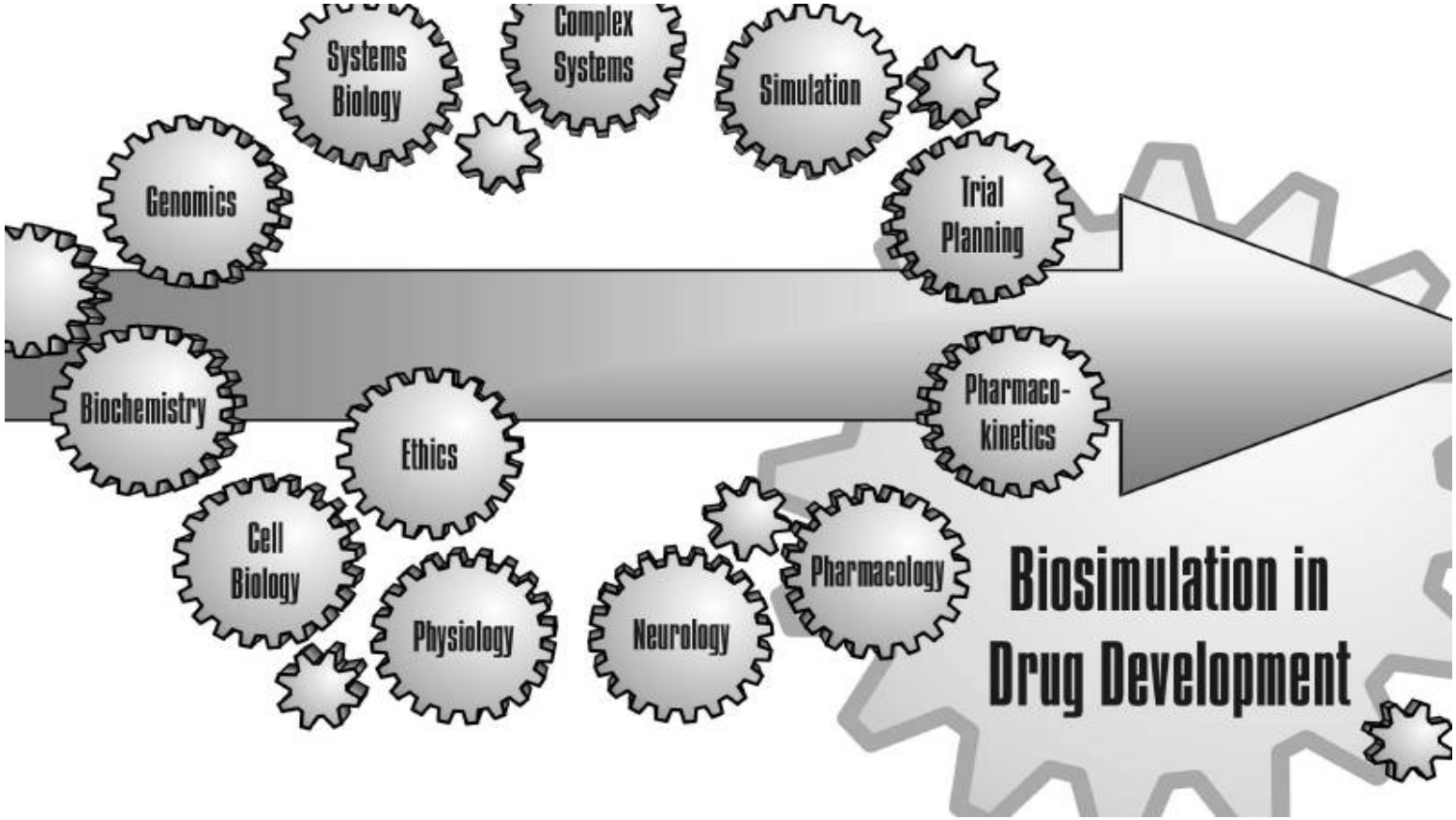
BioSim group at the 1st BioSim conference

The BioSim Network

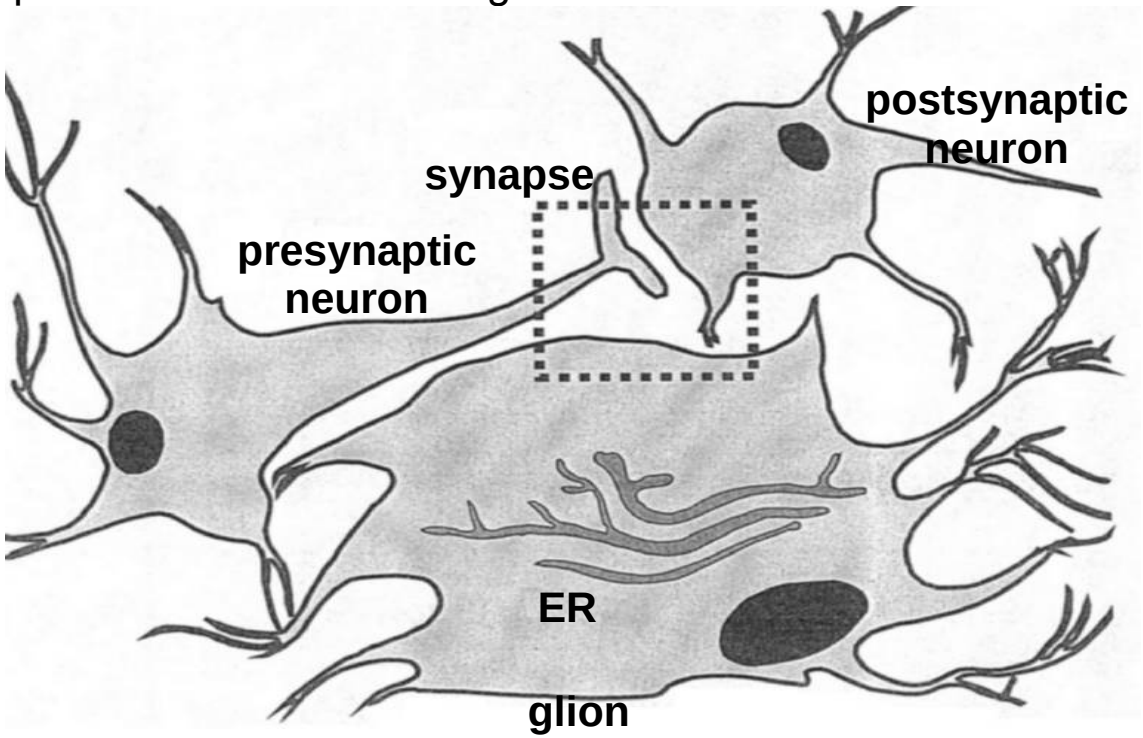


Through coordination of a broad range of scientific disciplines the BioSim Network will bridge biochemistry and genomics from the drug discovery phase with trial planning and pharmacokinetics of the drug development phases by more detailed insights into the normal and pathological processes and by professional modelling and information techniques.

Systems Biology

Systems Biology aims at developing an integrated and mathematically based description of the functioning of living organisms from the genetic and cellular levels over cell-to-cell communication and the control of tissues, functional units and organs to the overall regulation of the organism and its response to external challenges.

Biosimulation is the application of Systems Biology to solve practical problems in the pharmaceutical industry as well as in the health sector at large.



Donald Marsh, School of Medicine, Brown University:

The success we have had in the medical treatment of many diseases by far outstrips our understanding of the underlying biological and pathological processes

Activity Areas and Work Packages

The purpose of the BioSim Network is to illustrate how the use of simulation models can contribute to a more rational drug development process and a better health care.

1 Regulatory issues
- Public relations
- Simulation / 3R
- Drug absorption
- PK/PD models

2 Diabetes
- Pancreatic cells
- Fat cells
- Metabolic regulation
- Disease models

3 Hypertension
- Heart cells
- Full heart model
- Kidney models
- Vascular system

4 Cancer
- New drugs
- Drug testing
- Circadian rhythms
- Chronotherapy

5 Mental disorders
- Gene expression
- Trauma
- Cell communication
- Deep brain stimulation

6 Methodology
- Network models
- Complex systems
- Nonlinear data analysis
- Simulation tools

26 Academic Partners

Technical University of Denmark: Physics, bioinformatics
Oxford University: Physiology, cell biology, diabetes[H]
University of Copenhagen: Physiology, cell biology, biochemistry
Pharmaceutical University of Denmark: Pharmacology
Free University of Amsterdam: Biochemistry
University of Manchester: Pharmacokinetics
Universite Libre de Bruxelles: Physical chemistry
University of Marburg: Depression[H]
University of Bordeaux: Neurology
Jülich Research Center: Tremor[H]
University of Valencia: Pharmacokinetics
University of Leeds: Physiology
Linköping University: Medicine
Lund University: Medicine
Slovak Academy of Science: Pharmacokinetics
Hungarian Academy of Science: Drug development
Humbolt University: Biophysics
University of Potsdam: Physics
University of Warwick: Mathematics
University of Balearic Islands: Physics
Hôpital Paul Brousse, Paris: Cancer[H]
University of Sheffield: Pharmacokinetics
Technical University of Dresden: Biochemistry

Industrial and Regulatory Partners

Large pharmaceutical companies
- Novo Nordisk A/S, Denmark

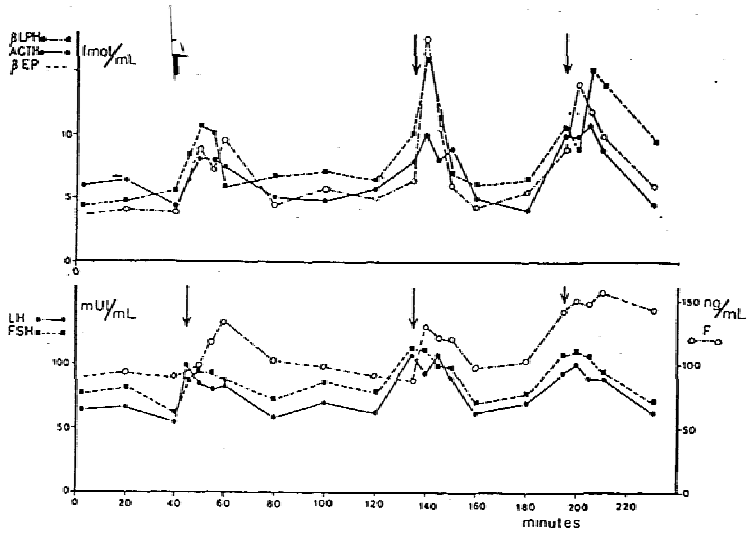
SMEs
- European Media Lab, Heidelberg
- Simcyp Ltd., Sheffield
- InNetics AB, Linköping
- MXM Laboratories, Vallauris
- Amarin Neuroscience, Oxford
- interActive Systems GmbH, Marburg
- Fraunhofer-Chalmers Center for Industrial Mathematics, Linköping
- SOLVO Biotechnology Rt., Budapest
- Zealand Pharma A/S, Copenhagen

Regulatory agencies
- Danish
- Swedish
- Dutch
- Spanish

Everything Changes all the Time – That's what Life is

- Oscillatory phenomena typically arise from negative feedback mechanisms.
- Oscillations may serve as pacemakers or biological clocks that can coordinate different processes in time.
- Interaction between two or more oscillatory processes produces complex temporal phenomena and various forms of synchronization.
- The cells, functional units, etc. actually make use of the complex temporal patterns in their mutual communication.
- For systems of many coupled oscillators, local coupling produces propagating waves (heart) and global coupling produces synchronization clusters (tremor).

