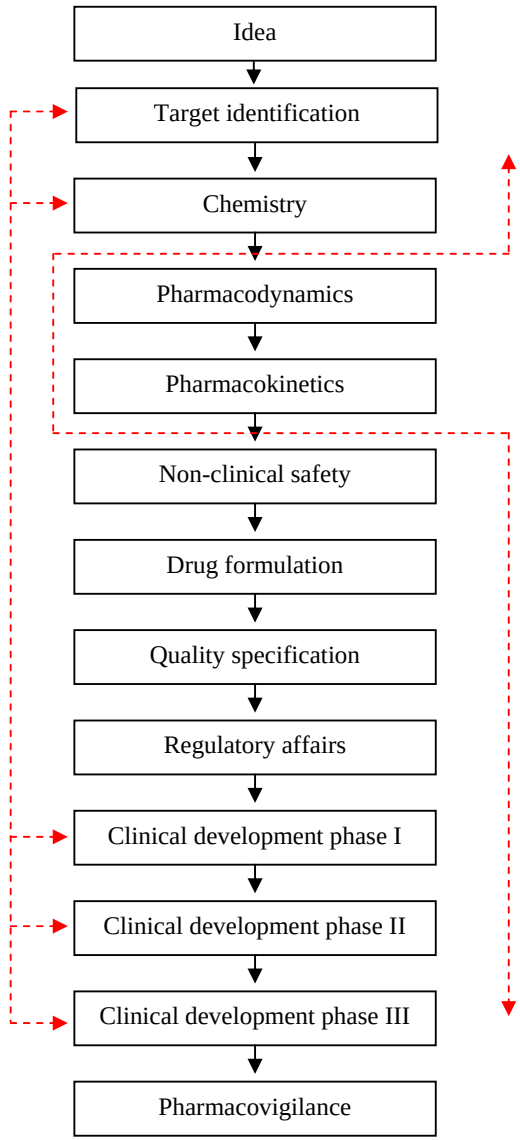
Biosimulation in the drug development process

2 The process needs stronger inputs from cell biology, physiology, endocrinology, etc.

3 A better understanding of the role of feedback phenomena (systems biology)

4 Development of multi-scale modeling methods

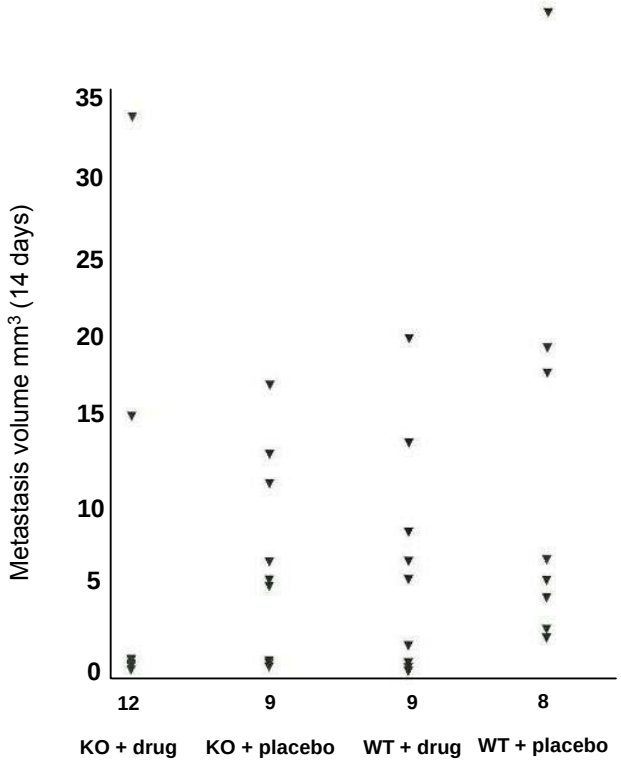
5 Mathematical concepts that can describe the complex phenomena we observe in living systems (chaos theory)

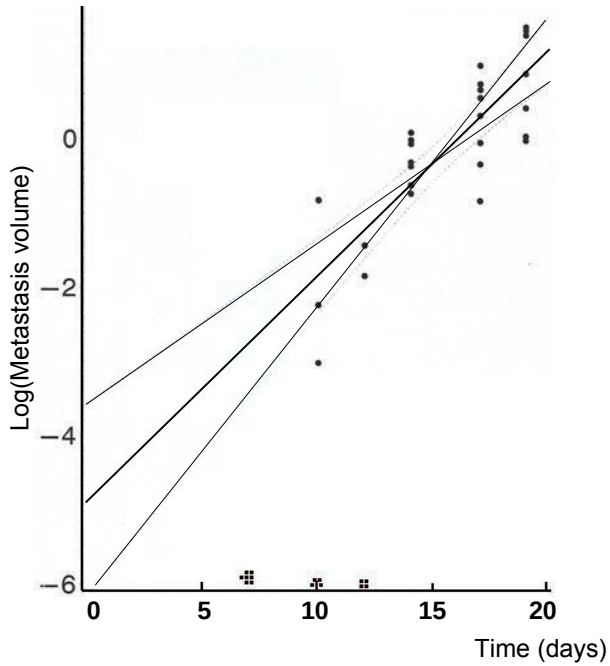


1 Modeling should occur as an integrated part all along the drug development process.

6 This will allow us to increase the information obtained in each individual trial and, hence, to reduce the development costs.

