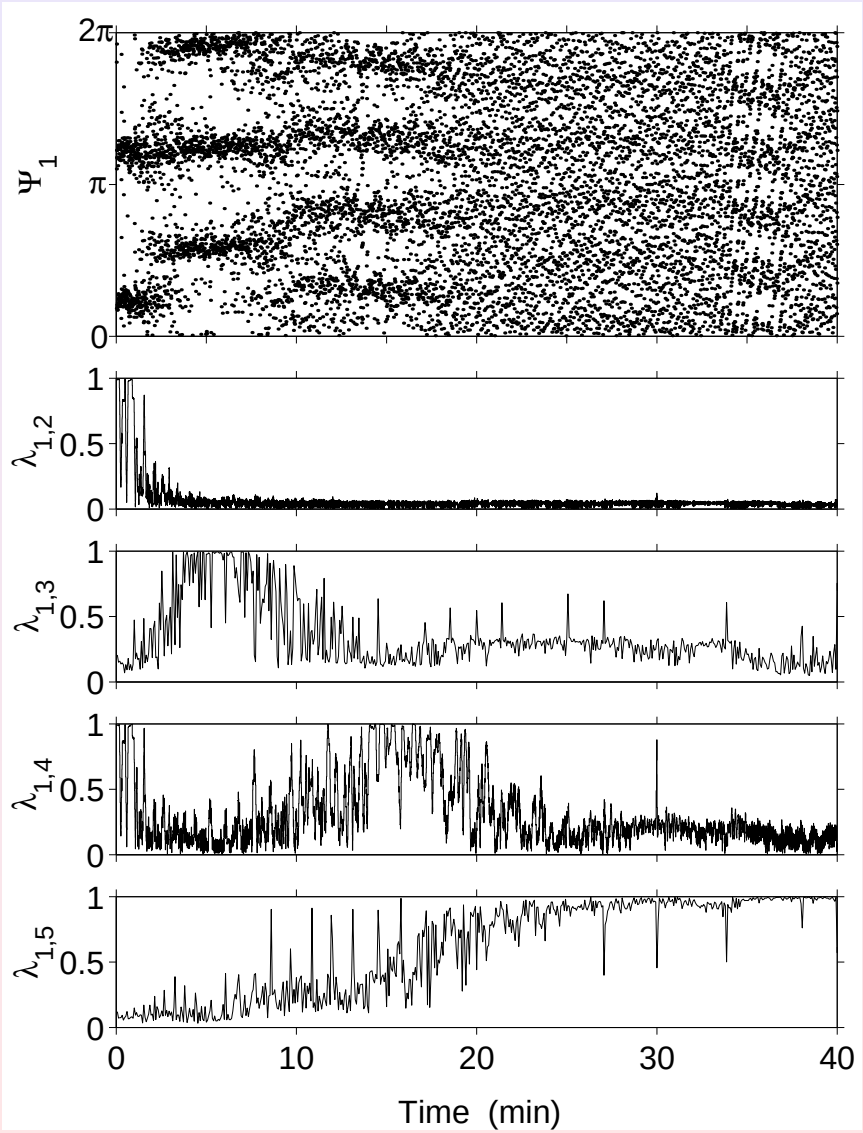
Author	Date	Sample	Awareness %
Hutchinson	1960	656	1.2
Harris	1971	120	1.6
McKenna	1973	200	1.5
Wilson	1975	490	0.8
Liu *et al*	1990	1,000	0.2
Lennmarken & Sandin	2004	1,238	0.9
R. Coll. of Anæsth. (NAP5)	2014	3,000,000	0.005

- So need a reliable measure of depth of anæsthesia.
- Can physics (of coupled oscillators) help? Maybe...

Example – cardio-respiratory synchronisation in rats

- Initially, studied rats.
- *a* Administer anæsthetic;
  b Measure heart-rate & respiration;
  c Anæsthesia lasts about 100 min.
- Synchronisation effects are much stronger during anæsthesia.
- Starts wearing off after typically 40–50 min.
- Depth of anæsthesia related to synchronisation ratio.

