Coupled oscillators: Why may they be used to describe cardiovascular dynamics?

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Outline

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The cardiovascular system takes care of the energy supply for an organism.

- 1616 William Harvey (1578-1657) announced his discovery of the circulatory system.
- 1628 Harvey published his work *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, where, he argued for the idea that blood was pumped around the body by the heart before returning to the heart and being re-circulated in a closed system.

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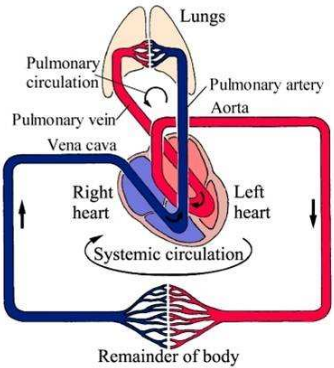

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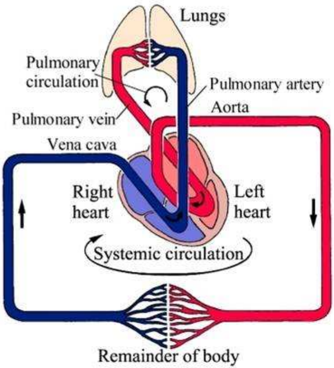
Harvey proposed that blood flowed through the heart in two separate loops

- Pulmonary circulation, connected the circulatory system to the lungs, and
- Systemic circulation, causes blood to flow to the vital organs and body tissue.



- Galen of Pergamon's (129 - ca. 200 or 216) theories still dominated medical science during Harvey's time. Galen identified venous (dark red) and arterial (brighter and thinner) blood, each with distinct and separate functions. Venous blood was thought to originate in the liver and arterial blood in the heart; the blood flowed from those organs to all parts of the body where it was consumed.

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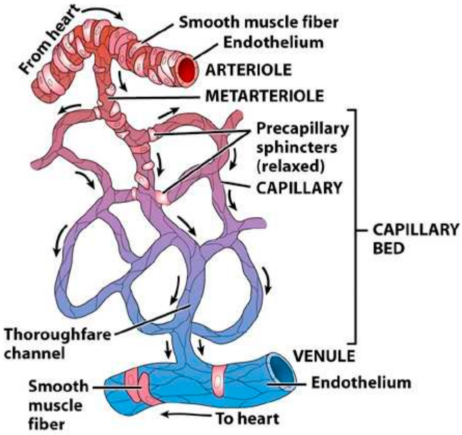
- Hence, also Harvey's work was attacked and criticized, but eventually accepted during his lifetime.
- Marcello Malpighi in 1661, using a microscope that was not available to Harvey, identified the capillary network and proved that Harvey's ideas were correct.

Q: What is the importance of the capillary network?



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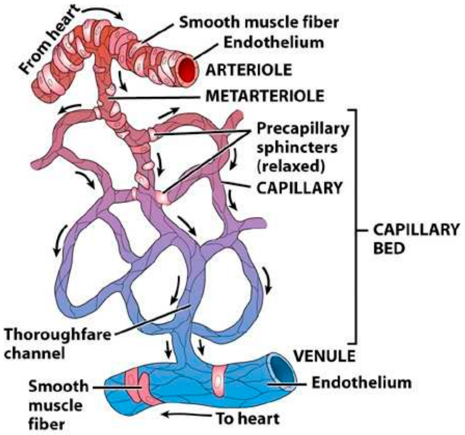

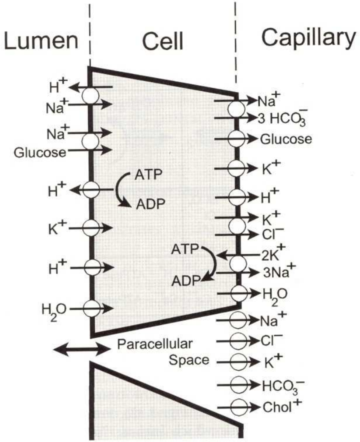

From Glaser 2001 and after Verkman and Alpern 1987

A: Because it is at the capillaries that the continuous exchange of energy and matter happens.

Harvey's work is still not completed today

Q: So, where are we?

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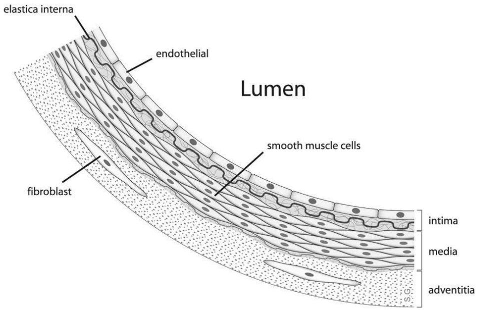

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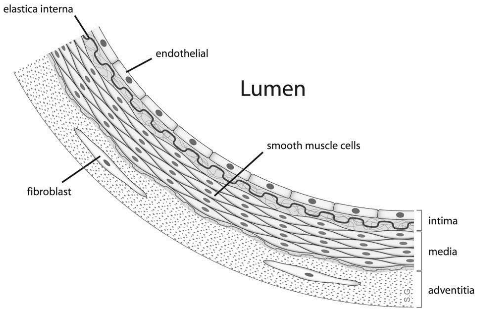

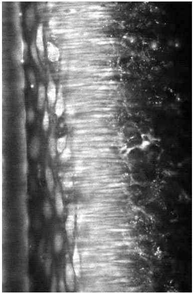

Courtesy of Christian Aalkjær, 2008

Quick glance at entropy

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- In thermodynamically non-isolated systems (can be either closed, i.e. can exchange energy but not matter with the environment; or open, i.e. can exchange energy and matter), the entropy can either increase or decrease. The total entropy balance is

$$\frac{\mathrm{dS}}{\mathrm{dt}} = -\nabla \mathrm{J}_{\mathbf{s}} + \sigma,$$

  where $\nabla \mathrm{J}_{\mathbf{s}}$ is divergence of the entropy flux, $\mathrm{J}_{\mathbf{s}}$, i.e. the exchange between the system and the environment through its borders.

Maxwell's demon...