Growth of Lung Tumors in Mice





$$\frac{dN}{dt} = \lambda N - \alpha N$$

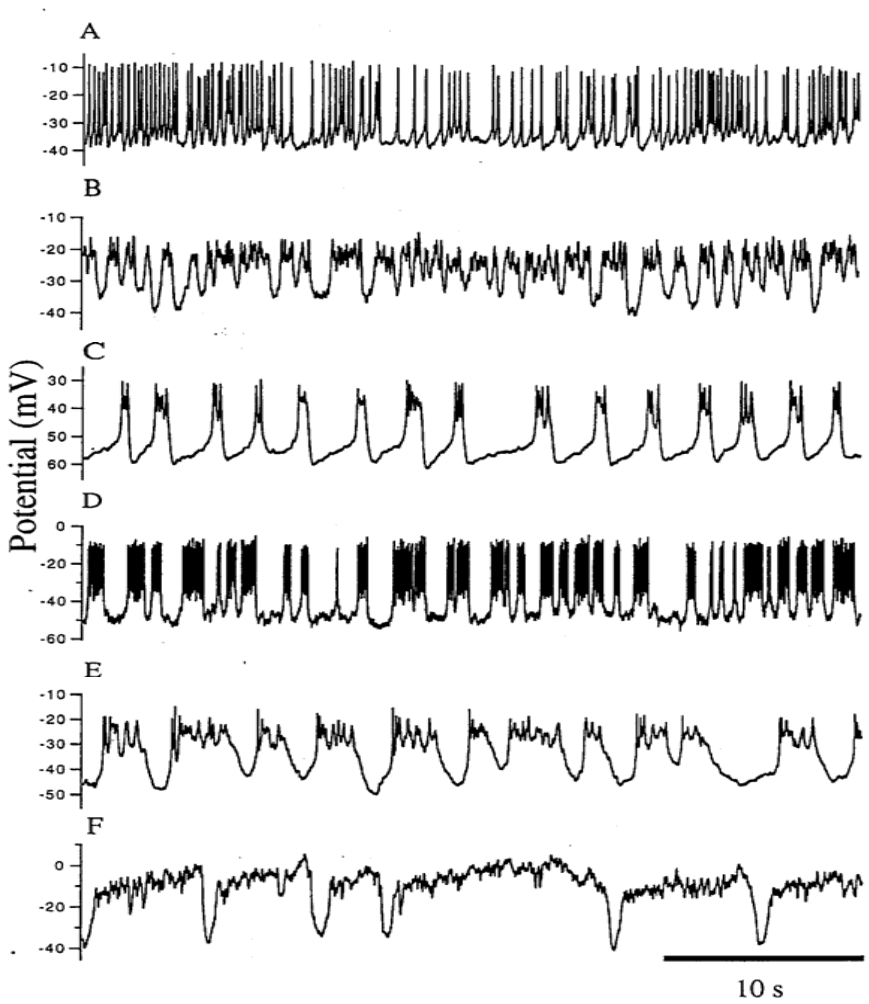
$$\frac{dM}{dt} = \alpha N + \lambda M$$

$$M(t) \cong \alpha t N_0 e^{\lambda t} \qquad (\lambda >> \alpha)$$

$$\log(\frac{M(t)}{t}) = \log(\alpha N_0) + \lambda t$$

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.



A. Sherman (NIH)

The mechanism-based modeling approach

Donald Marsh, Former Dean, School of Medicine, Brown University, US (2005):

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

In mechanism-based modeling

- The relevant biological processes are represented as realistically as possible, and the parameters and nonlinear relations are determined from independent experiments.
- The model is initially validated by its ability to reproduce observed wave forms, frequencies, amplitudes, phase relationships, parameter dependences, and stability properties.
- Further validation of the model is based on its ability to predict the outcome of new experiments, performed under conditions not previously investigated.
- EFPIA strongly emphasizes the need for a simulation approach that can reduce the number of animal tests and generate a deeper understanding of drug functioning.