Changes in the temporal patterns can be part of a normal physiological regulation, or signal a state of disease



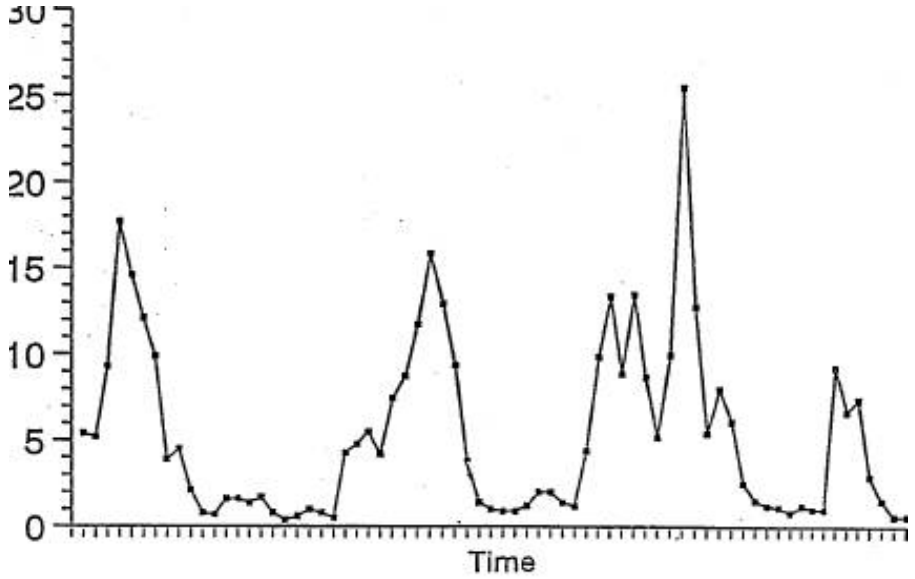
24 Hour Growth Hormone Profile

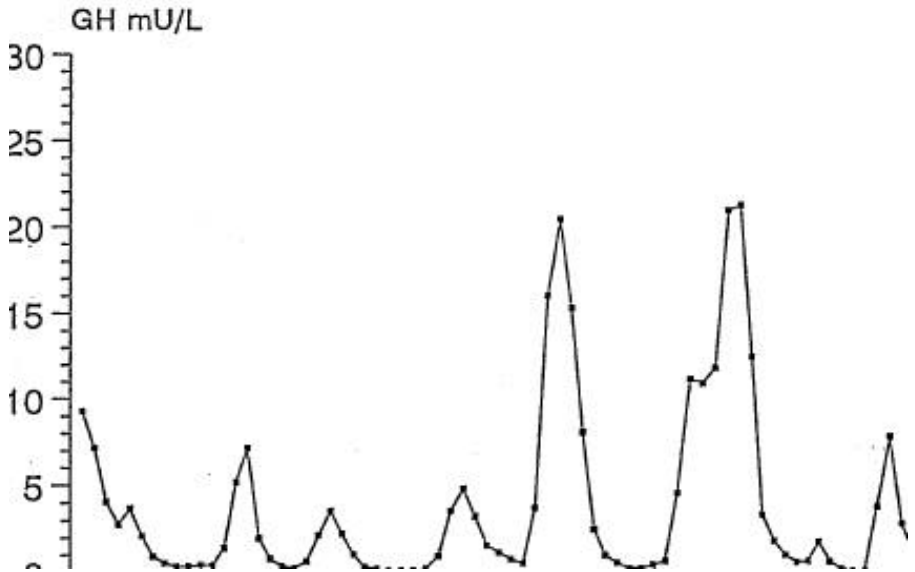
Some hormones (e.g. luteinizing hormone and testosterone are released in a regular train of pulses with 2-3 hour intervals.

Other hormones exhibit a more irregular pattern, and the question arises to what extent this can be given a deterministic explanation associated, for instance, with the interaction between several pulsatile systems.

A strongly varying hormone concentration may be more efficient than a constant concentration with the same average value.

Moreover, in the presence of such patterns, the time of administration of a drug may be significant. This is exploited, e.g. in connection with the treatment of cancer (chronotherapy).





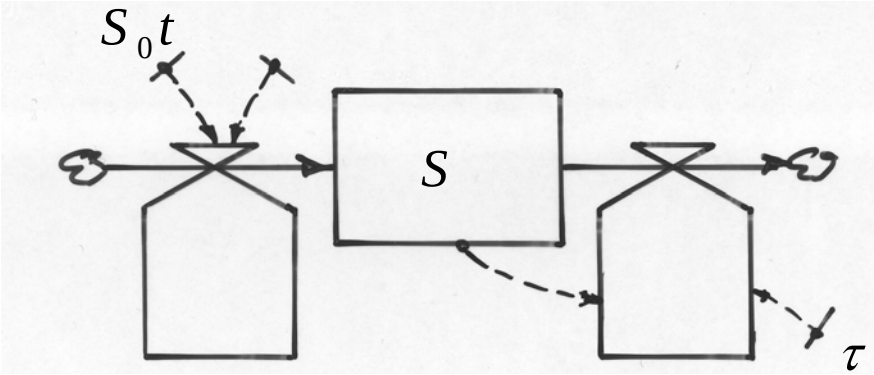
Onset of Self-Sustained Oscillations 1

1. Single reaction step

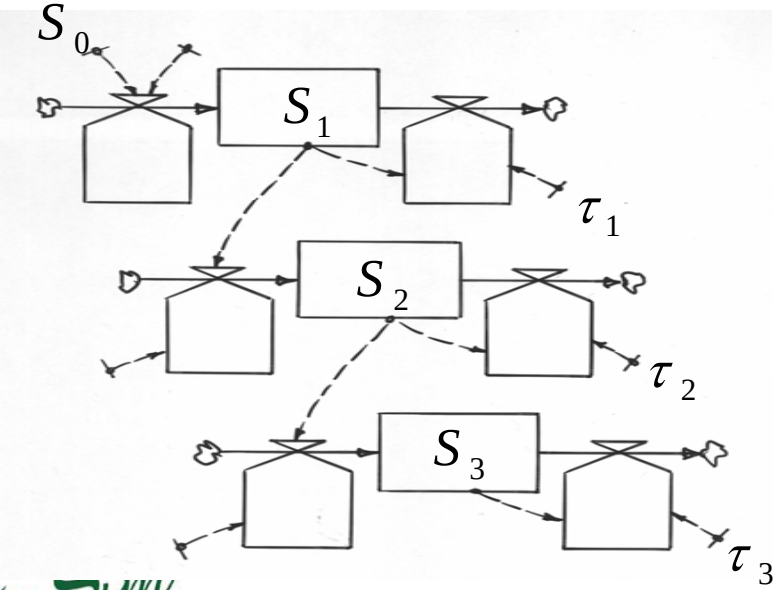
$$\frac{dS}{dt} = \frac{aS_o}{b + S_0} - \frac{S}{\tau}$$