[Stefanovska et al., *Phys. Rev. Lett.* **85**, 4831 (2000).]



Aims and challenges

Interested in how to characterise signals so as to reveal changes in anæsthesia. Challenges include –

- Numerous signals are potentially relevant – so which will be most useful?
- Inherent time-variations of the signals – how to accommodate or exploit them?
- How best to combine the information coming from many different analyses?

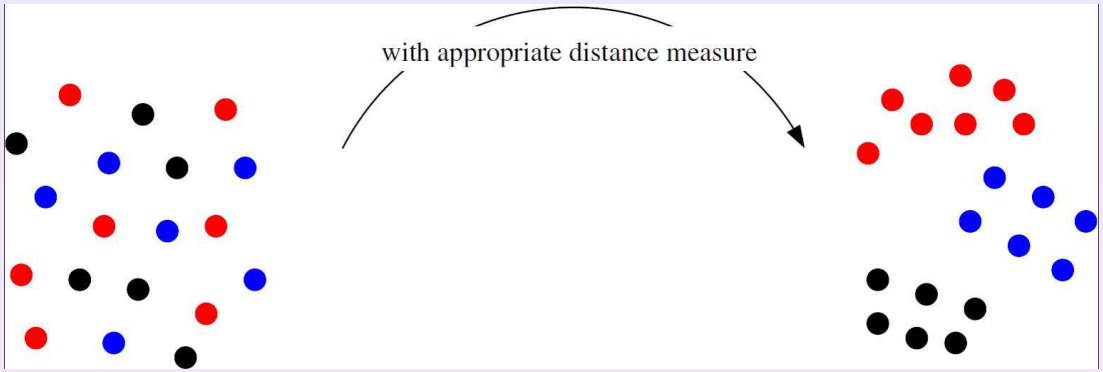
New analysis methods needed to be developed before BRACCIA could come to fruition.

Data analysis methods

- Wavelet analysis, the main “work horse”, provides –
  - Time-frequency information with logarithmic frequency resolution
  - Power in different spectral ranges
- Frequency variability analysis – measured directly from ECG R-peaks and respiration signal maxima, giving HRV and RFV.
- Wavelet phase coherence analysis – apply to any pair of signals. If phase coherence persists over time then –
  - Either the signals have a common source
  - Or they are synchronised
- Coupling function analysis – apply to any pair of signals. Extracts detailed quantitative information about the mutual interactions between the oscillators.

Result: a large number of different measures of the state, e.g. averages, powers in different spectral ranges for several signals, HRV, RFV, coherences at different frequencies between different signals, coupling functions...

Making optimal use of the results – classification



- Problem is how best to combine the diverse measures (attributes) of state, e.g. awake, or anaesthetised with propofol, or with sevoflurane.
- Use *distance-based classification* and *nearest neighbour classifier*.
- With an appropriate distance measure in the multi-dimensional space, the three states form separated clusters.
- Leads to a *confusion matrix* giving the likelihood of correct and incorrect classification for subjects in each group.
- Using a learning algorithm, the classification accuracy improves with number of subjects.

[Kenwright et al, *Anæsthesia* **70** 1356–1368 (2015), Suppl. Mat.]

Proposed BRACCIA Consortium

No.	Organisation	Abbreviation	Town	Country
1	University of Ljubljana, Faculty of Elec. Eng.	UNILJFE	Ljubljana	Slovenia
2	Lancaster University	UNILANCS	Lancaster	UK
3	Royal Lancaster Infirmary	MBHT	Lancaster	UK
4	Swiss Federal Inst, of Tech.	EPFL	Lausanne	Switzerland
5	University of Ljubljana, Faculty of Medicine	UNILJFM	Ljubljana	Slovenia
6	University of Oslo Ulleval Hospital	UOUH	Oslo	Norway
7	University of Potsdam Inst. of Complex Systems	UP	Potsdam	Germany
8	Academy of Sciences Inst. of Computer Sciences	ICSASCR	Prague	Czech Repub.