The BioSim Network

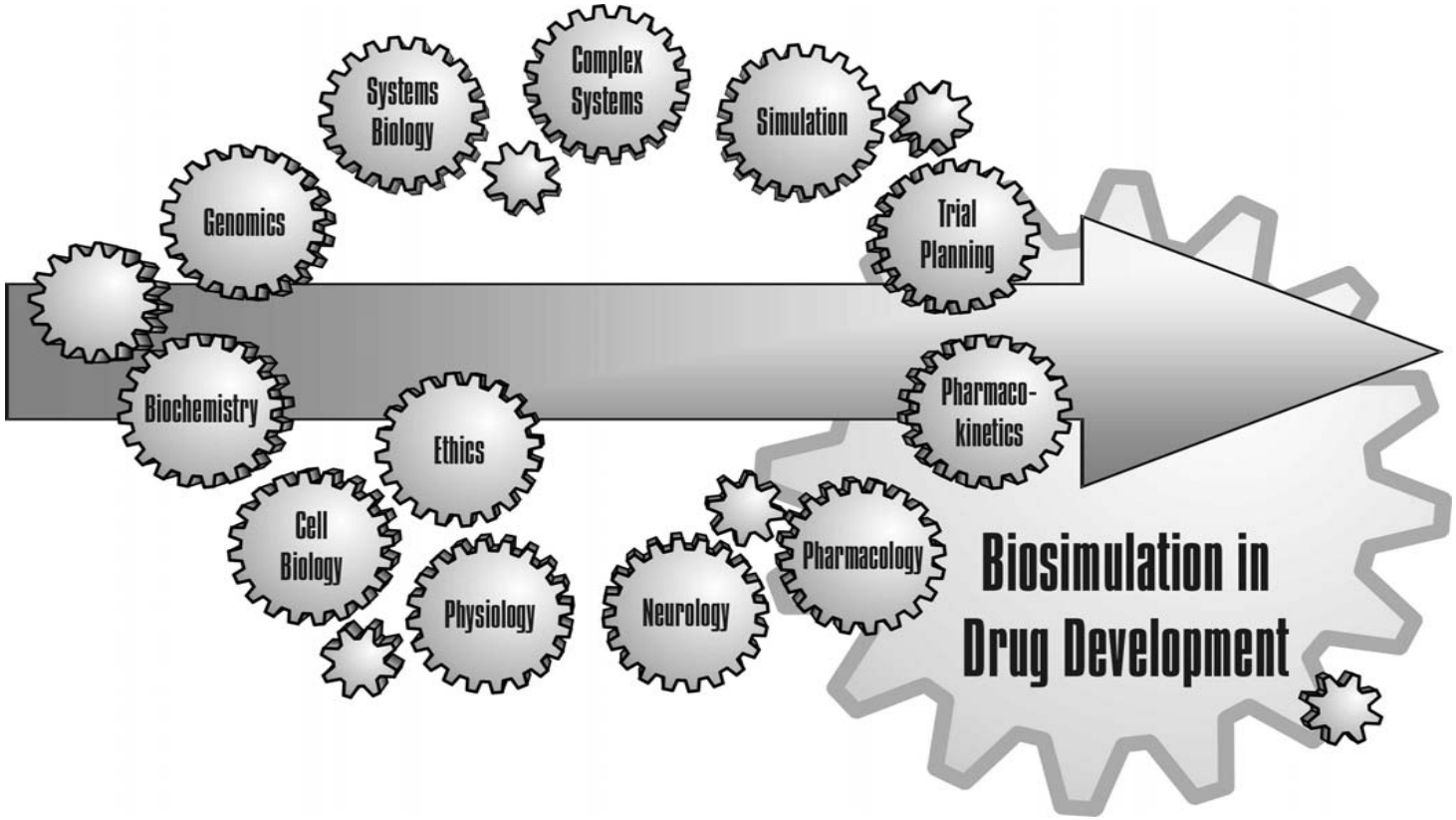


Illustration of the coordinated interaction of different scientific disciplines established in the BioSim Network. Through this coordination the Network will bridge biochemistry and genomics from the drug discovery phase with trial planning and pharmacokinetics of the drug development phases by more detailed insights into the (normal and pathological) processes and by professional modeling and information technologies.