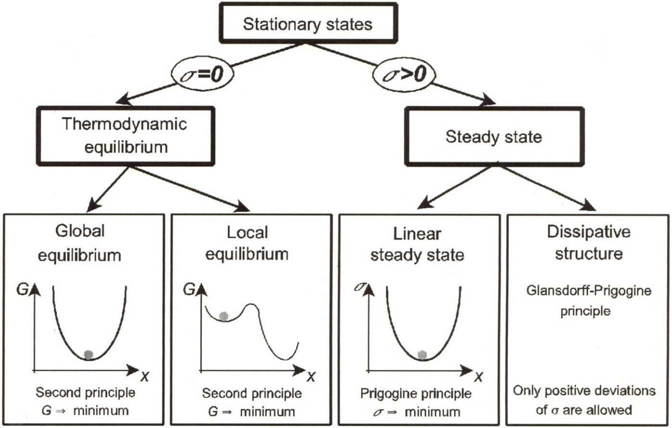
... or the relationship between entropy and information.

The interconnection of information with entropy in terms of thermodynamics may be illustrated by the experiment Maxwell performed in 1881.

The example illustrated by Maxwell's demon raises the question: what is the threshold value of information which is required to control the processes of living systems?

Or, when solving an inverse problem: what is the threshold value of information which is required to understand a process of a living system?

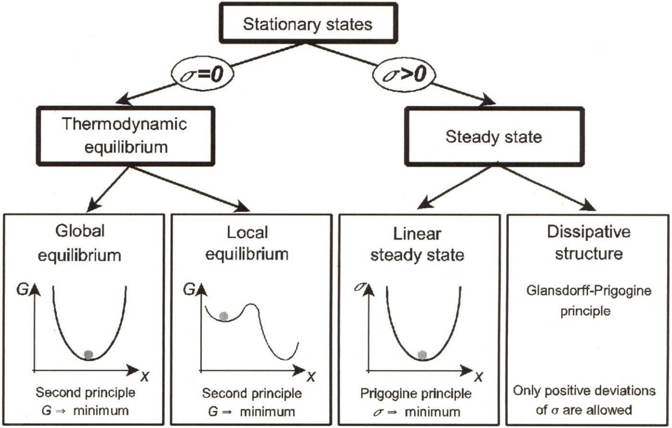
Closed and open systems



Types of stationary states:

The entropy production σ is an indicator for distinguishing between equilibrium and steady states.

Closed and open systems



Types of stationary states:

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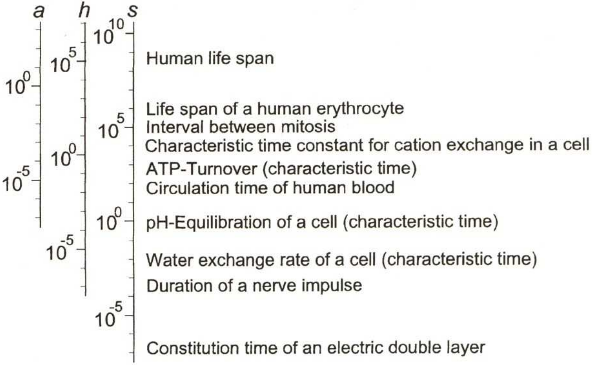
- In contrast to equilibrium structures which are structures in space, dissipative structures can also be structures in time, or in a space-time continuum.

A hierarchy of time scales

All living systems are dissipative and open systems.

A biological system consists of subsystems, each of which is associated with a different time scale for its stationary state.



s – seconds, *h* – hours, *a* – years

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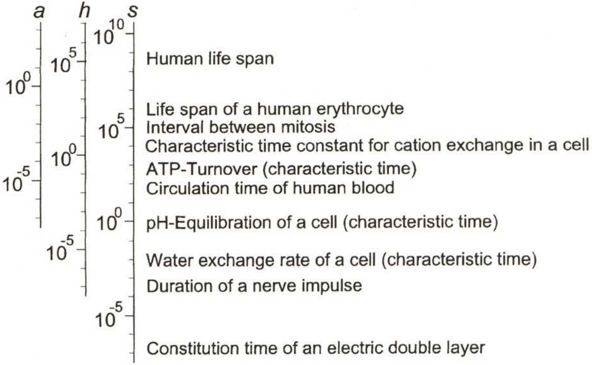

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Which are the time scales of the oscillations in blood circulation, including the time scale(s) of the endothelial function?

Simultaneous non-invasive measurements

"Nothing exists until it is measured" – Niels Bohr

For dynamical systems the results of measurements are time series, or signals.

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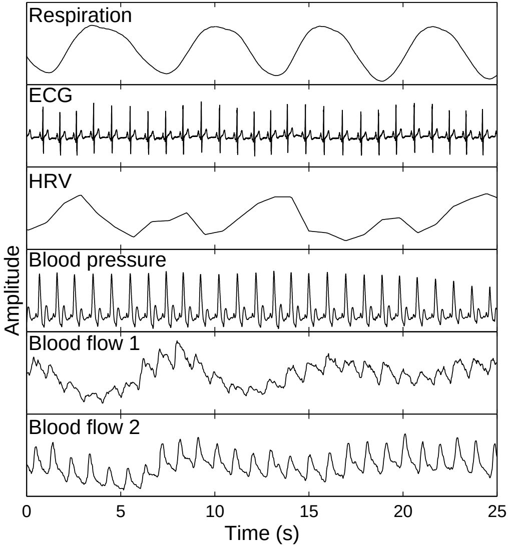
Measured quantities

- Cardiac activity (from ECG)
- Respiration (belt+sensor on thorax)
- Blood pressure (sensor on finger)
- Blood flow rate (laser-Doppler flowmetry)
- Temperature (semiconductor sensor)

Signals



Note –

- "HRV" is derived from ECG and represents the time-evolution of cardiac frequency.
- Several frequencies in blood flow are already evident in the time domain...

Nonlinear and stochastic dynamics

Two developments in parallel –

- Analysis of complex signals (Grassberger & Procaccia, 1983), applications to ECG and HRV...
  - Chaotic behaviour?
  - Scaling behaviour, multifractal properties.
  - $1/f$ spectra, etc... etc...

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We draw on results of both enterprizes.