Coordinator: Aneta Sefanovska

Measurements

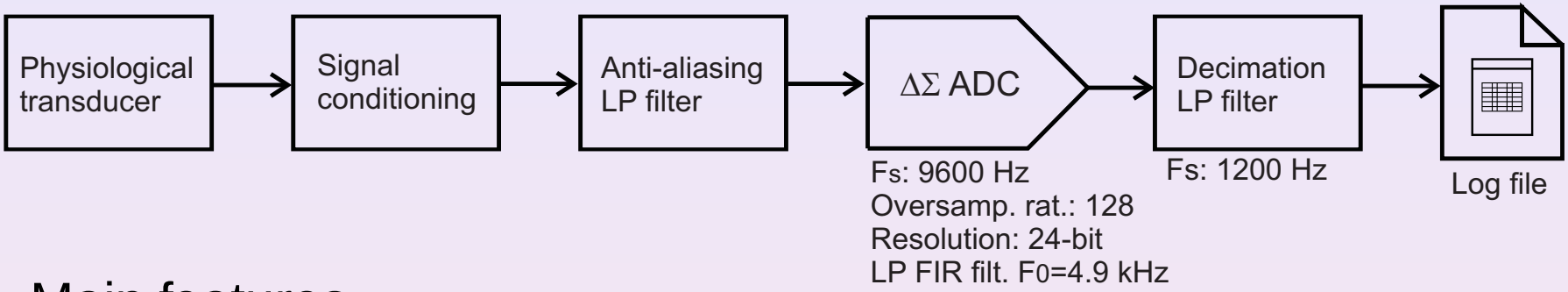
The simultaneous measurements included time series of –

- Electrical activity of the heart (ECG)
- Respiratory activity
- Skin temperature
- Skin conductivity
- Brain activity (EEG)

For patients (a) awake, (b) anæsthetised with propofol, (c) anæsthetised with sevoflurane.

All measurements used the *Cardo&BrainSignals* signal conditioning unit specially designed for BRACCIA by Jozef Stefan Institute (Ljubljana).

