

Complex Phenomena in Biomedical Systems

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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

Background for the Network Funding

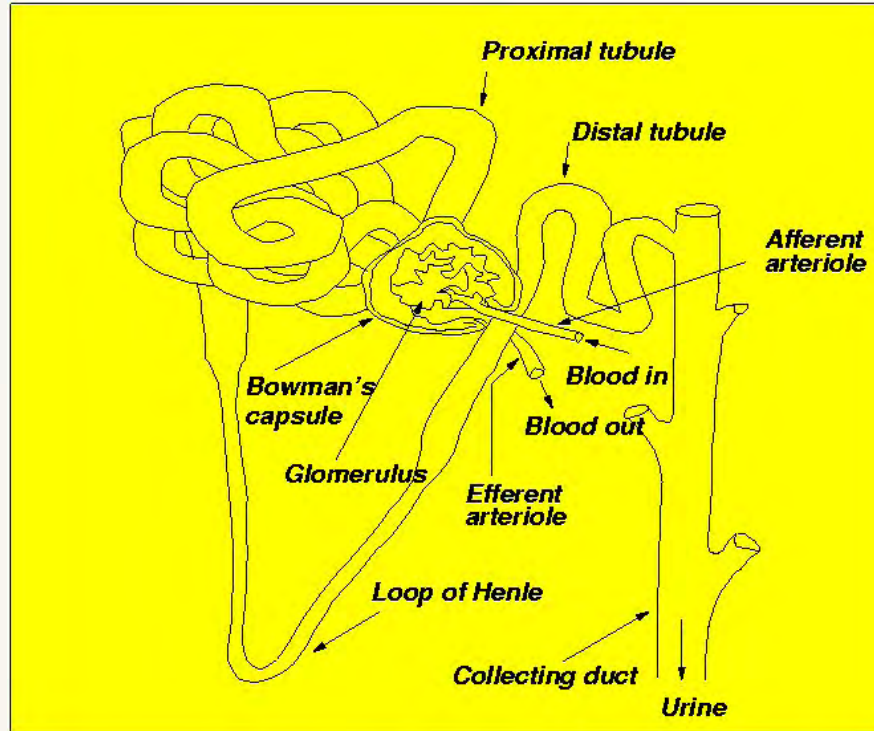
The existing system fails

- to provide new effective drugs at acceptable costs
- to make effective use of the enormous amount of information available in the life sciences
- to take advantage of the potential that application of mechanism-based modeling/simulation approaches and today's computer technologies offer
- to exploit the insights and results of modern nonlinear science and complex systems theory
- to train a sufficient number of highly skilled candidates to work on the multidisciplinary problems of modern drug development

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

Nephron Pressure and Flow Regulation



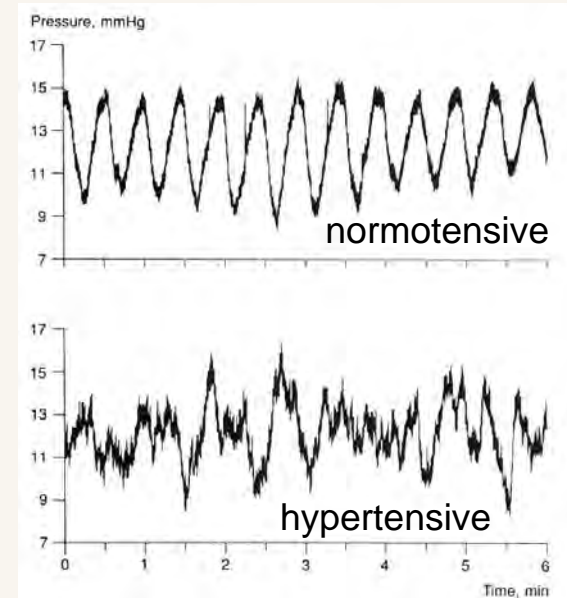
The nephron is the functional unit of the kidney. A human kidney contains approx. 1 mill. nephrons.

With Niels-Henrik Holstein-Rathlou, Copenhagen University

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.