Frequencies and amplitudes

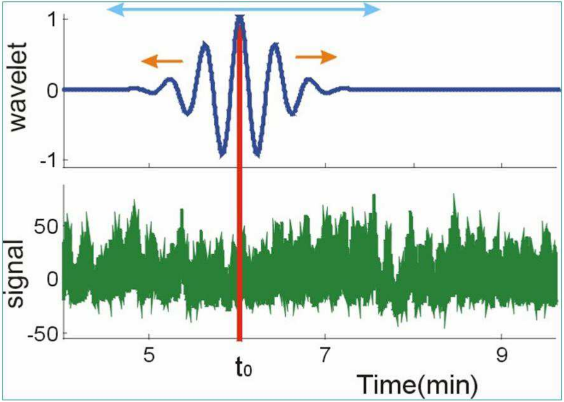
- Finite length of recordings
- Oscillations vary in time
- Several oscillations within a relatively wide frequency interval (0.005–2 Hz)

Solution?

- Time–frequency analysis
- Wavelet transform with the Morlet mother wavelet

Wavelets

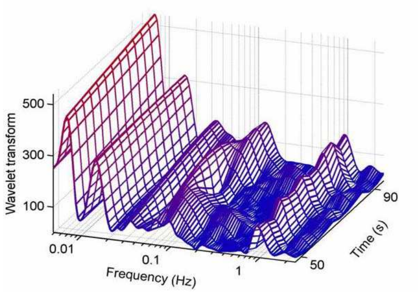
- Transformation from time to the time-frequency domain

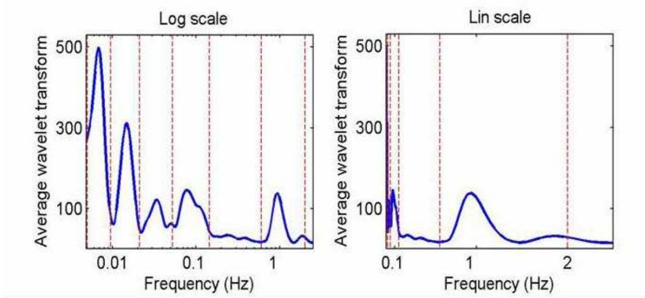


- Morlet mother wavelet $\Rightarrow$ family of wavelets
- Time resolution: shifting the wavelet along the signal
- Frequency resolution: stretching/shortening of the wavelet

- Continuous WT – tracing the oscillations in time

Wavelet transform





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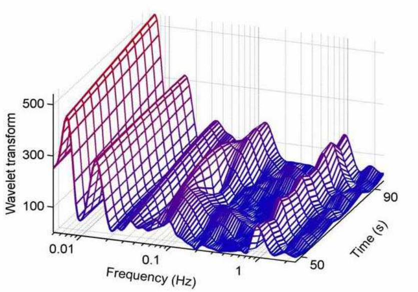
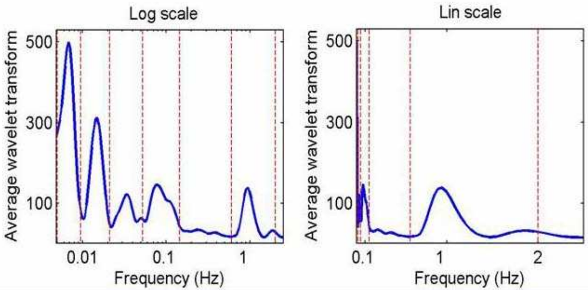


- WT coefficients in the time-frequency plane



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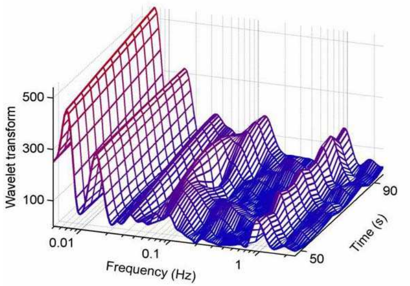
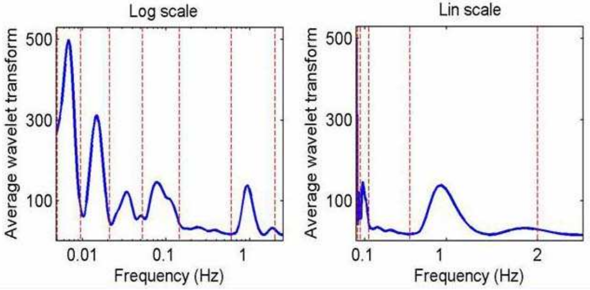
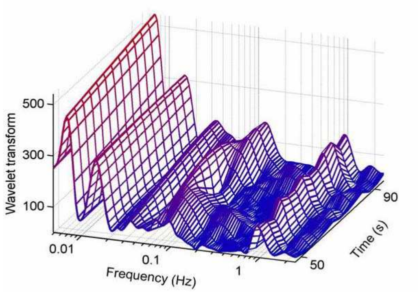


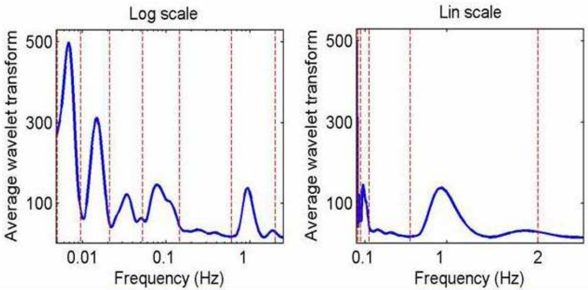
- WT coefficients in the time-frequency plane
- Six peaks in the interval from 0.005 Hz to 2 Hz



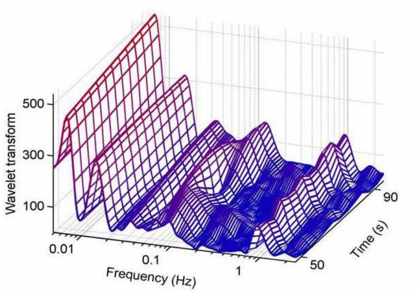
Wavelet transform



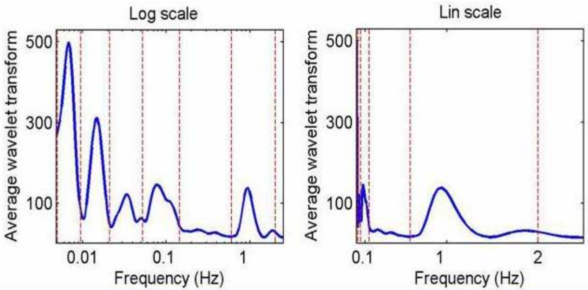
- WT coefficients in the time-frequency plane
- Six peaks in the interval from 0.005 Hz to 2 Hz
- Average wavelet transform with interval boundaries