Equilibrium: $S_{eq} = \frac{a\,\tau S_o}{b + S_0}$

Eigenvalue: $-\frac{1}{\tau}$



2. Reaction cascade



$$\frac{dS_1}{dt} = \frac{a_0 S_o}{b_0 + S_0} - \frac{S_1}{\tau_1}$$

$$\frac{dS_2}{dt} = \frac{a_1 S_1}{b_1 + S_1} - \frac{S_2}{\tau_2}$$

$$\frac{dS_3}{dt} = \frac{a_2 S_2}{b_2 + S_2} - \frac{S_3}{\tau_3}$$

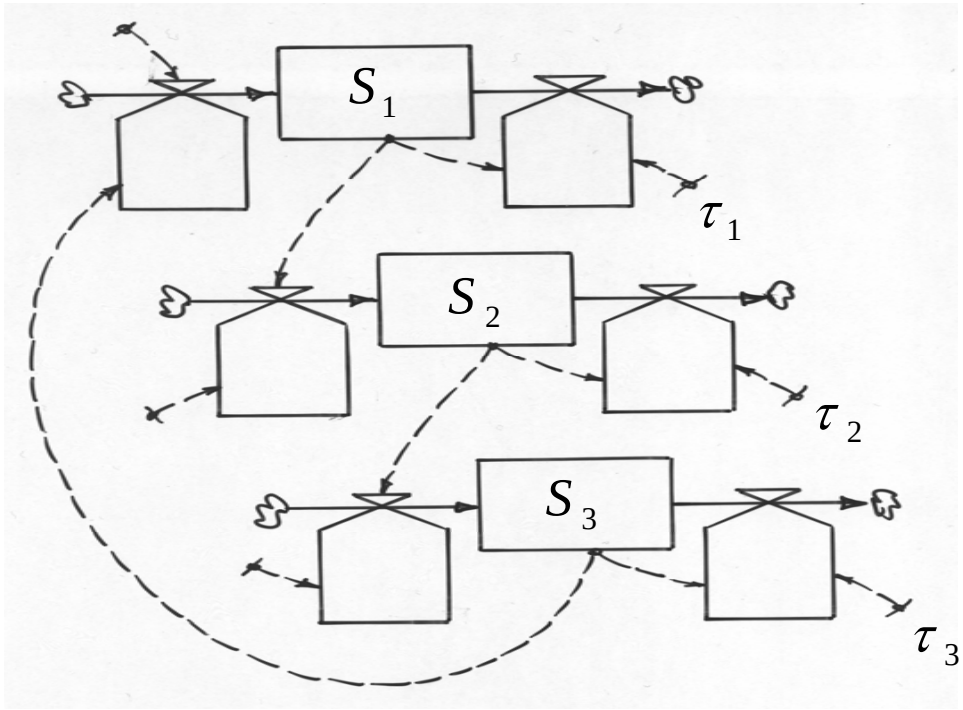
Eigenvalues: real and negative

No oscillatory dynamics

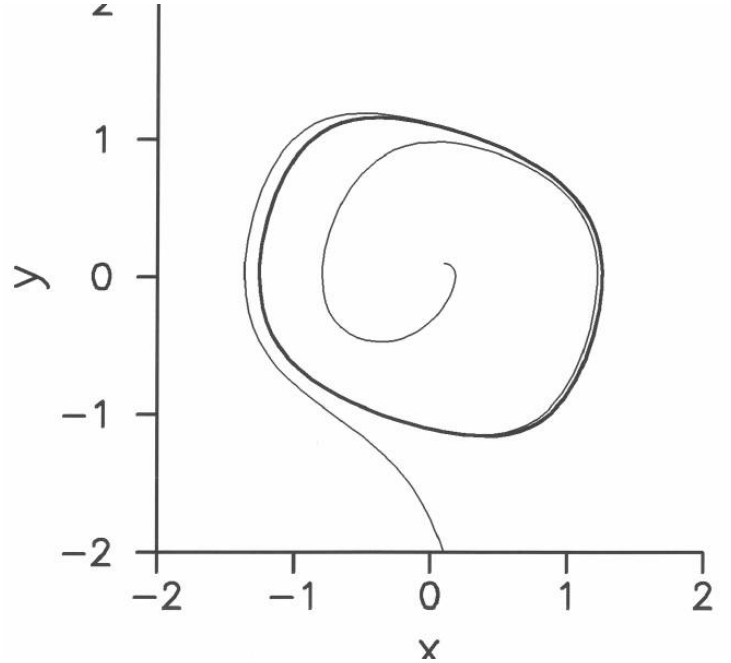
Onset of Self-Sustained Oscillations 2

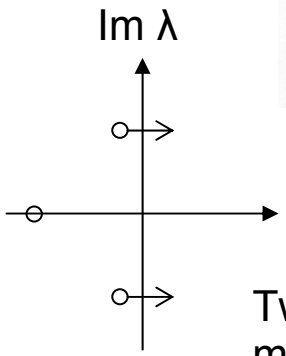
3. Negative feedback

   Eigenvalues can become complex conjugated: Oscillatory response



4. Larger loop gain

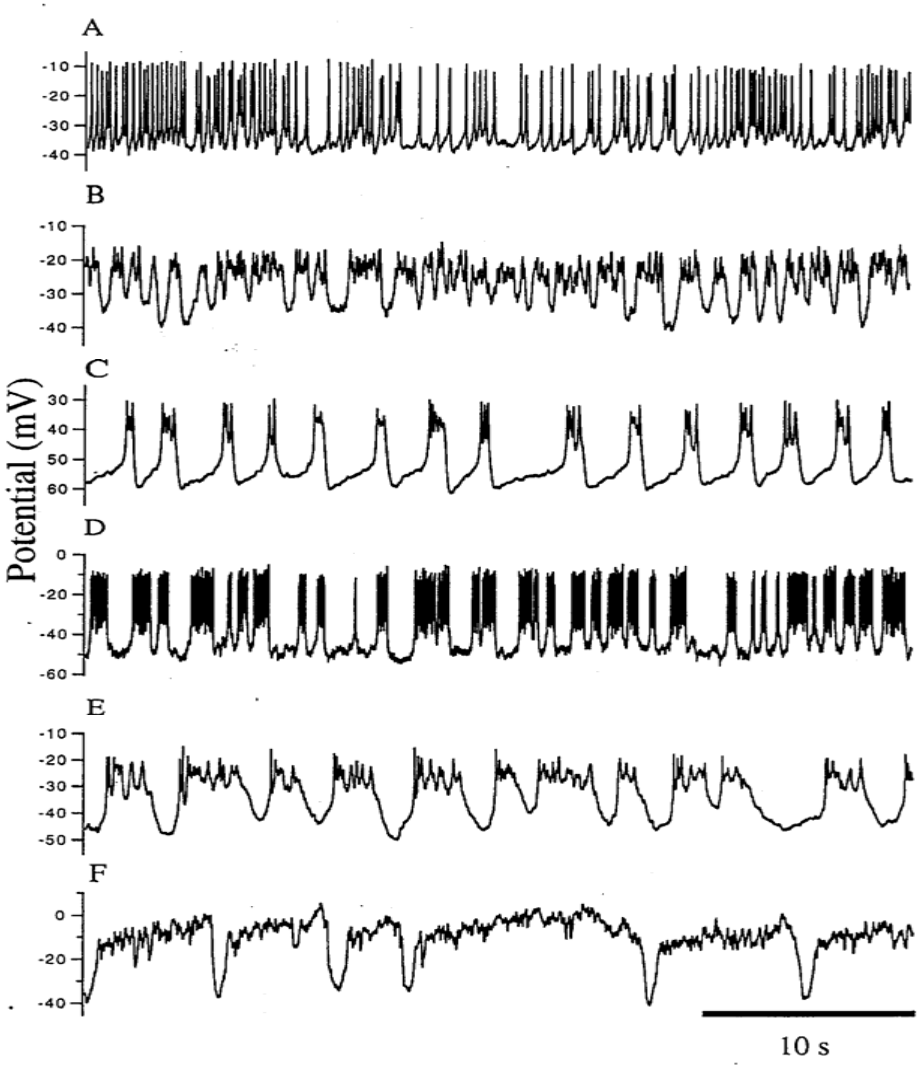




Two complex conjugated eigenvalues may cross the imaginary axis. The equilibrium point turns unstable (Hopf bifurcation) and the system starts to perform self-sustained oscillations.

Membrane Potentials for Bursting and Spiking Pancreatic Beta-cells

- Isolated beta-cells tend to produce randomly looking spike sequences
- Intact cells in pancreatic islets produce bursts of spikes with a bursting fraction that varies with the glucose concentration
- Insulin is released during the bursting period. Isolated cells typically release insulin at significantly lower rates than islet cells.
- Several diseases (such as Parkinsonian tremor, epilepsy, depression, etc.) are likely to involve a malfunctioning interaction among the cells.



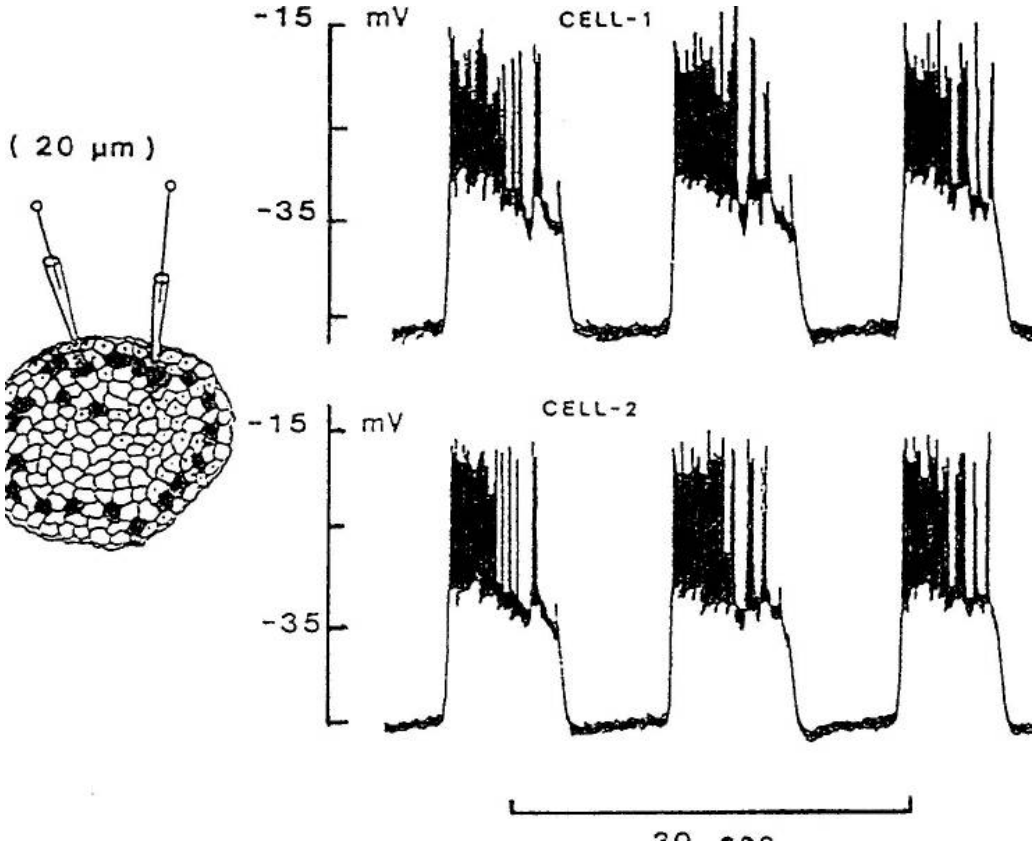
Synchronization

Two beta-cells can synchronize both their bursting and their spiking behavior, even if they are not particularly close to one another in an islet of Langerhans

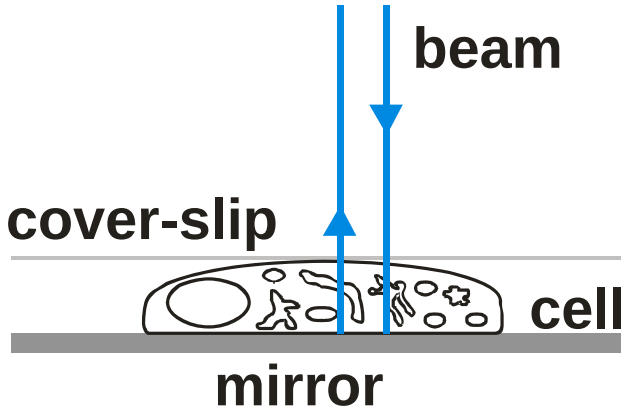
The beta-cells interact via gap-junctions, via variations in the intercellular ionic concentrations, and via hormonal and nerve signals.

