# Bimodal Dynamics in Nephron Autoregulation

Olga V. Sosnovtseva, Alexey N. Pavlov
Department of Physics, Saratov State University,
83 Astrakhanskaya Str., 410026 Saratov, Russia
olga@chaos.ssu.runnet.ru, http://chaos.ssu.runnet.ru

Erik Mosekilde
Department of Physics, Technical University of Denmark,
2800 Kgs. Lyngby, Denmark

Niels-Henrik Holstein-Rathlou
Department of Medical Physiology, Panum Institute,
University of Copenhagen, 2200 Copenhagen N, Denmark

**Abstract**

The individual functional unit of the kidney (the nephron) displays oscillations in its pressure and flow regulation at two different time scales: fast oscillations associated with a myogenic dynamics of the afferent arteriole, and slower oscillations arising from a delay in the tubuloglomerular feedback. We investigate the intra- and inter-nephron entrainment of the two time-scales. Besides full synchronization, both wavelet analyses of experimental data and numerical simulations reveal a partial entrainment in which neighboring nephrons attain a state of chaotic synchronization with respect to their slow dynamics, but the fast dynamics remain desynchronized.

## 1 Introduction

The concept of homeostasis [1], i.e. the ability of the body to maintain a nearly constant internal milieu despite of changes in the external conditions, plays an essential role in the description of physiological control systems.

It is sometimes assumed that homeostasis implies that the physiological variables are kept near a stable steady state by means of an effective feedback regulation. While this may be the case in certain situations, biological systems in general should be considered as open dissipative systems that are maintained under far-from-equilibrium conditions. Regular and irregular oscillations associated with various forms of instability are common features of behavior that can be observed during normal functioning or arise in connection with particular states of disease [2].

The kidneys play an important role in regulating the blood pressure and maintaining a proper environment for the cells of the body. At the same time, to protect its function against variations in the arterial blood pressure, the individual functional unit of the kidney (the nephron) disposes of the so-called tubuloglomerular feedback (TGF) mechanism that regulates the incoming blood flow in dependence of the NaCl concentration of the fluid that leaves the nephron. Experiments by Leyssac and Holstein-Rathlou [3] have demonstrated that this feedback regulation can become unstable and generate self-sustained oscillations in the proximal intratubular pressure with a typical period of 30-40 $s$. With different amplitudes and phases the same oscillations are manifest in the distal intratubular pressure and in the chloride concentration near the terminal part of the loop of Henle [4]. While for normal rats the oscillations have the appearance of a limit cycle with a sharply peaked power spectrum (Fig. 1a), highly irregular oscillations, displaying a broadband spectral distribution with significant subharmonic components, are observed for spontaneously hypertensive rats (Fig. 1b). Observation of both in-phase and antiphase synchronization was reported for the regu-

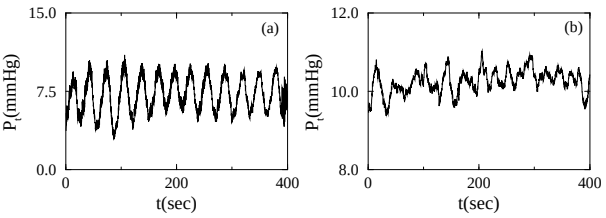


**Figure 1:** Wavelet analysis of the two time-series presented in Fig. 1.

lar pressure oscillations in normal rats while spontaneously hypertensive rats revealed signs of chaotic phase synchronization [5, 6].

While entrainment of single-mode deterministic or stochastic oscillations is well understood, the dynamics of systems with several oscillatory modes is less studied. In the present paper we describe the individual nephron as a two-mode oscillator demonstrating relatively fast oscillations associated with the myogenic regulation of the arteriolar diameter and slower oscillations related with the delay in the tubuloglomerular feedback. We study numerically as well as experimentally the entrainment between these time-scales both within the individual nephron and between neighboring nephrons.

## 2 Nephron Autoregulation

### 2.1 Data analysis

Signals generated by living systems are typically nonstationary and inhomogeneous, and processing of such signals by means of conventional techniques such as Fourier analysis can lead to problems with respect to the interpretation of the obtained results. Among the various approaches developed to study nonstationary data, wavelet analysis is probably the most popular [7]. In particular, this method gives us the possibility to investigate the temporal evolution of signals with different rhythmic components.

Figure 2 shows the different components detected in the time series of Fig. 1. Inspection of the figure reveals that the slow oscillations, whether they are periodic or chaotic, maintain a nearly constant frequency through the observation time. The fast oscillations, on the other hand, fluctuate around some average value. This may be related to a complex modulation of the fast oscillations by the slow dynamics or to the influence of noise (since the fast oscillations are small in amplitude, they are more sensitive to fluctuations).