Experience with Biomedical Modelling

1977 Respiratory control and the safe operation of anaesthetic systems (J. Ingemann-Jensen, Aarhus University)

1984 Subcutaneous absorption of insulin and the role of polymerization (Chr. Binder, Steno Memorial Hospital)

*1986 Nephron pressure and flow regulation (N.-H. Holstein-Rathlou, Copenhagen Univ.; D. Marsh, Brown Univ.; A. Gorbach, NIH)

1992 Insulin-glucose feedback regulation and pulsatile secretion of insulin (K. Polonsky, J. Sturis, Chicago Univ.; Morten Colding-Jørgensen, Novo Nordisk)

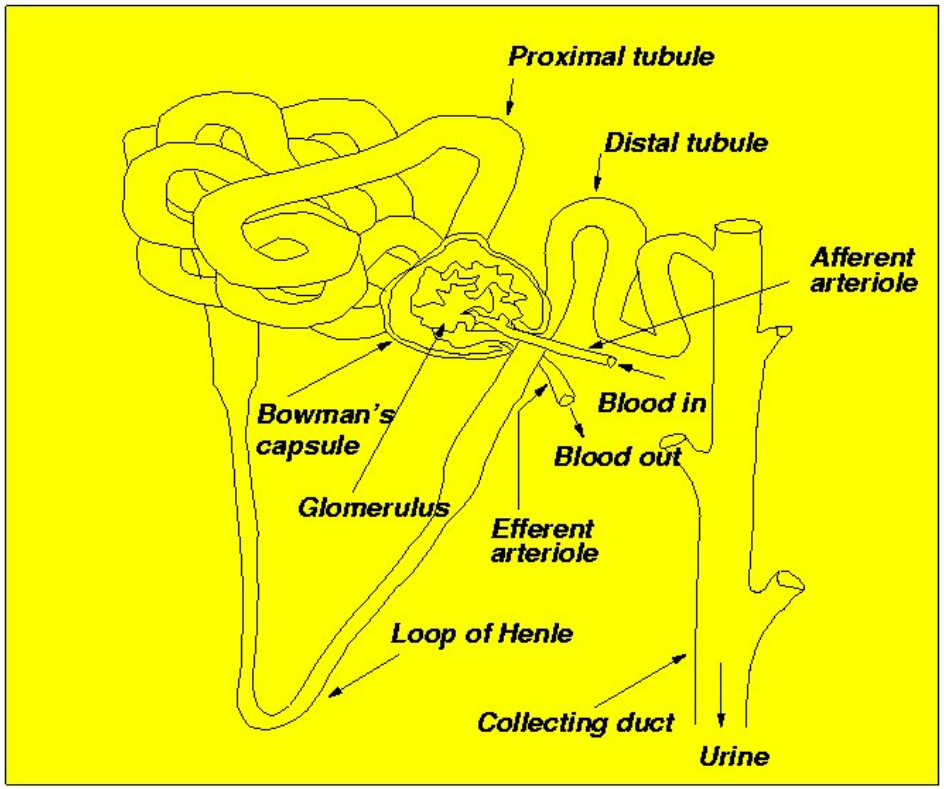
1994 HIV vaccine development and gene therapy of AIDS (O. Lund et al., Hvidovre Hospital)

1996 Bone remodelling and treatments of osteoporosis (L. Mosekilde, Aarhus Univ.)

*2002 Cellular electrophysiological and metabolic processes (H. Braun, Marburg Univ.; A. Sherman, NIH; G.V. Maksimov, Univ. of Moscow)

2005 Biology of affective disorders (I. Antonijevic, Lundbeck USA)

Nephron Pressure and Flow Regulation

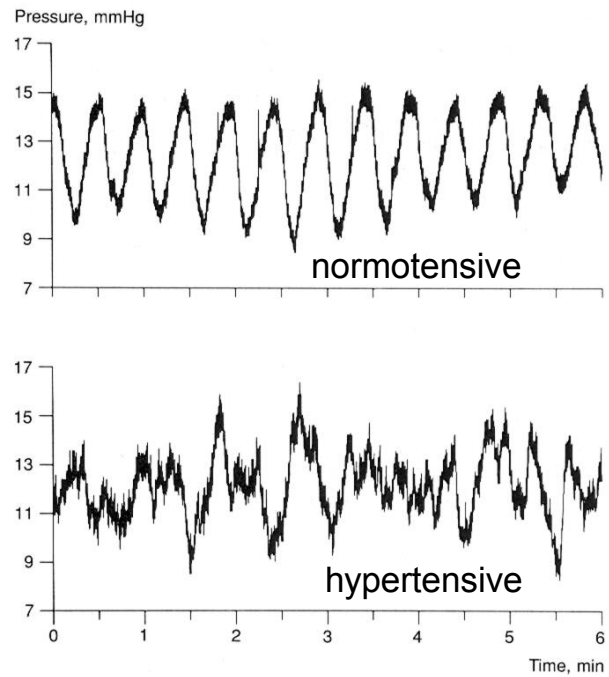


The nephron is the functional unit of the kidney.
A human kidney contains approx. 1 mill. nephrons.