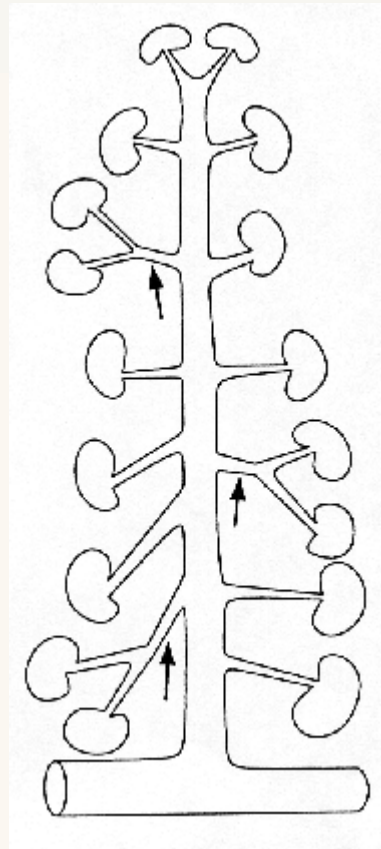
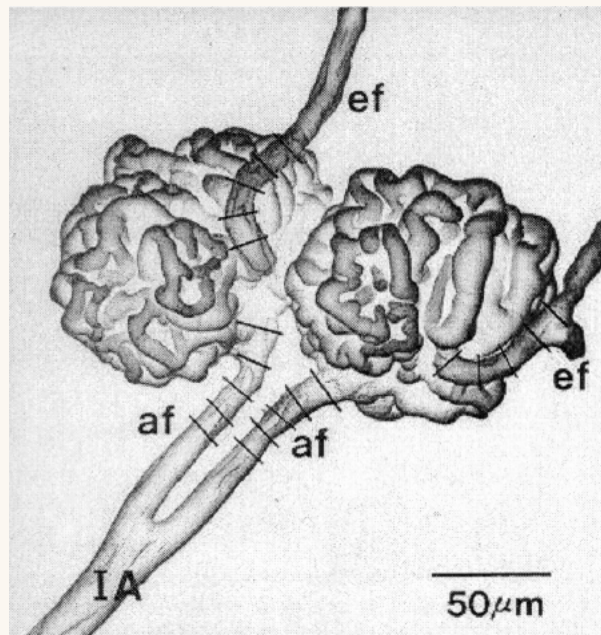
For hypertensive rats, the tubular oscillations are often chaotic:



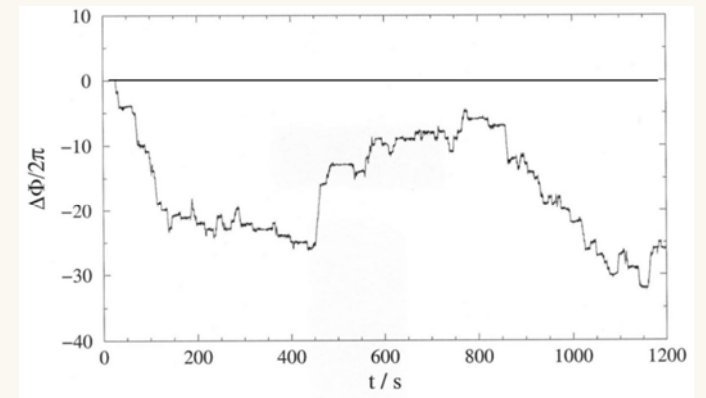
Interacting nephrons

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

Paired glomeruli at the end of an interlobular artery

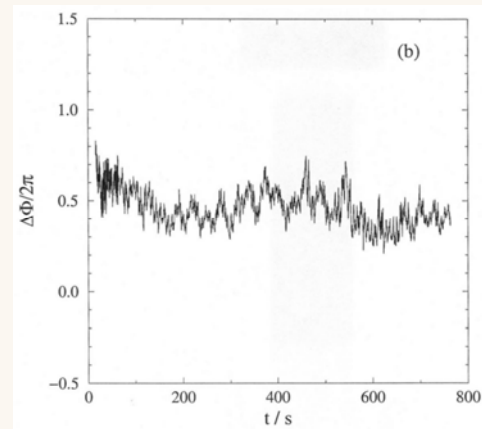
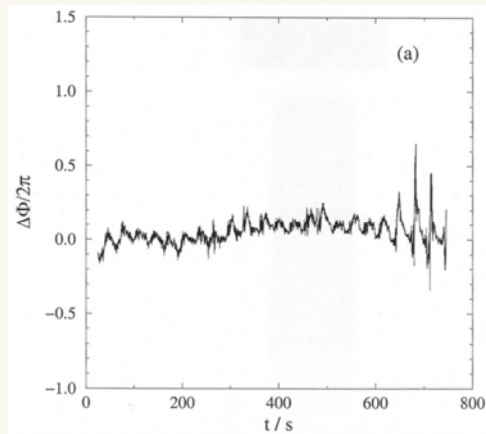
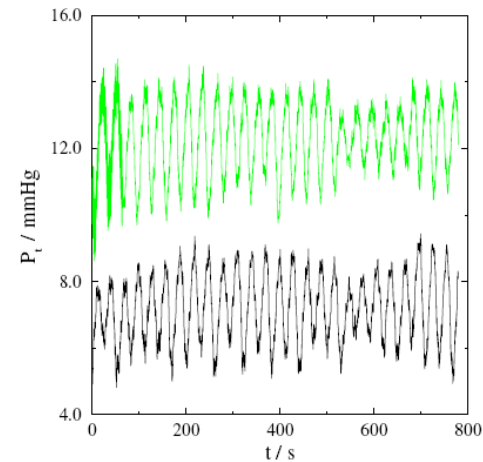
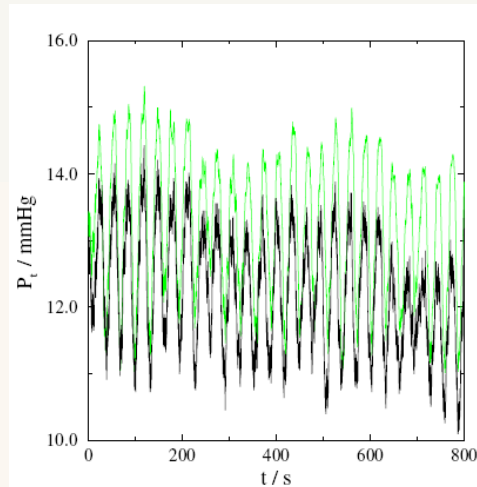


Synchronous and non-synchronous behavior



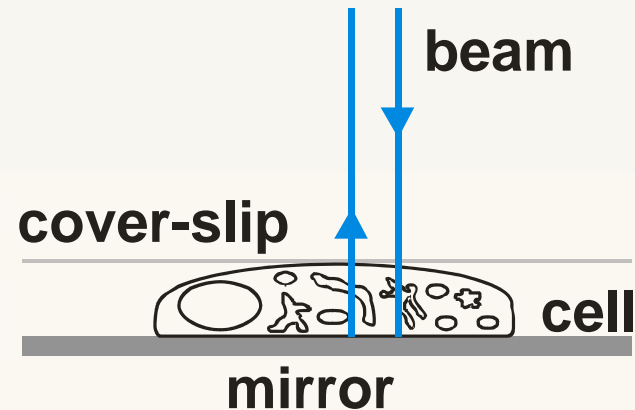
Nephrons branching off from the same interlobular artery interact via a vascular propagated coupling as well as a hemodynamic coupling.

Inphase and Antiphase Synchronization



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.

Interference Microscopy: The Phase Height Relief



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

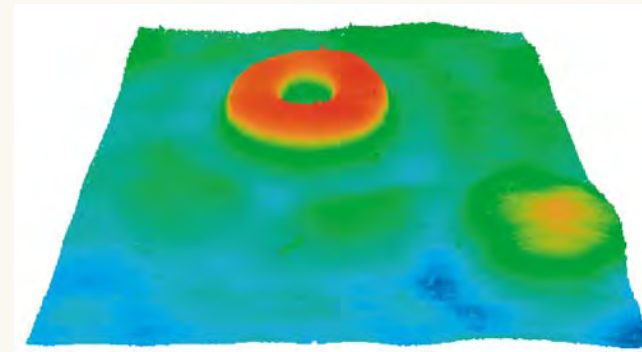
For erythrocytes we can detect changes in the distribution of haemoglobin and in the micro-tubular structure below the cellular membrane.

Combined with Raman scattering we can determine changes in the haemoglobin binding capacity and the ability to release oxygen.