Activation of smooth muscle cells (e.g., in the arteriolar walls) similarly involves synchronization of the cellular oscillations in the cytosolic Ca^{2+} concentrations.

Tremor is associated with synchronization of spiking activity of a group of brain cells.



Phase height relief of transparent objects



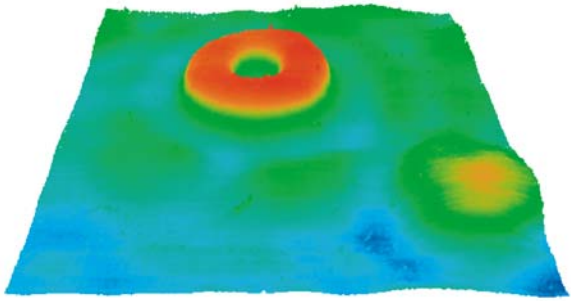
The delay of the light beam depends on the cell size, the compartmentalisation of the cytoplasm, and the plasma membrane structure.

For erythrocytes we can detect changes in the distribution of haemoglobin and in the structure of the cellular membrane.

The cellular phase height relief can be obtained from:

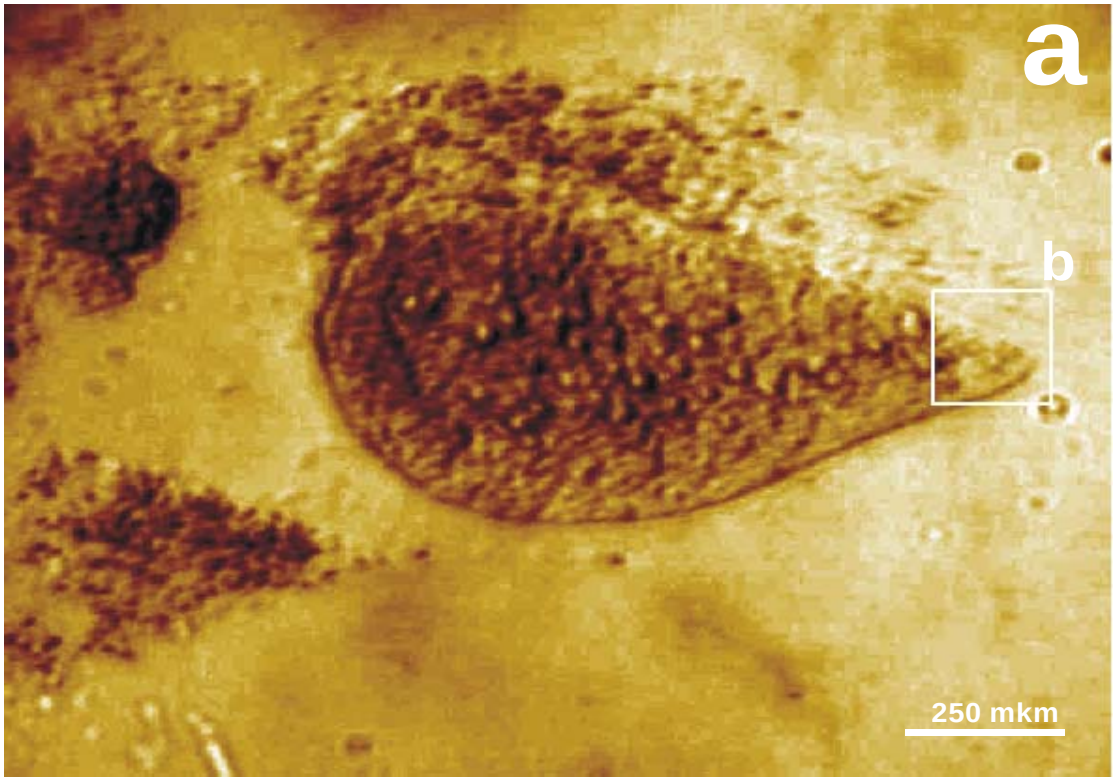
$$\Phi = \frac{(\varphi_0 - \varphi_{obj})}{2\pi}\frac{\lambda}{2} - \Phi_0$$

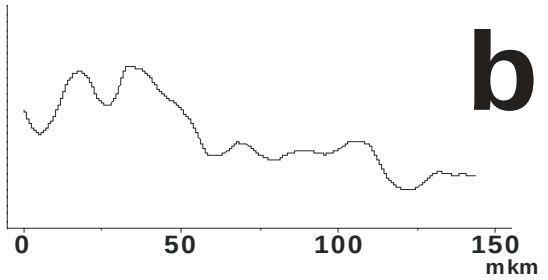
Dept. of Biophysics, Moscow University

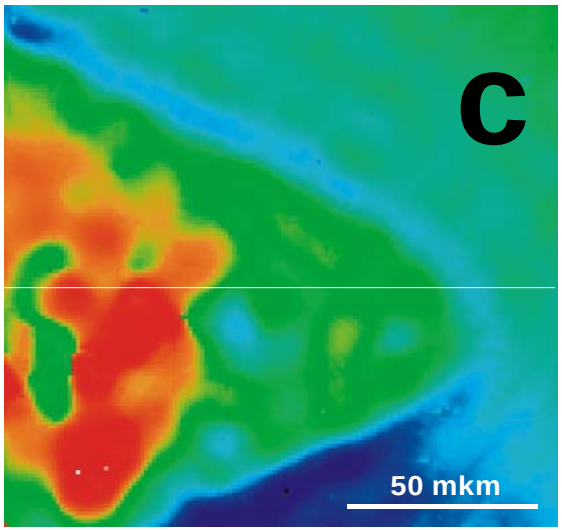


Isolated neuron of the pond snail L. stagnalis

Optical photograph (a) and a phase height relief (c) of a neuron. (b) displays the phase height along the scan-line shown in (c).
Lens magnification 5; the wavelength of the laser beam is 532 nm





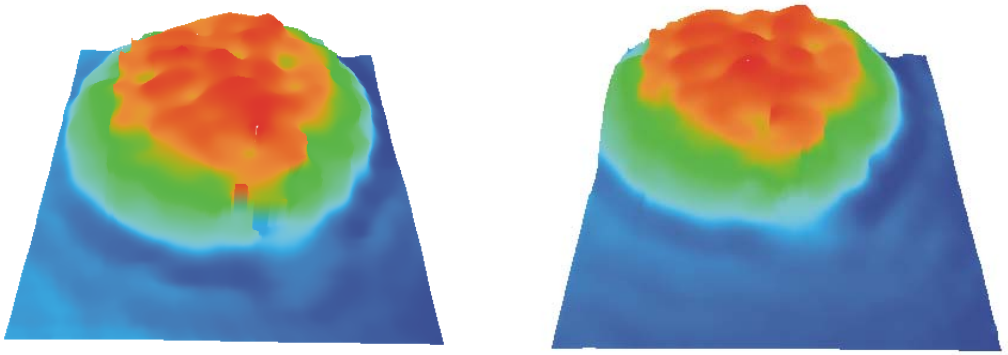


Studying the dynamics

Cellular processes span over a broad range of time scales. These processes include:

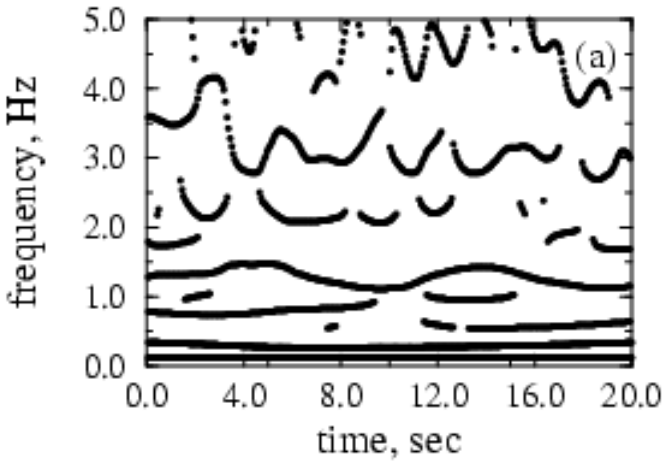
- Shape and volume changes
- Rearrangements of organelles
- Electrical activity
- Changes in membrane fluidity and motion of membrane bound proteins
- Sorption and desorption of membrane bound Ca^{2+} ions
- Motion of vesicles carrying, e.g. neurotransmitters or hormones

A manifestation of this intrinsic activity can be seen in the dynamics of the refractive index.

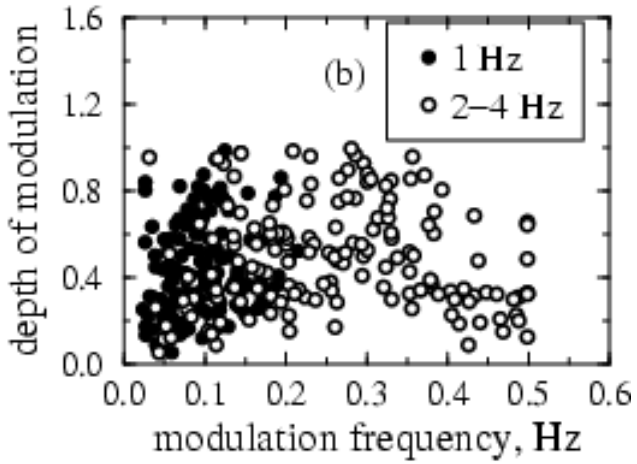


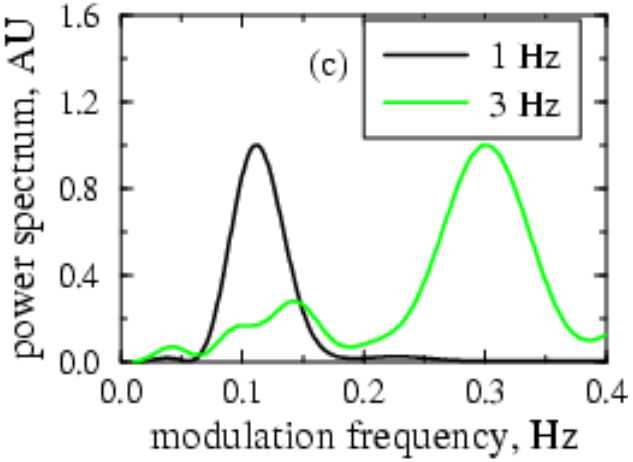
Frequency modulation of high frequency modes