The *Cardo&BrainSignals* signal conditioning unit



Main features –

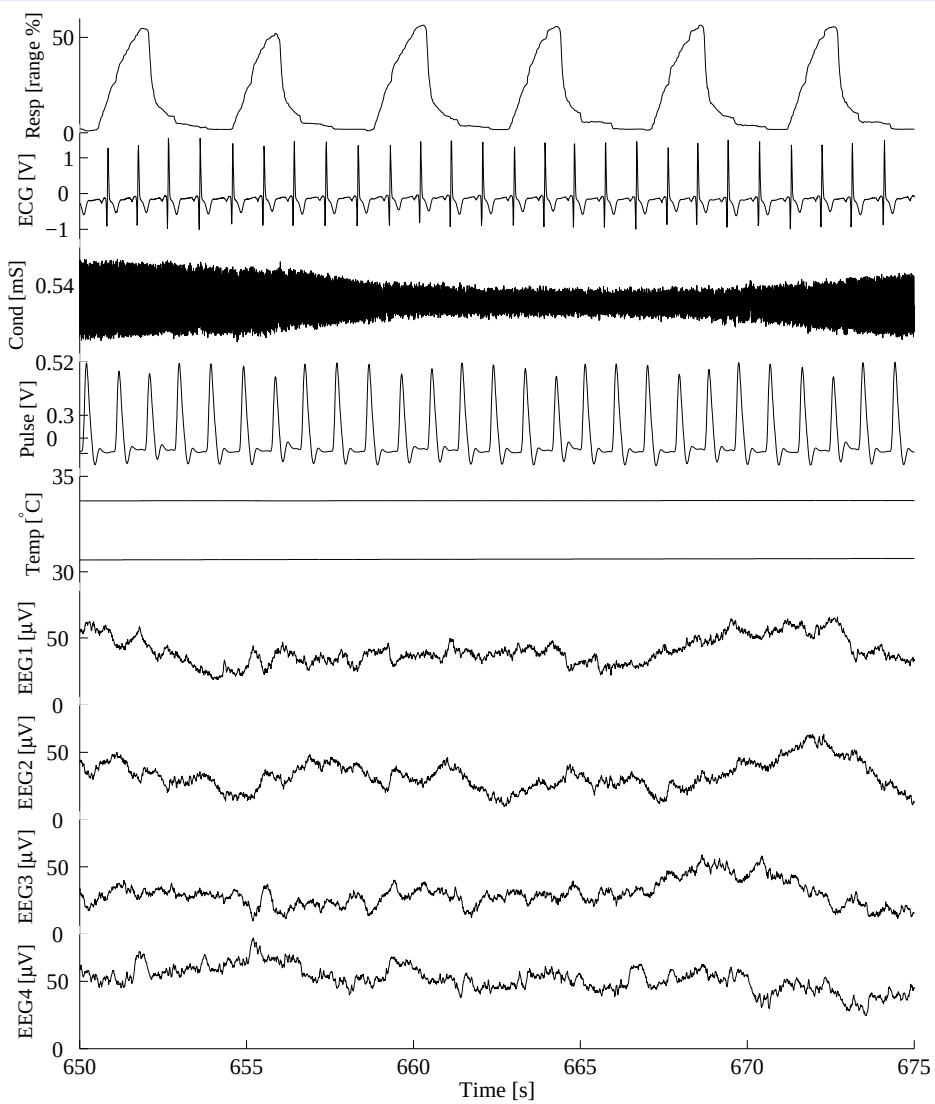
- 12 identical channels
- Synchronized parallel operation of ΔΣ ADCs
- 24-bit A/D conversion
- 9.6 kHz sampling frequency
- Optical interface, to reduce interference

Same measurement set-up in both hospitals, as well as for healthy subjects (Lancaster) and rats (Ljubljana).

Measurements

Channel	Signal
1	ECG
2	EEG-1
3	EEG-2
4	EEG-3
5	EEG-4
6	BP Pulse
7	Respiration
8	Conductivity
9	Temperature 1
10	Temperature 2
11	Gen. purpose 1
12	Gen. purpose 2

All recorded (i) without and (ii) with anæsthesia.