The cellular phase height relief can be obtained from:

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

Nadezda and Alexey Brazhe
Dept. of Biophysics, Moscow University

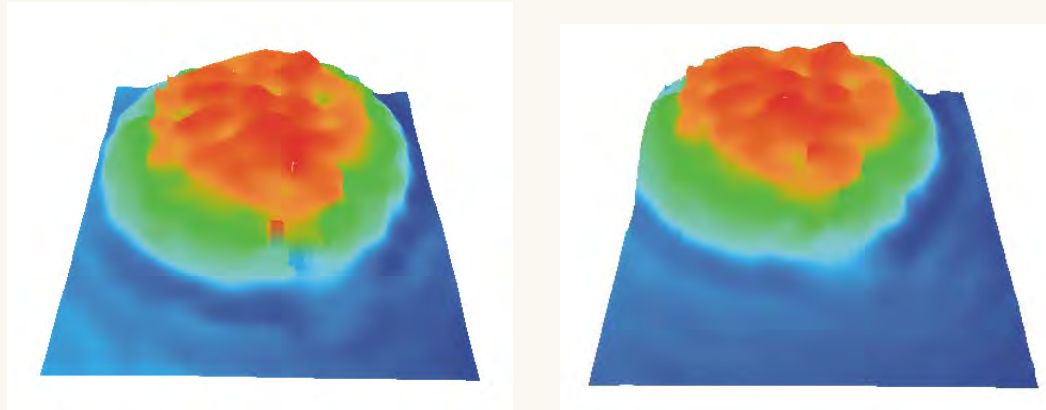


Studying the dynamics: Time-Resolved Interference Microscopy

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

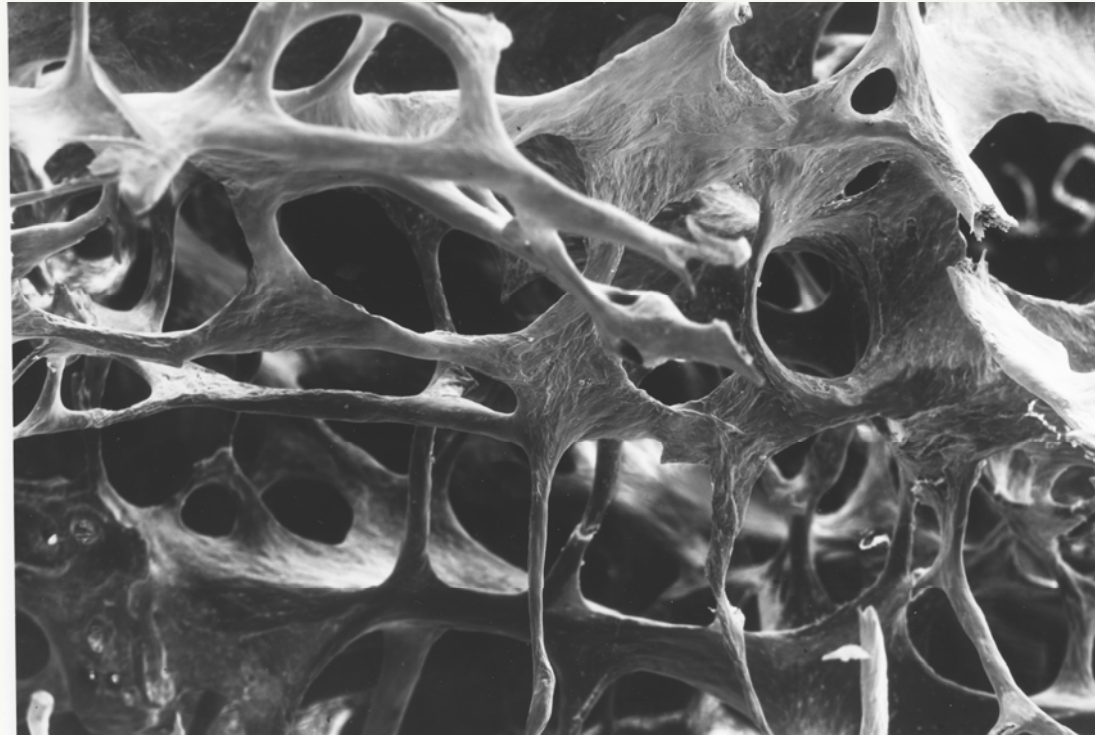
A manifestation of this intrinsic activity can be seen in the dynamics of the refractive index.



Bone structure

The interior of the vertebral bodies and other large bones consists of a complex network of plates, columns and struts with diameters varying from 10 to 400 μm .

One can determine the strain-stress relation for such a structure by means of computer programs that were used by engineers many years ago to design railroad bridges.



This allows us to calculate the bone strength in terms of parameters such as the material properties of the individual trabecula, its form (diameter and length), the regularity of the structure, and the density of the network.

With Lis Mosekilde and Jesper Skovhus Thomsen, Aarhus University