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:



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:

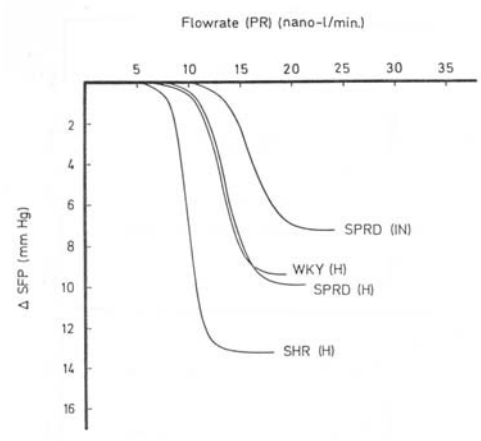
$$R_a = R_{a0}\left[\beta + (1-\beta)\, r^{-4}\right]$$

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:

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

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:

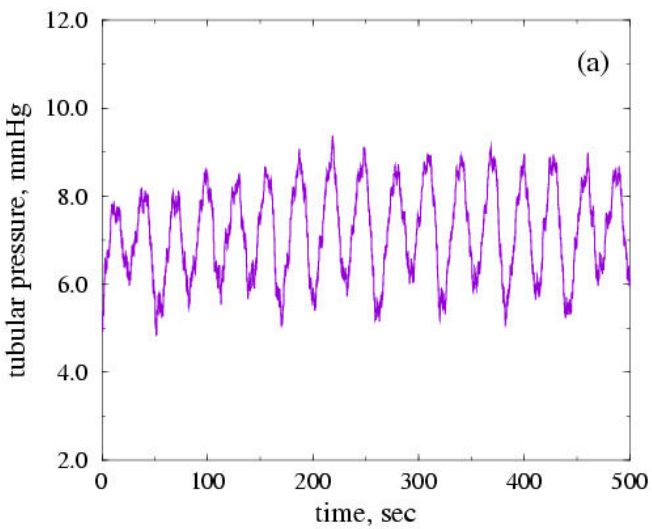
$$\psi(\tau) = \pi^{-1/4} \exp(j2\pi f_0 \tau) \exp\left[-\frac{\tau^2}{2}\right]$$

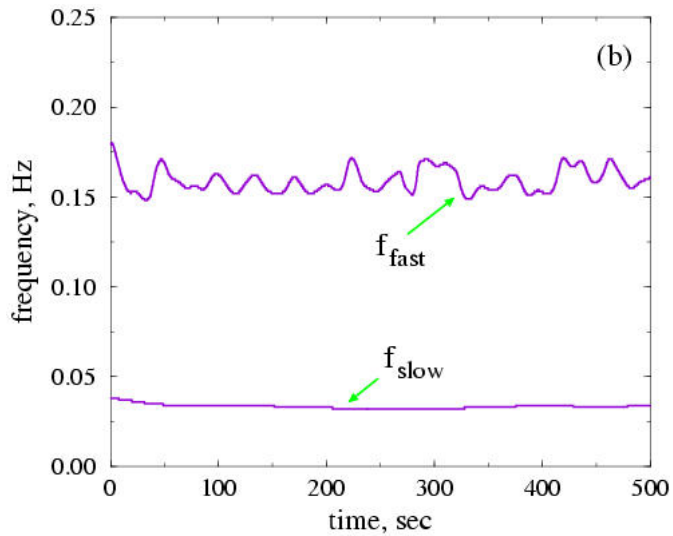
The central frequency of the wavelet:

$$f_0 = 0.1\ Hz$$

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

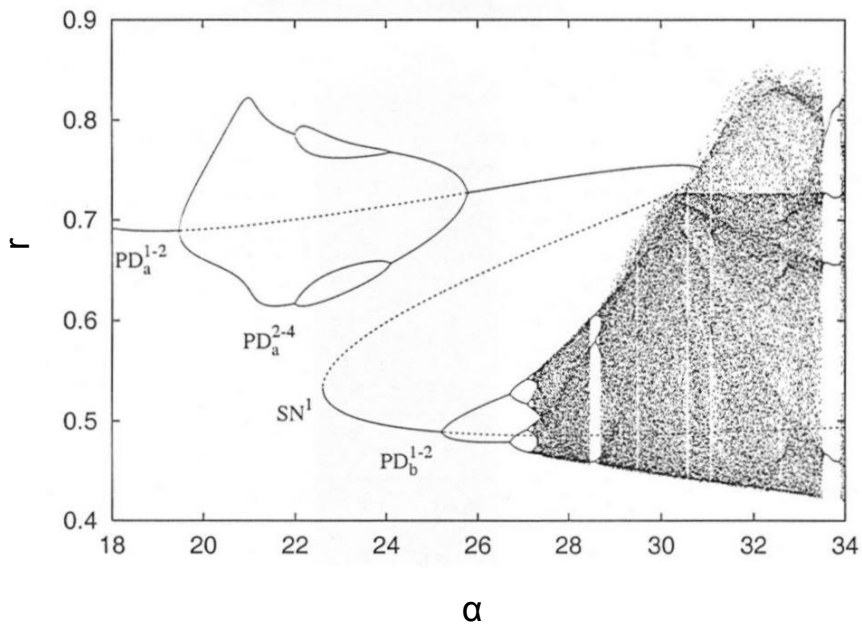
$$E_x(f,t) \sim |\ T_x(f,t)\ |^2,\ f = 1/a$$