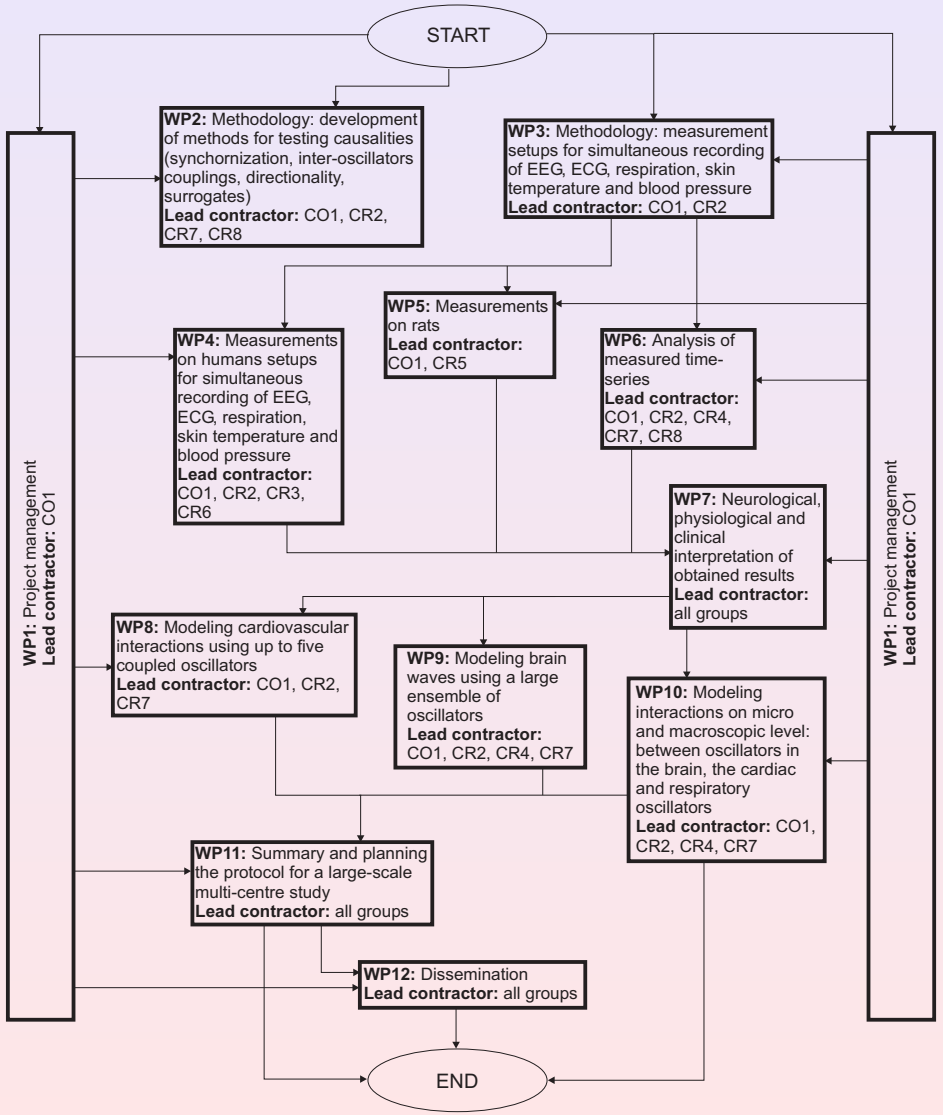
BRACCIA Project Plan

Logistics

- Measurements in Oslo, Lancaster, Ljubljana.
- Resultant time series uploaded to database in Lancaster.
- Data downloaded to Lancaster, Lausanne, Potsdam, Prague, for analysis.
- Joint, collaborative interpretation

Schedule

Proposal	2005-2008
Extended	2005-2009
Actual	2005-2016...



Summary – not including outcomes

- Physiological oscillations carry information about the state of the organism.
- Powerful time series data analysis methods are now available to analyse the oscillations.
- BRACCIA uses these to explore whether the oscillations can quantify depth of anæsthesia.
- Following about 11 years of work, the BRACCIA enterprise is coming to fruition and a clear answer is now emerging...
- ...to be reported in the presentations by Andy Smith and Johan Ræder!

Acknowledgements and recent publications

Acknowledgements

We are grateful to the entire BRACCIA team for their collaboration, and to European Community (FP6), the Engineering and Physical Sciences Research Council (UK) and ARRS (Slovenia) for funding the research.

Recent BRACCIA publications

1. D A Kenwright, Bernjak, T Draegni, S Dzeroski, M Entwistle, M Horvat, P Kvandal, S A Landsverk, P V E McClintock, B Musizza, J Petrovčič, J Ræder, L W Sheppard, A F Smith, T Stankovski and A Stefanovska, “The discriminatory value of cardiorespiratory interactions in distinguishing awake from anæsthetised states: a randomised observational study”, *Anæsthesia* **70** 1356–1368 (2015).
2. T Stankovski, S Petkoski, J Ræder, A F Smith, P V E McClintock, and A Stefanovska, “Alterations in the coupling functions between cortical and cardio-respiratory oscillations due to anæsthesia with propofol and sevoflurane”, *Phil. Trans. R. Soc. A* **374**, 20150186 (2016).