Wavelet and double-wavelet analysis (on neurons of *L.stagnalis*)

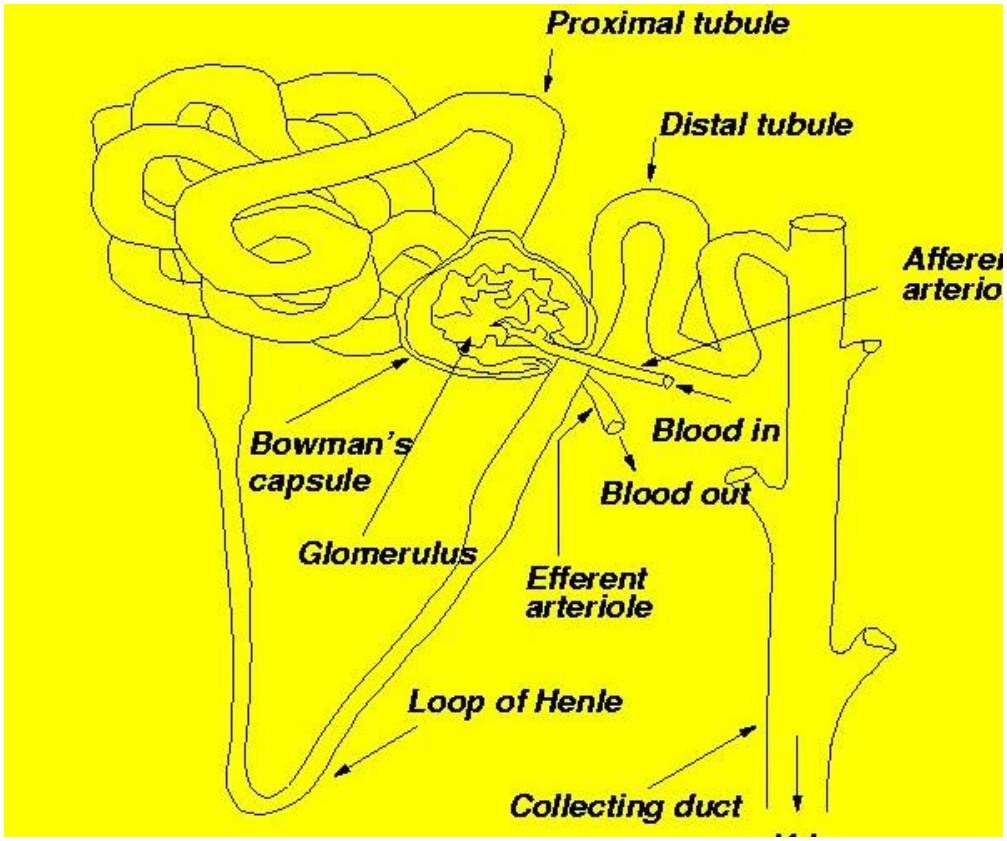


Typical dynamics of the local maxima of the energy density for the low frequency range (a). The observed 0.1, 0.3, 0.8, 1.3, and 2-4 Hz rhythms represent different components of the cellular dynamics.
(b) Depth of the amplitude modulation for the 1 and 2-4 Hz rhythms as a function of the modulation frequency. (c) Normalized spectra for the amplitude modulation process.





Nephron Pressure and Flow Regulation

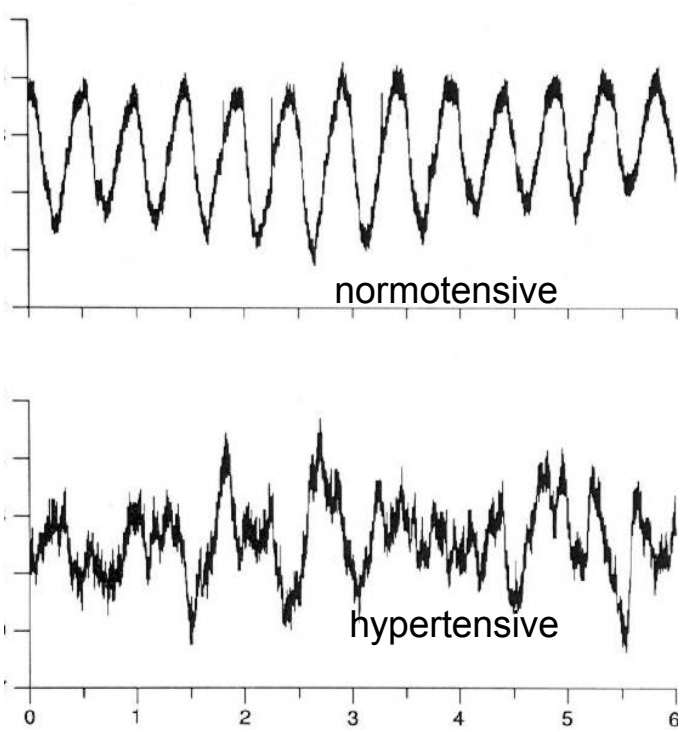


The nephron is the functional unit of the kidney.
A human kidney contains approx. 1 mill. nephrons.

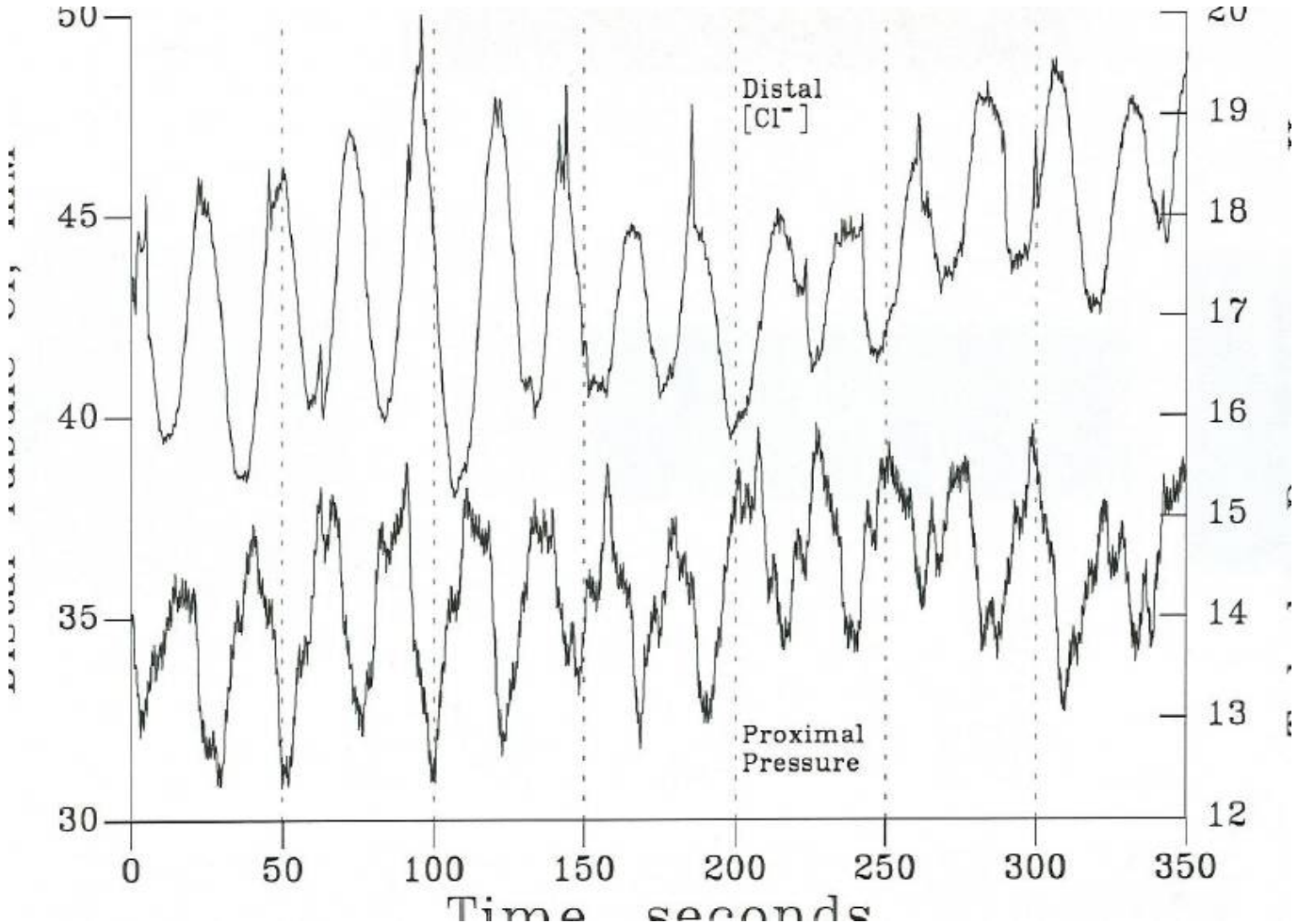
The individual nephron disposes of two different mechanisms (a tubuloglomerular and a myogenic mechanism) to regulate the incoming blood flow.

Both of these mechanisms may become unstable, and measurements of the proximal tubular pressure in rats show self-sustained oscillations with a period of about 30 sec.

For hypertensive rats, the tubular oscillations are often chaotic:



Variations in distal tubular NaCl concentration



The variation in NaCl concentration is delayed 12-15 sec relative to the proximal tubular pressure variations. The distal tubular pressure variations do not display a similar delay.