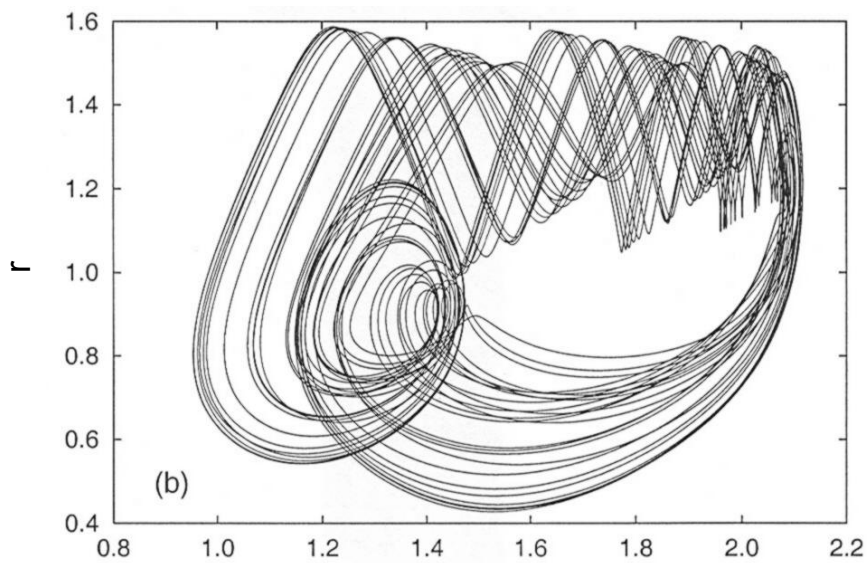
Double-wavelet analysis: *$f_{fast}(t)$ or $A_{fast}(t)$ are considered as input signals for the next wavelet transform*

One-dimensional bifurcation diagram

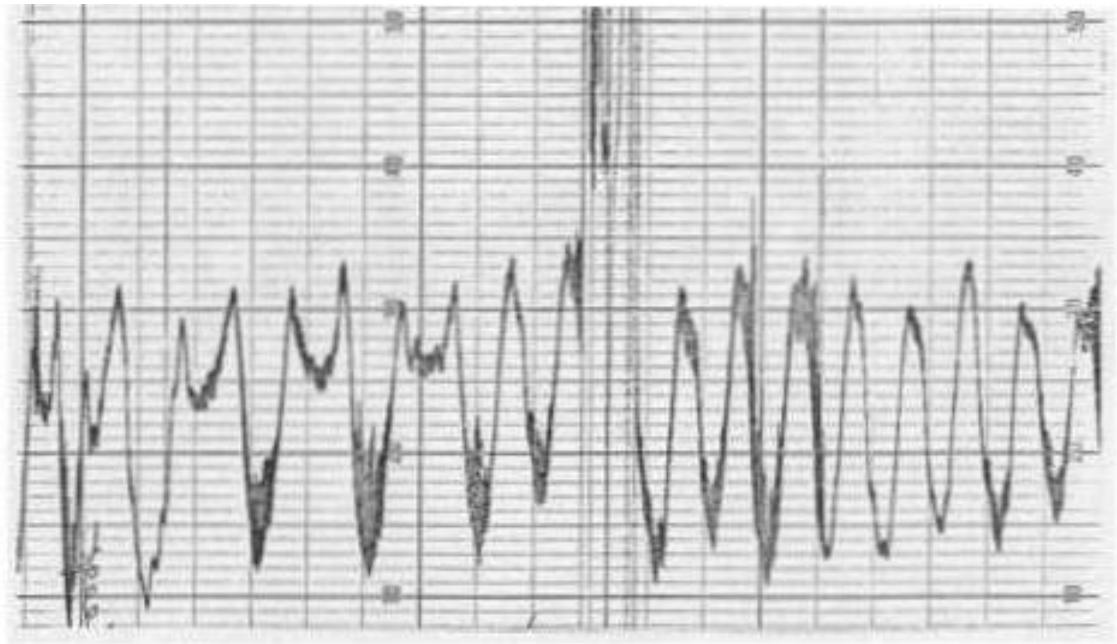


An incomplete and a complete period-doubling cascade are folded on top of one another. Dotted curves denote unstable period solutions.