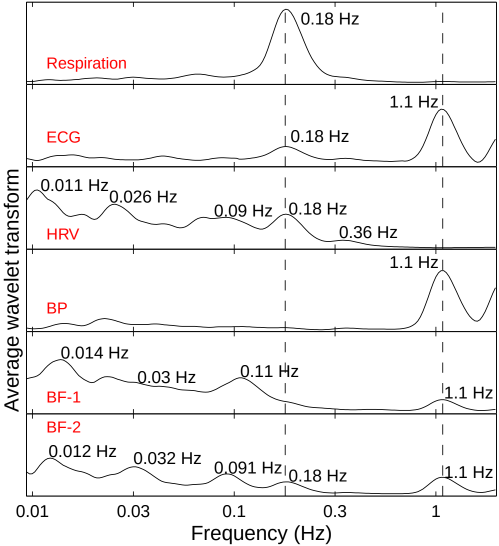
Wavelet transform



- WT coefficients in the time-frequency plane
- Six peaks in the interval from 0.005 Hz to 2 Hz
- Average wavelet transform with interval boundaries
- Logarithmic frequency resolution



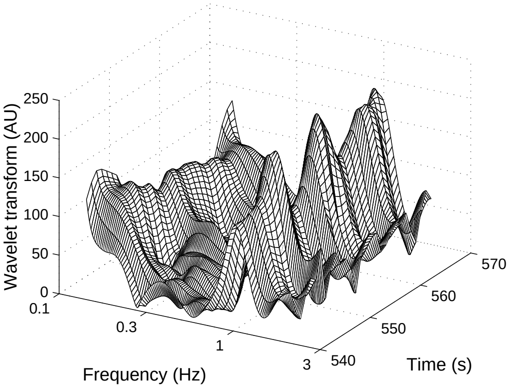
Averaged wavelet spectra



Note –

- Same spectral peaks in all data, but amplitude varies with site
- Peaks are broad

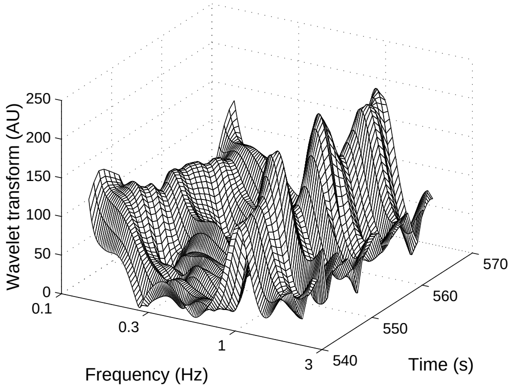
Time–frequency wavelet transform



Time variation of maxima –

- Amplitudes
- Frequencies

Time–frequency wavelet transform



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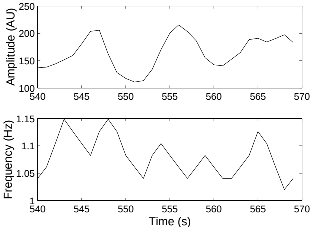
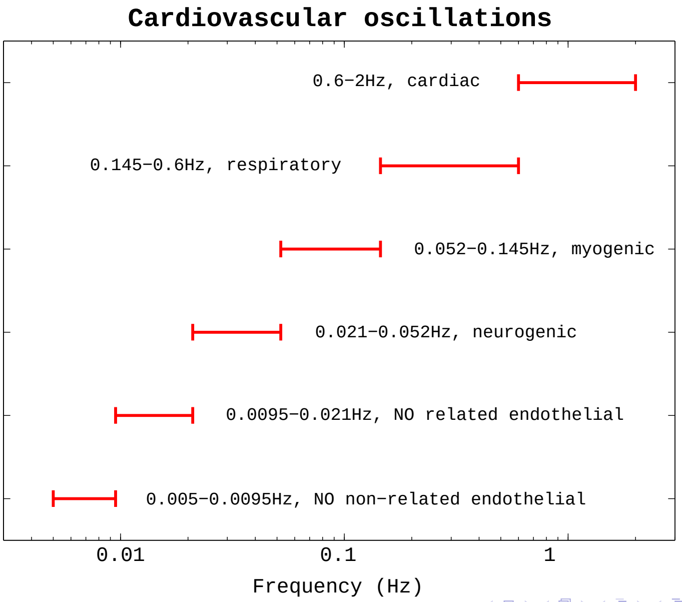
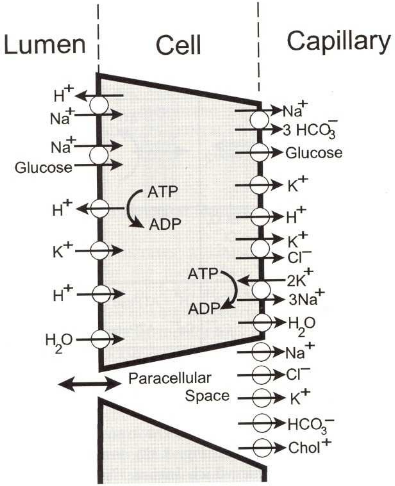


Time-variation of spectral peaks

Time scales in humans



Why then endothelial oscillations?



From Glaser 2001 and after Verkman and Alpern 1987

- LDF recordings refer to flow within a hemisphere of radius 1 mm containing several hundred capillaries and a few arterioles and venules.