Simple Single Nephron Model

Tubular pressure: $\frac{dP_t}{dt} = \frac{1}{C_{tub}}\left[F_{filt} - F_{reab} - F_{Hen}\right], \quad F_{Hen} = \frac{P_t - P_d}{R_{Hen}}$

Arteriolar oscillations: $\frac{dv_r}{dt} + kv_r - \frac{P_{av} - P_{eq}}{\omega} = 0, \quad \frac{dr}{dt} = v_r, P_{eq} = P_{eq}(r, \psi)$

Single nephron filtration rate:

$$F_{filt} = (1 - H_a)\left(1 - \frac{C_a}{C_e}\right)\frac{P_a - P_g}{R_a}$$

Arteriolar resistance:

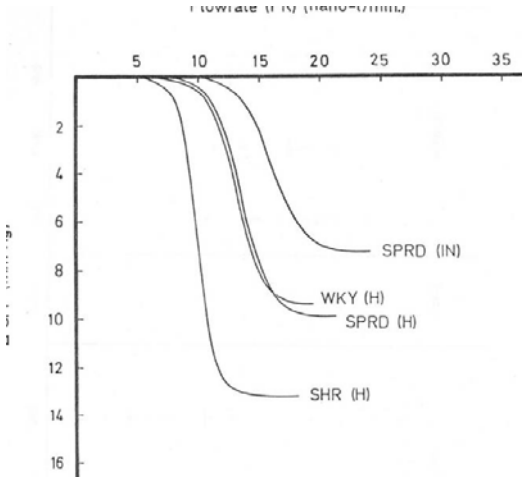
$$R_a = R_{a0}\left[\beta + (1 - \beta)\, r^{-4}\right]$$

Delay in loop of Henle:

$$\frac{dx_1}{dt} = F_{Hen} - \frac{3}{T}x_1,$$

$$\frac{dx_2}{dt} = \frac{3}{T}(x_1 - x_2),$$

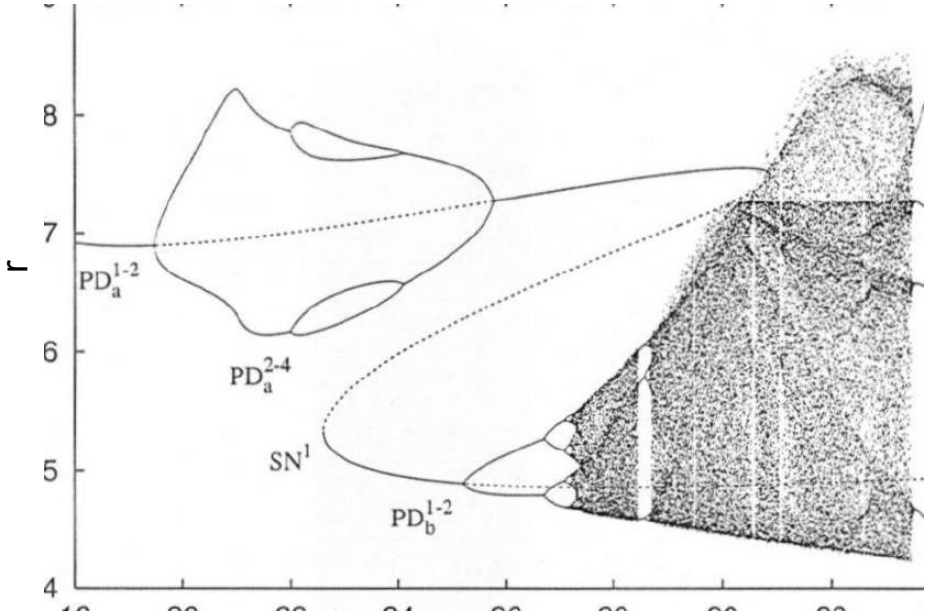
$$\frac{dx_3}{dt} = \frac{3}{T}(x_2 - x_3),$$



Tubuloglomerular feedback:

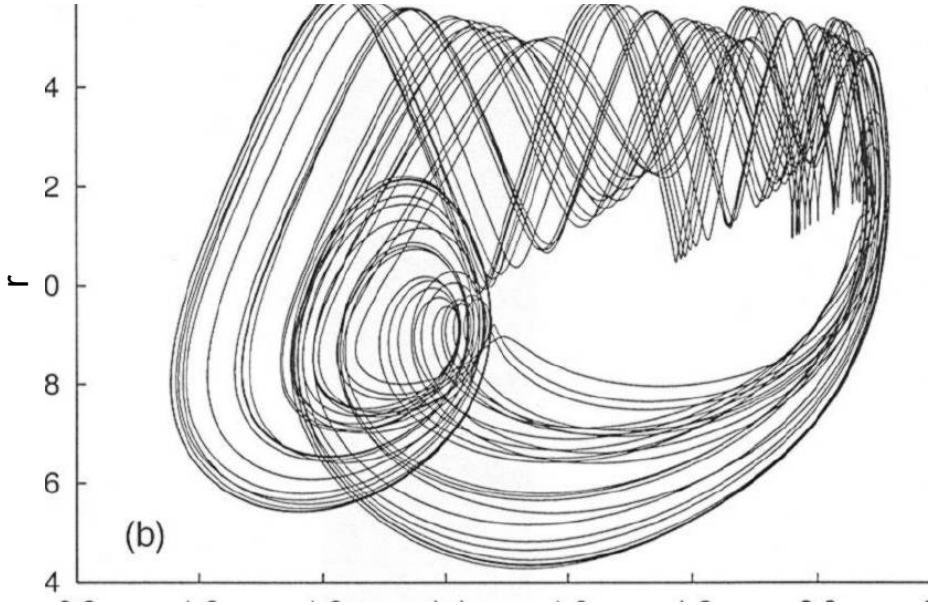
$$\psi = \psi_{\max} - \frac{\psi_{\max} - \psi_{\min}}{1 + \exp\left[\alpha\left(3x_3/TF_{Hen0} - S\right)\right]}$$

One-dimensional bifurcation diagram

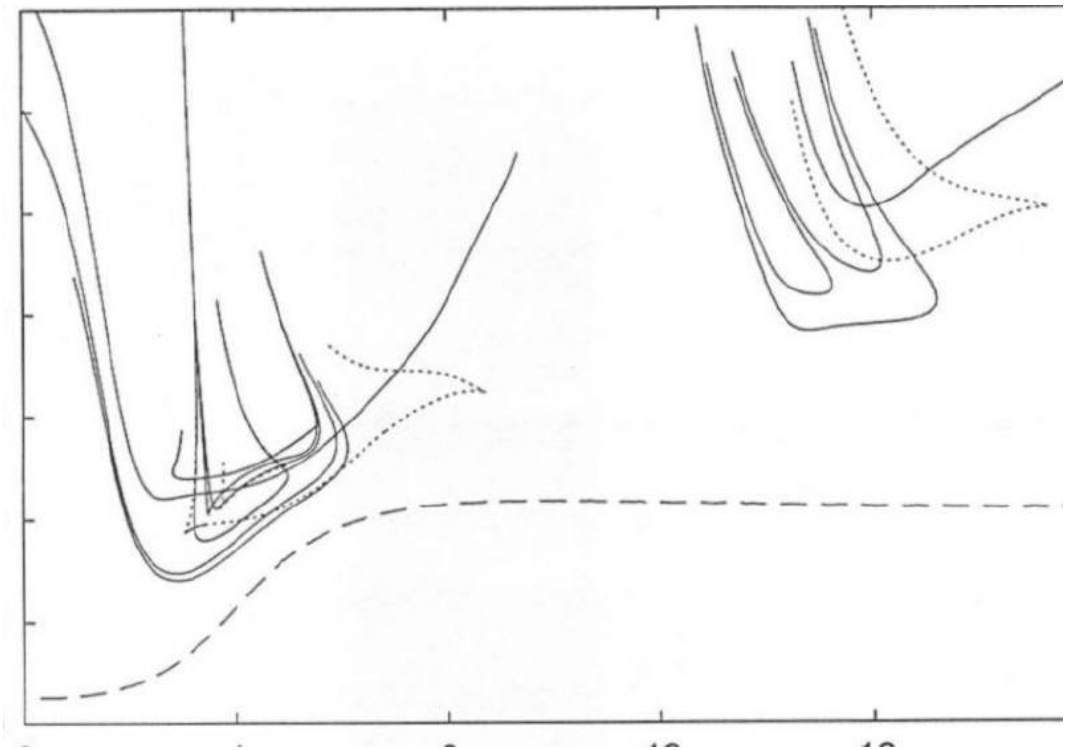


An incomplete and a complete period-doubling cascade are folded on top of one another. Dotted curves denote unstable period solutions.

In the chaotic regime, the fast myogenic oscillations no longer lock to the slower TGF-mediated oscillations.



Two-dimensional bifurcation diagram



Bifurcation curves:

– – – – Hopf

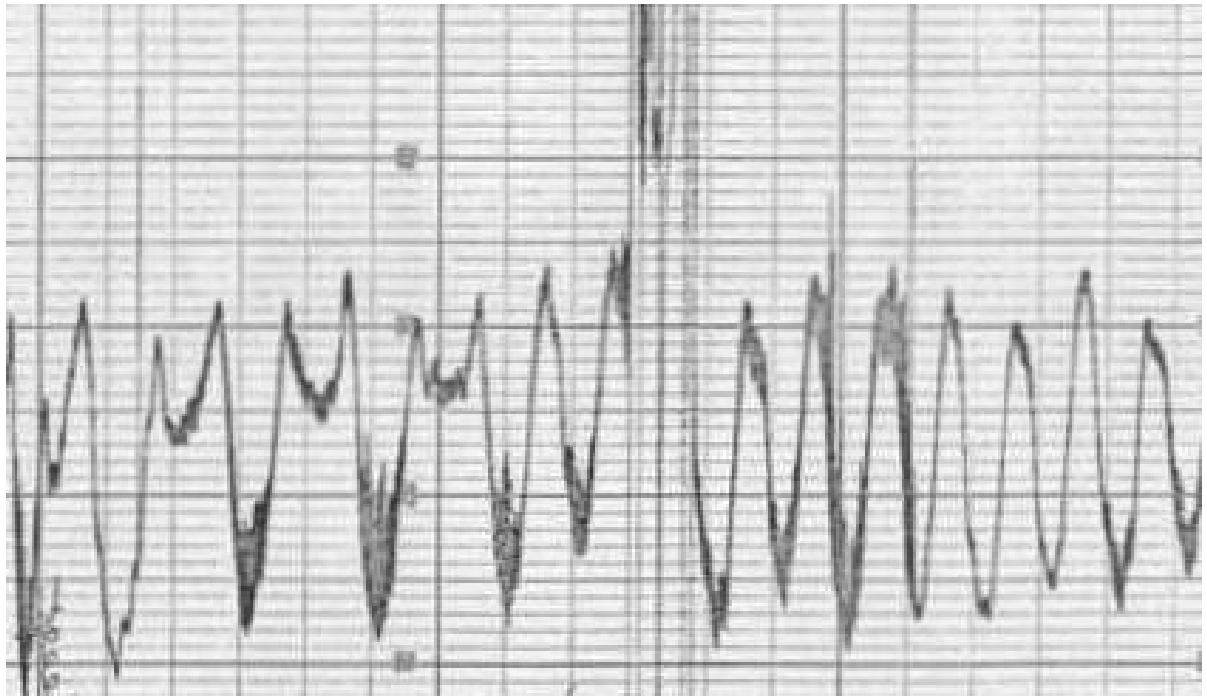
..... saddle-node

____ period-doubling

Each time the point of operation in parameter plane crosses a bifurcation curve, the dynamics changes qualitatively.