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



Experimental evidence of period doubling



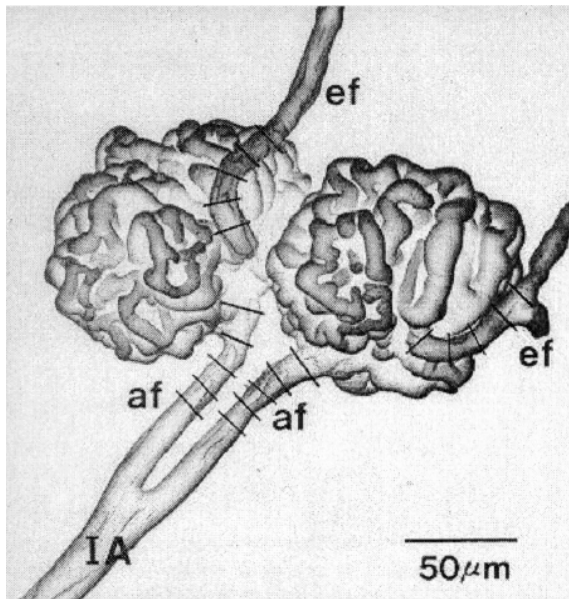
The nephron operation is accidentally disturbed by clotting of blood in the afferent arteriole. After recovery, the nephron reassumes its oscillatory dynamics, initially though, in a period-2 mode.

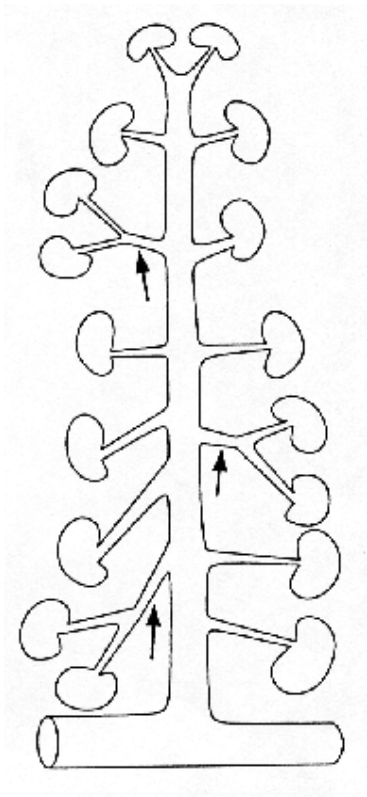
The nephron model also exists in an extended version that provides a detailed account of the reabsorption of water and salt in the loop of Henle.

Interacting nephrons

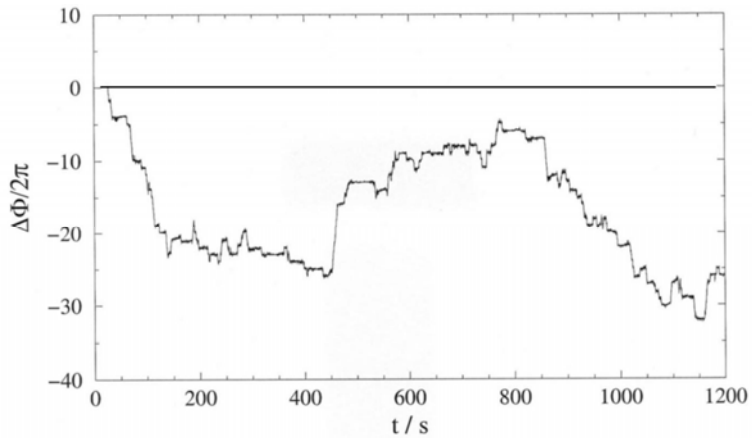
Typical arrangement of glomeruli with their afferent arterioles branching off from the same interlobular artery

Paired glomeruli at the end of an interlobular artery



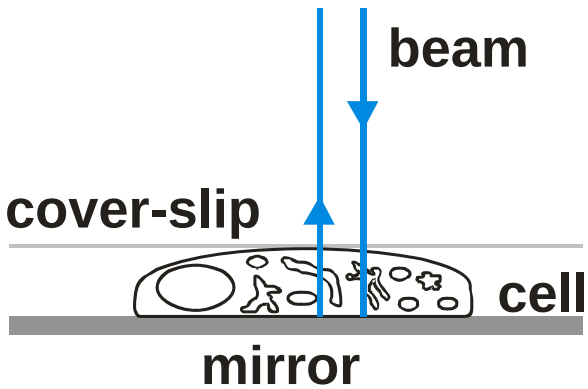


Synchronous and non-synchronous behavior



Nephrons branching off from the same interlobular artery interact via a vascularly propagated coupling as well as a hemodynamic coupling. We are trying to investigate the extend of this spatial synchronization.