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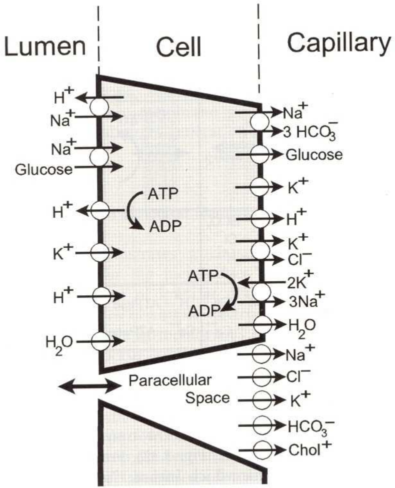

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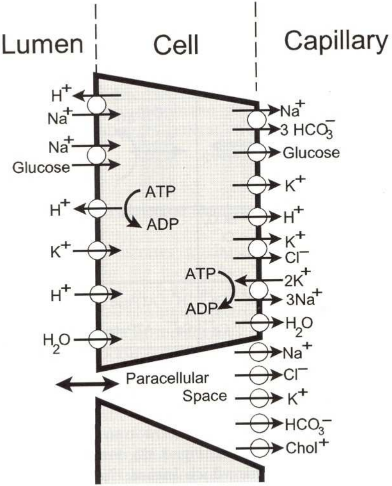

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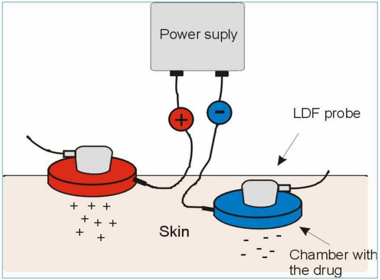
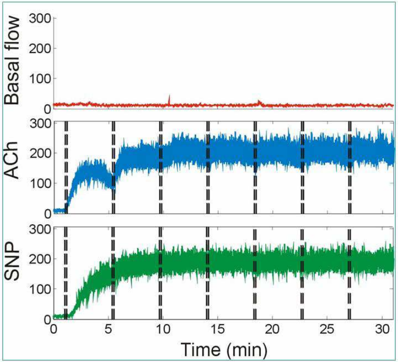
- It is at the capillary level that exchange of ions and gases occurs across the endothelial barrier – a thermodynamically nonequilibrium process subject to fluctuations.
- The blood flow through the capillaries introduces a deterministic component into these fluctuations, providing a basis for synchronization of the oscillations.

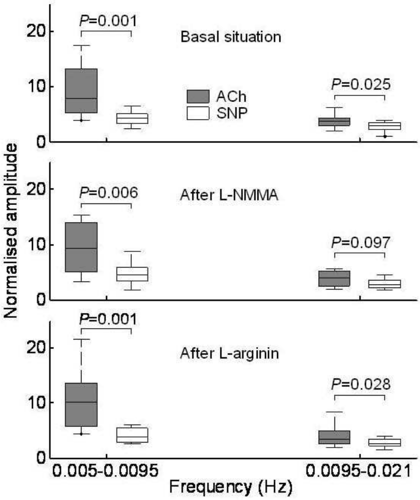
How to observe the endothelial-related oscillations?





By iontophoretic administration of endothelial-dependent (ACh) and endothelial-independent (SNP) vasodilators and comparison of their responses in the frequency domain.

NO- and non-NO-related oscillations

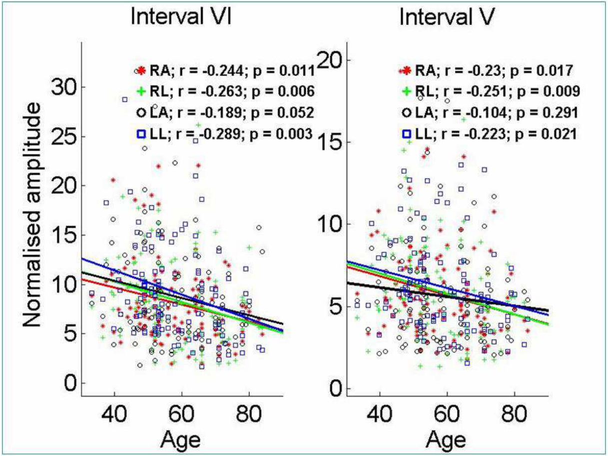


- Interval V: 0.0095–0.021 Hz
  - Endothelial-related (*Kvernmo et al., 1998, Stefanovska et al., 1999, Kvernmo et al., 1999, Kvandal et al., 2003, Landsverk et al., 2006*)
  - NO-related (*Kvandal et al., 2003*)
- Interval VI: 0.005–0.0095 Hz

  Endothelial; not related to NO (*Kvandal et al., 2006*)

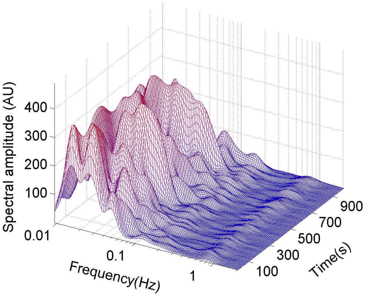
Endothelial ageing

- Simultaneous flow measure-ments on all four extremities
- 134 healthy subjects aged 24–84
- Decreased endothelial activity with age

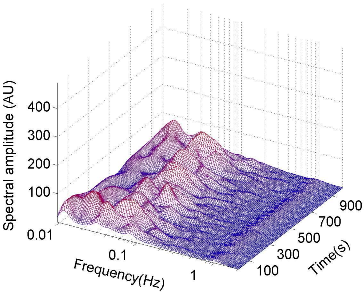


More evidence for low frequencies in blood flow

no anæsthesia



local anæsthesia



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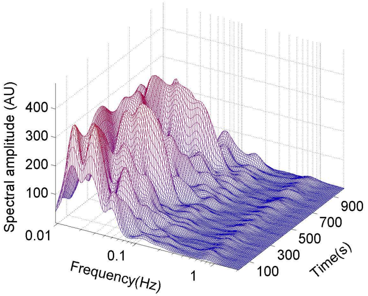

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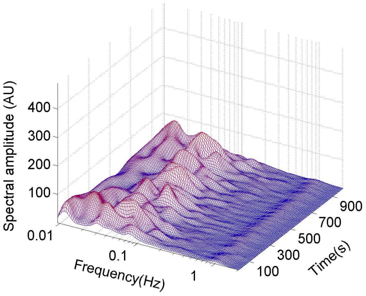
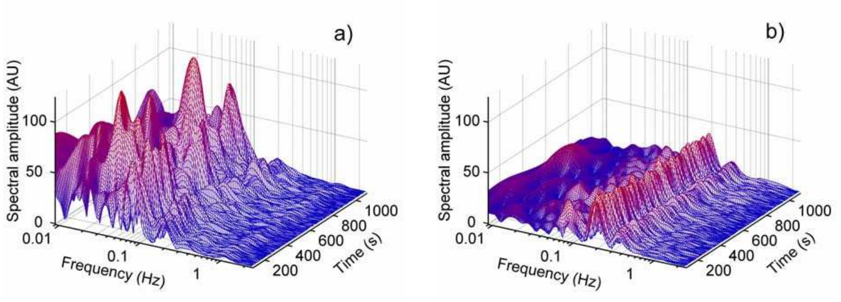


Low frequencies components in blood flow (endothelial and neurogenic) are strongly suppressed during local anæsthesia, Landsverk *et al*, 2006.