The delay in the feedback regulation is typically T ≈ 16s. Normotensive rats have gain factors α ≈ 12, and typically operate just above the Hopf bifurcation curve. For hypertensive rats the slope of the open loop feedback curve is α ≈ 18.

Experimental evidence for period doubling



The nephron operation is accidentally disturbed by clotting of blood in the afferent arteriole. After recovery, the nephron reassumes its oscillatory dynamics, initially though, in a period-2 mode.

The nephron model also exists in an extended version that provides a detailed account of the reabsorption of water and salt in the loop of Henle.

Wavelet-analysis

The wavelet-transform of a signal *x(t)*:

$$T_x(a,t) = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} x(u)\psi^*\left(\frac{u-t}{a}\right)du$$

The simplified expression of the Morlet function:

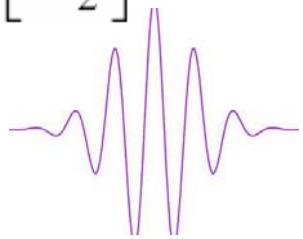
$$\psi(\tau) = \pi^{-1/4} \exp(j2\pi f_0 \tau) \exp\left[-\frac{\tau^2}{2}\right]$$

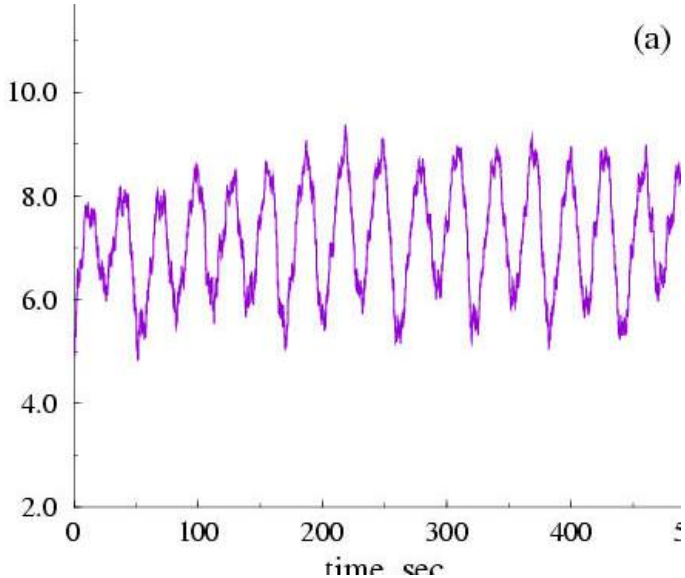
The central frequency of the wavelet:

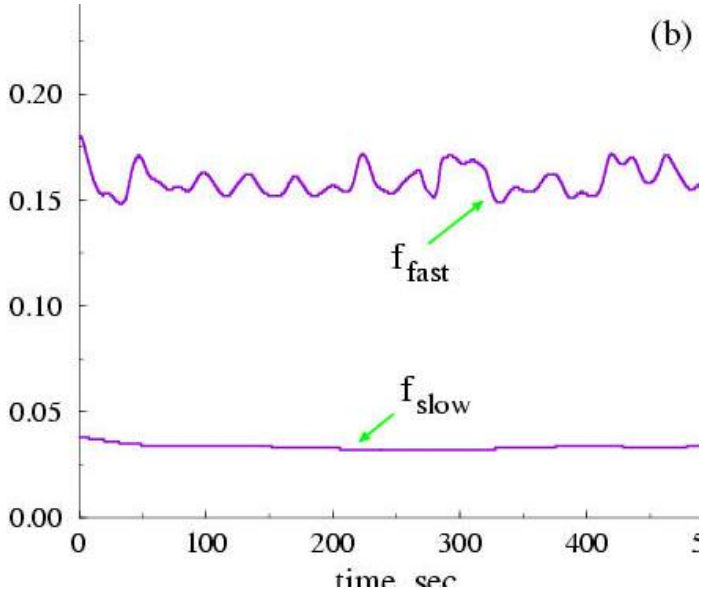
$f = 1/a\,,\ f_0 = 0.1$ *Hz*

The energy density of the signal *x(t)* in the time frequency plane:

$$E_x(f,t) \sim |\ T_x(f,t)\ |^2$$



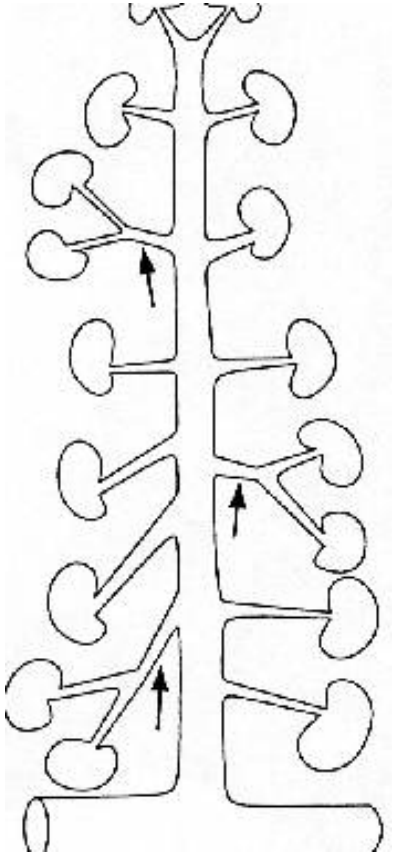




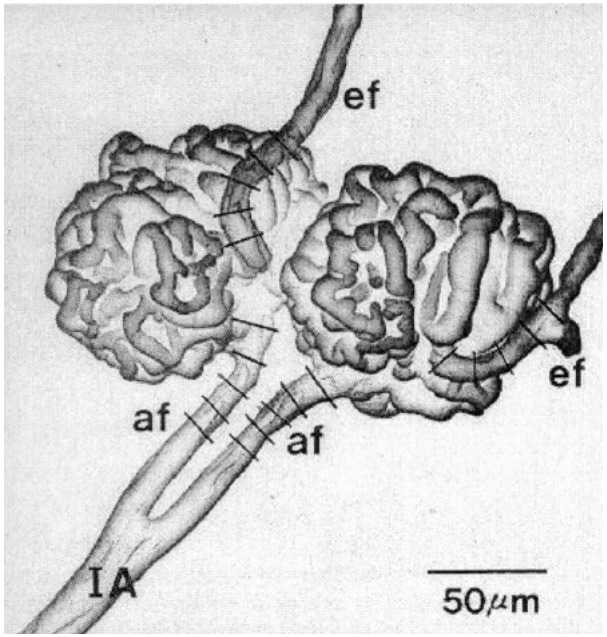
Double-wavelet analysis: *$f_{fast}(t)$ or $A_{fast}(t)$ are considered as input signals for the next wavelet transform*

Interacting nephrons

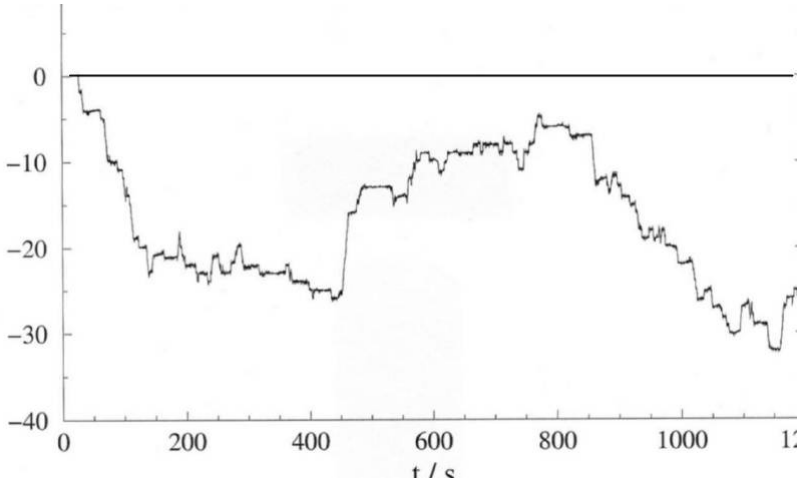
Typical arrangement of glomeruli with their afferent arterioles branching off from the same interlobular artery