Phase height relief of biological structures



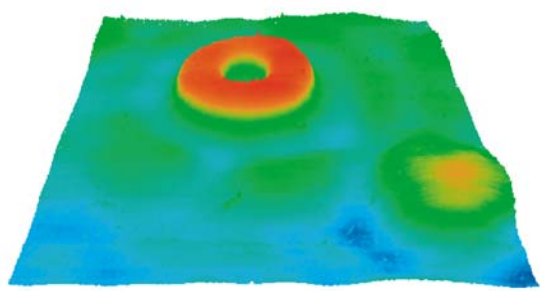
The delay of the light beam depends on the cell size, the compartmentalisation of the cytoplasm, and the plasma membrane structure.

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

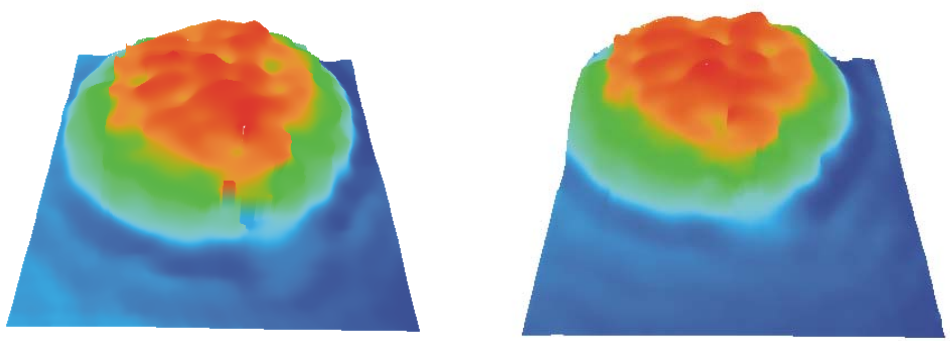


Studying the dynamics

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

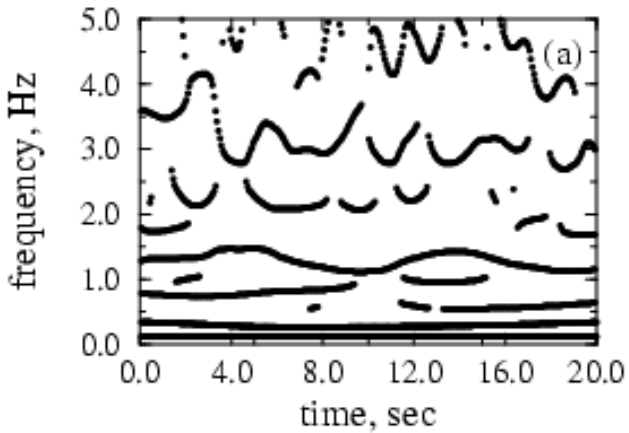
- Shape and volume changes
- Rearrangements of organelles
- Electrical activity
- Changes in membrane fluidity and motion of membrane bound proteins
- Sorption and desorption of membrane bound Ca^{2+} ions
- Motion of vesicles carrying neurotransmitters or hormones

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

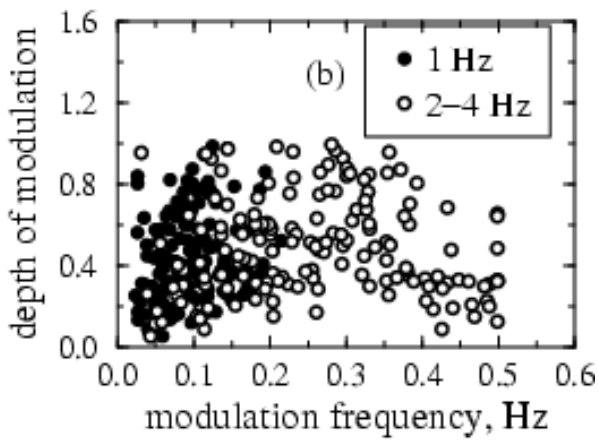


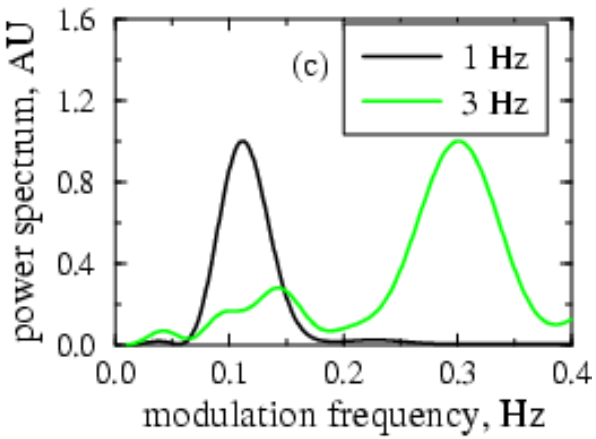
Frequency modulation of high frequency modes

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.





BioSim group at the 1st BioSim conference