More evidence for low frequencies in blood flow

awake | in anæsthesia



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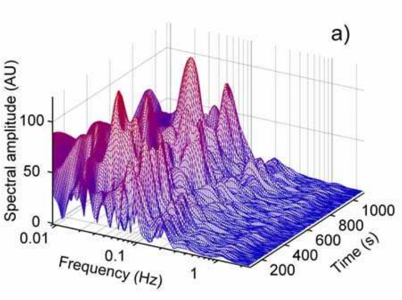
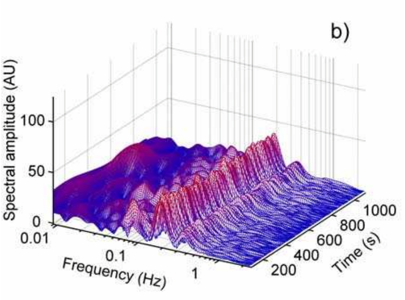
awake

in anæsthesia

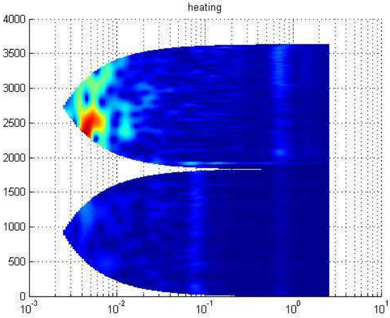




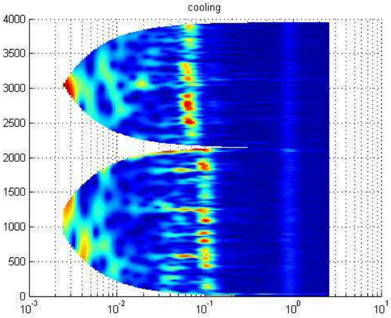
Low frequencies components in blood flow are strongly suppressed during general anæsthesia, Landsverk *et al*, 2007.

Low-frequency oscillation and local heating and cooling

heating



cooling



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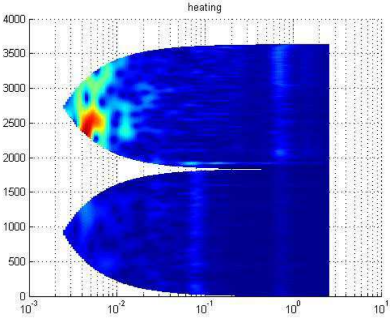
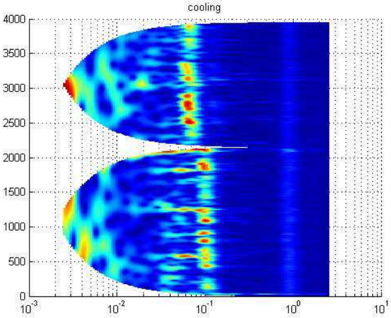


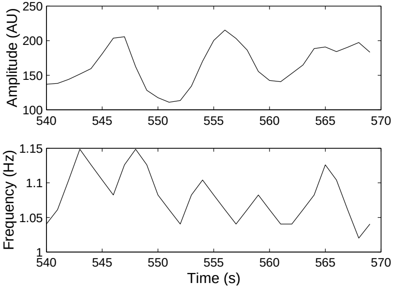
cooling



Sheppard *et al*, in preparation.

Evidence of inter-oscillator couplings?

Modulation



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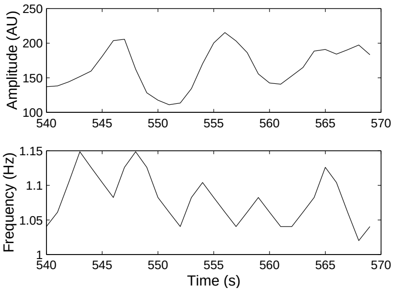
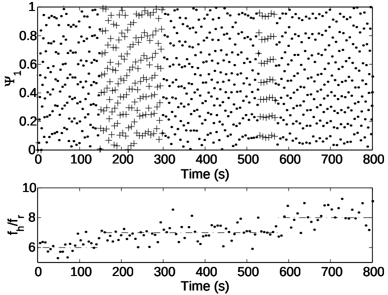


Synchronization



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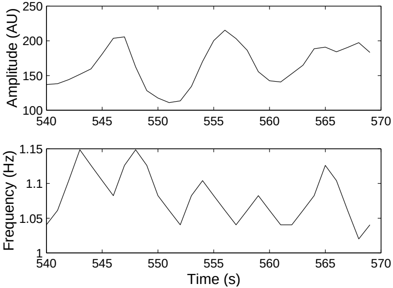

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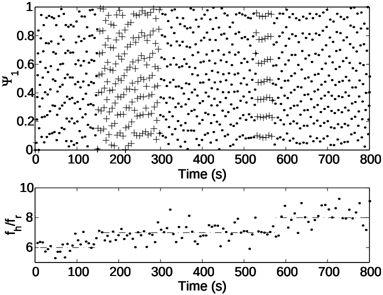

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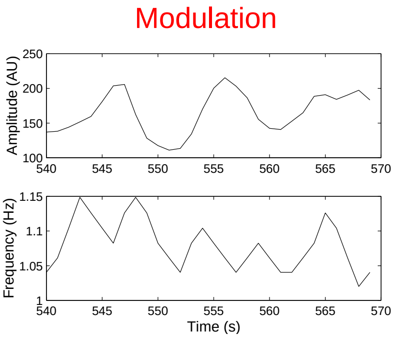
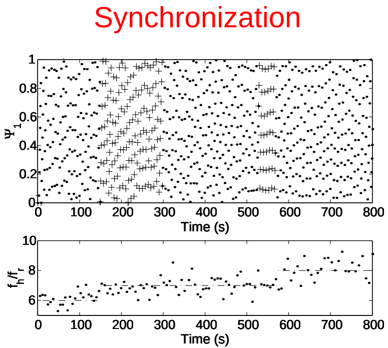
Evidence of inter-oscillator couplings?