Paired glomeruli at the end of an interlobular artery

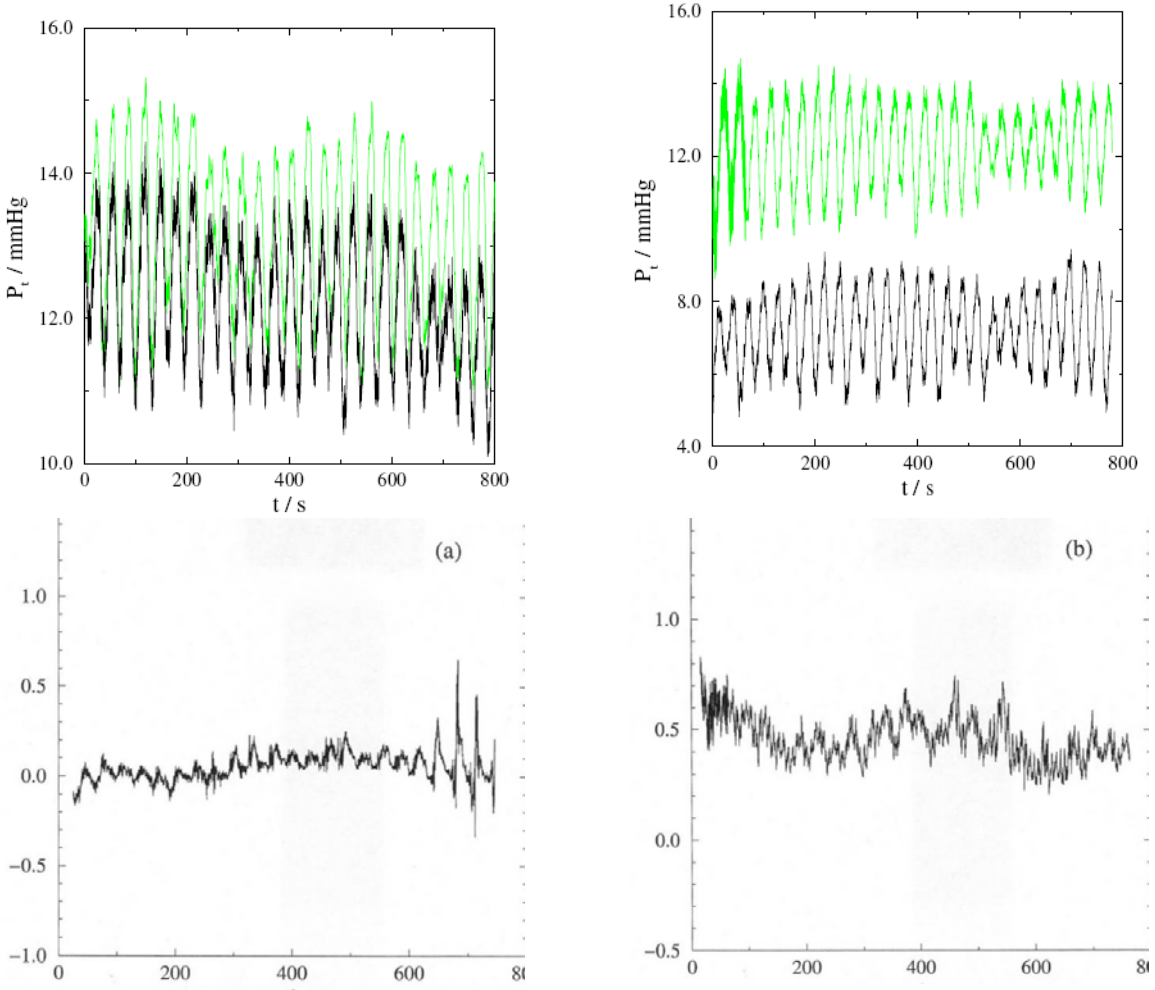


Synchronous and non-synchronous behavior



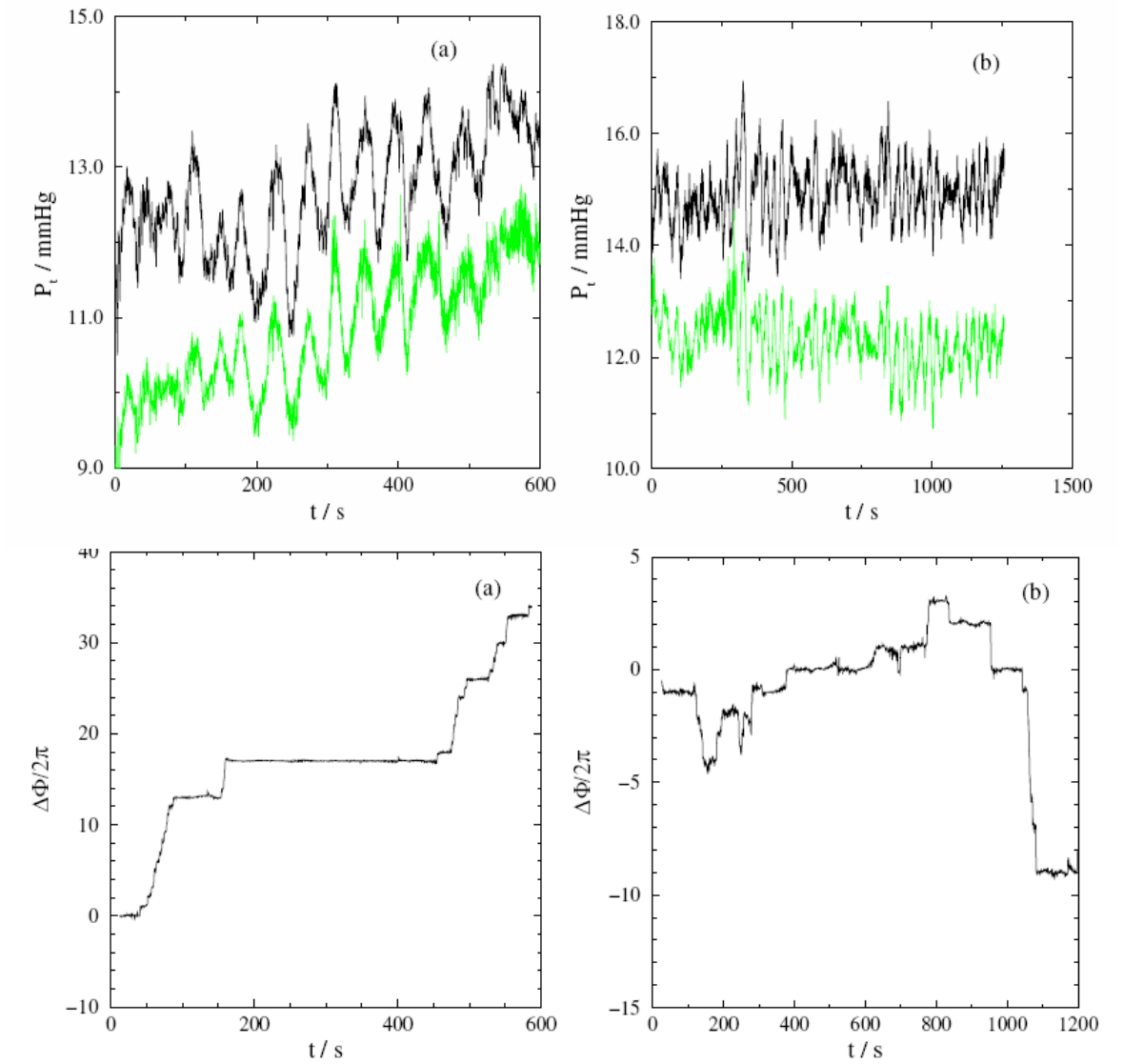
Nephrons branching off from the same interlobular artery interact via a vascular propagated coupling as well as a hemodynamic coupling.

Inphase and Antiphase Synchronization (experiments)



The vascular propagated coupling is very fast and tends to produce in-phase synchronization. The hemodynamic coupling is significant for paired glomeruli and produces out-of-phase synchronization.

Hypertensive rats: Synchronous and Asynchronous Regimes (experiments)



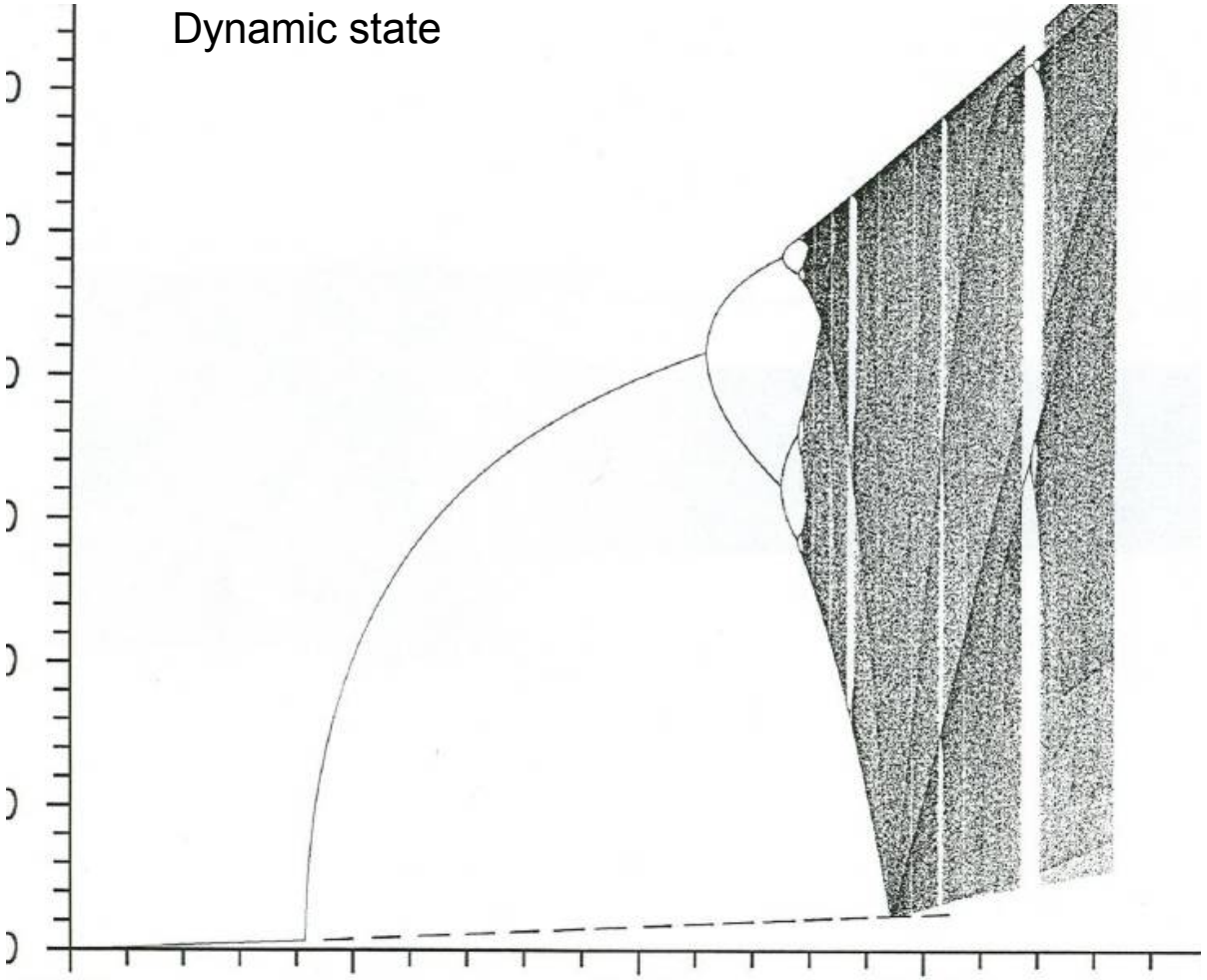
The instantaneous phase and amplitude of the chaotically oscillating tubular pressure can be defined through an extension to the complex plane (Hilbert transformation)

Operation under Far-From-Equilibrium Conditions

- As the supply of energy to a dissipative system increases, the equilibrium point will lose its stability, and complex spatial patterns and/or temporal behaviours will start to unfold.

- Nonlinear Dynamics aims at unravelling the sequence of instabilities that take place as the system is carried further and further into the unstable regime.

- Living systems generally operate under far-from-equilibrium conditions.



Hopf or saddle-node bifurcation