- Closely analogous to coupled-oscillator phenomena seen elsewhere in physical science and engineering...
- Methods to analyse couplings?
- Several possibilities: phase synchronization, directionality of amplitude and phase coupling, time-bispectral analysis, time-phase coherence analysis,. . .

Applications to date

The approach provides a way of characterizing the cardiovascular system – the oscillator parameters and strengths of interaction describe the state of the system.

There are characteristic changes with e.g. exercise, aging, and pathophysiological conditions.

Applications include –

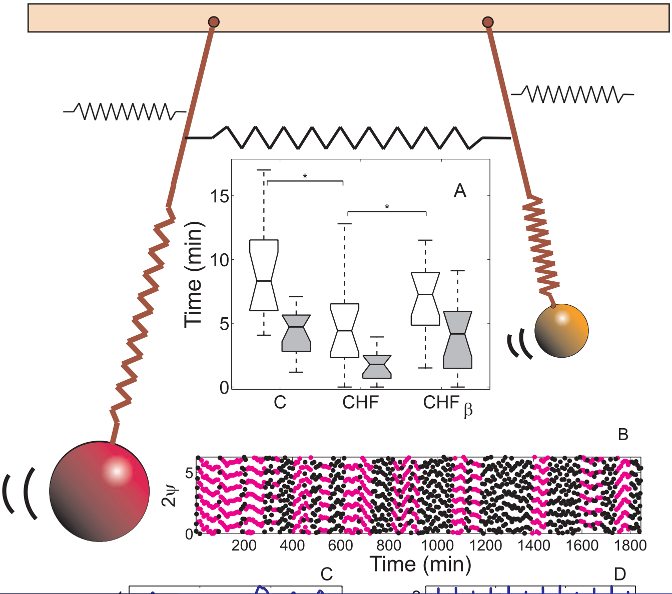
- Heart failure
- Diabetes mellitus
- Post-acute-myocardial infarction
- Anæsthesia
- Exercise
- High altitude

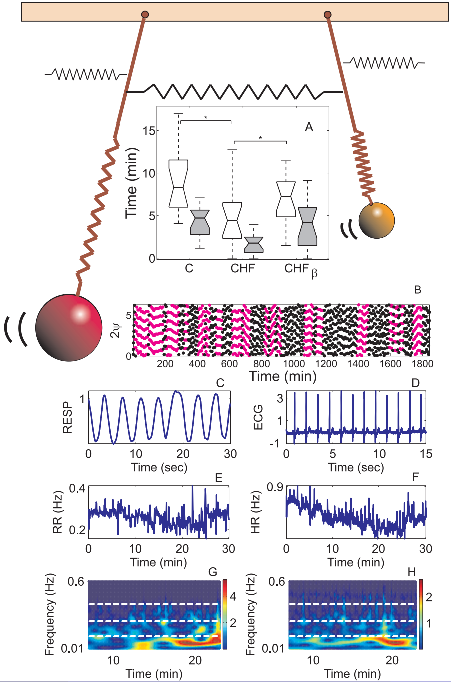
Cardio-respiratory interactions in heart failure

To see if changes in cardio-respiratory interactions and synchronization phenomena – with Peter Clarkson, Alireza Bahraminasab and Peter McClintock –

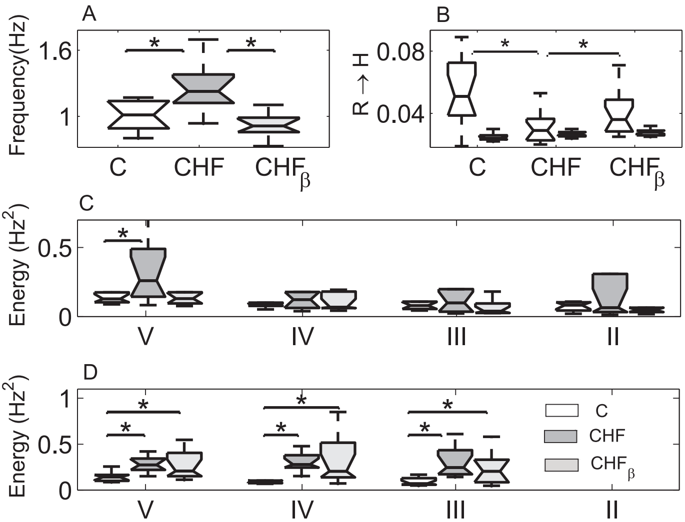
- In this study, 17 patients with newly diagnosed congestive heart failure, defined as an ejection fraction of less than 35% by echocardiography, were compared to 21 healthy matched controls.
- Repeat measurements made 5 weeks after a stable dose of β-blockers were given.

Cardio-respiratory interactions in heart failure




A
15
10
5
0
Time (min)
C
CHF
CHF β
B
2ψ
200 400 600 800 1000 1200 1400 1600 1800
Time (min)
C
RESP
Time (sec)
D
ECG
Time (sec)
E
RR (Hz)
Time (min)
F
HR (Hz)
Time (min)
G
Frequency (Hz)
Time (min)
H
Frequency (Hz)
Time (min)

Low-frequency modulation

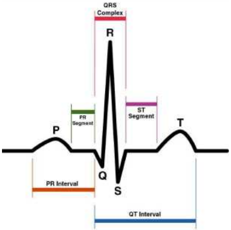


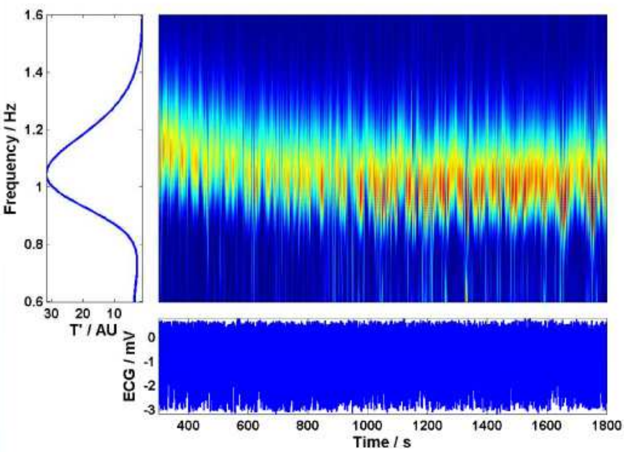
Cardio-respiratory interactions in anæsthesia

To see if changes in cardiovascular interactions – with Andy Smith, Mike Entwistle, Peter Larsen, Bojan Musizza, Peter McClintock –

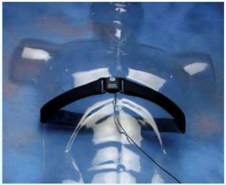
- Study volunteers – healthy males aged 25–40.
- Measure for 30 minutes prior to minor surgery in Royal Lancaster Infirmary. Respiration is non-assisted.
- Compare with measurements on wakeful humans.

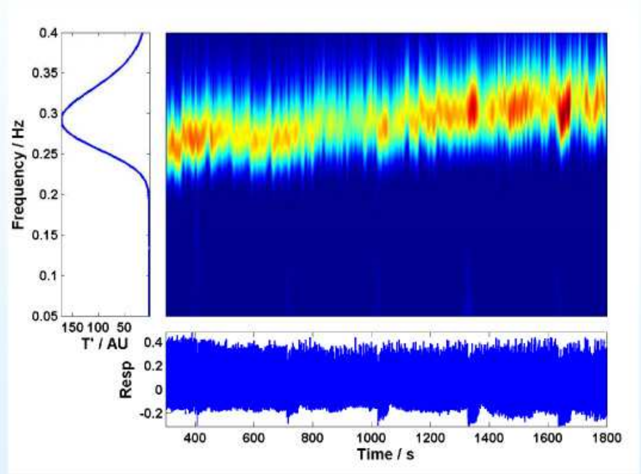
Cardiac oscillations



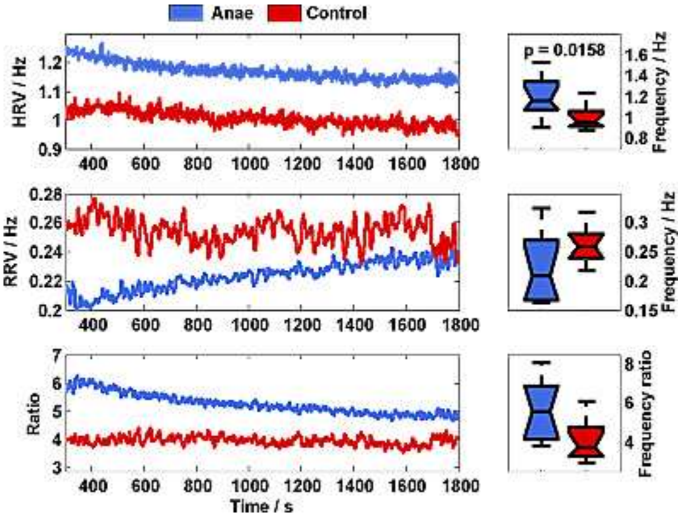


Respiratory oscillations



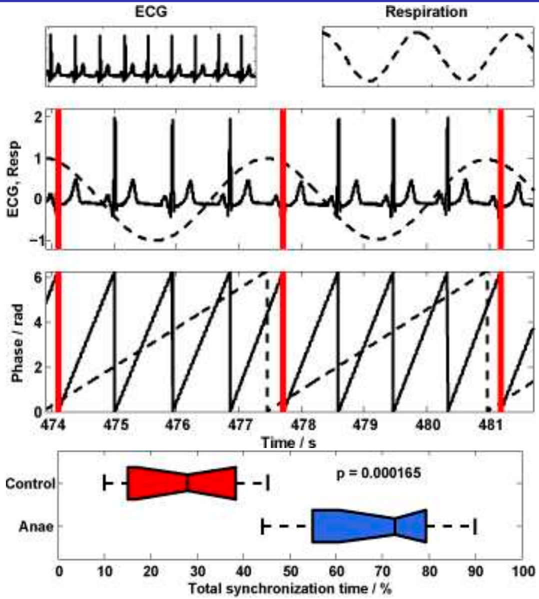


Instantaneous frequencies

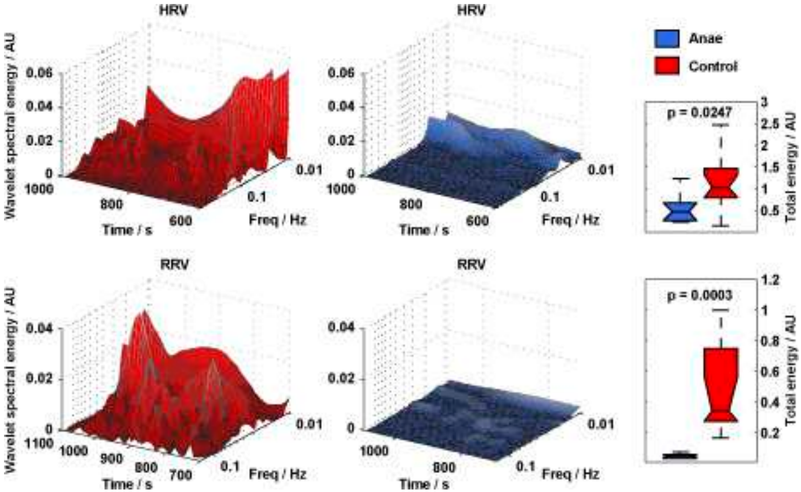


Larsen et al, in preparation

Phases and synchronization time



Heart and respiratory rate in anæsthesia



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Q: Possible explanation?
A: Yes, the low frequency oscillations again.

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- Interactions are signatures of the thermodynamic openness of the system. The respiratory frequency varies more when the system has higher intensity of exchange. In anæsthesia the respiratory frequency is much less variable than e.g. during exercise.
- The degree of openness corresponds to the degree of non-autonomicity of a system as formulated in mathematics. Hence, in the state of deep anæsthesia the system is almost autonomous.

Acknowledgements & References

Acknowledgements

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Selected references

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3. A Bahraminasab, F Ghasemi, A Stefanovska, P V E McClintock,and H Kantz H, “Direction of Coupling from Phases of Interacting Oscillators: A Permutation Information Approach”, *Phys. Rev. Lett.*, **100**, 084101, (2008).