However, this picture does not give information

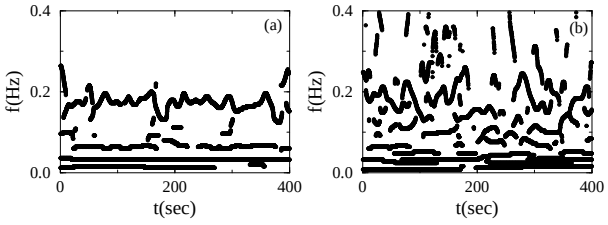


**Figure 2:** Wavelet analysis of the two time-series presented in Fig. 1.

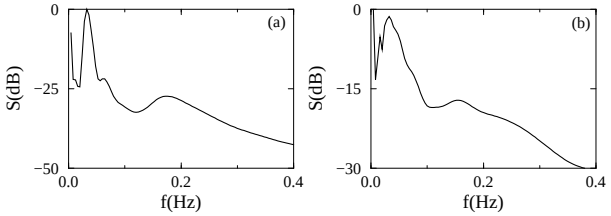


**Figure 3:** Power spectrum obtained from the wavelet analysis for the two time-series presented in Fig. 1.

about the dominant spectral components. This information can be obtained, for example, from a *scalogram*, i.e., a time averaged power spectrum, being an analogue to the Fourier power spectrum. Such a scalogram is illustrated in Fig. 3 where a well-pronounced peak around $0.03Hz$, corresponding to the slow TGF-mediated mode, is distinguishable. The other peak at $0.15-0.2Hz$ derives from the fast myogenic dynamics. It is interesting to note how clearly these oscillations can be detected from the tubular pressure variations. Since both the above frequency components are of physiological interest we extract them from the original wavelet transformation for further analysis of their coherence properties. For the periodic oscillations observed for normotensive rats, the fast and slow components adjust their periods in accordance to one another to maintain a $1:4$ entrainment during the observation time. For the chaotic oscillations observed for hypertensive rats, the ratio changes more randomly in time.

### 2.2 Model

The functional unit of the kidney may be considered as a filtration device with an internal feedback control that regulates the blood flow. Autoregulation of the pressures and flows in the individual nephron may be described by the following model [8]:

$$\begin{aligned}
\dot{P}_t &= \frac{1}{C_{tub}}\left\{F_f\left(P_t,r\right)-F_{reab}-\left(P_t-P_d\right)/R_{Hen}\right\},\\
\dot{r} &= v_r,\\
\dot{v}_r &= \frac{1}{\omega}\left\{P_{av}\left(P_t,r\right)-P_{eq}\left(r,\Psi(X_3,\alpha)\right)-\omega d v_r\right\},\\
\dot{X}_1 &= \frac{1}{R_{Hen}}\left(P_t-P_d\right)-\frac{3}{T}X_1, \qquad (1)\\
\dot{X}_2 &= \frac{3}{T}\left(X_1-X_2\right),\\
\dot{X}_3 &= \frac{3}{T}\left(X_2-X_3\right).
\end{aligned}$$

The first equation represents the pressure variations in the proximal tubule in terms of the in- and outgoing fluid flows. Here, $F_f$ is the single-nephron

glomerular filtration rate and $C_{tub}$ is the elastic compliance of the tubule. The flow into the loop of Henle is determined by the difference $(P_t - P_d)$ between the proximal and the distal tubular pressures and by the flow resistance $R_{Hen}$. The reabsorption in the proximal tubule $F_{reab}$ is assumed to be constant.

The following two equations describe the dynamics associated with the flow control in the afferent arteriole. Here, $r$ represents the radius of the active part of the vessel and $v_r$ is its rate of increase. $d$ is a characteristic time constant describing the damping of the oscillations, $\omega$ is a measure of the mass relative to the elastic compliance of the arteriolar wall, and $P_{av}$ denotes the average pressure in the active part of the arteriole. $P_{eq}$ is the value of this pressure for which the arteriole is in equilibrium with its present radius and muscular activation $\Psi$. The expressions for $F_f, P_{av}$ and $P_{eq}$ involve a number of algebraic equations that must be solved along with the integration of Eq. (3).

The remaining equations in the single-nephron model describe the delay $T$ in the TGF regulation. This delay arises both from the transit time through the loop of Henle and from the cascaded enzymatic processes between the macula densa cells and the smooth muscle cells that control the contractions of the afferent arteriole. The feedback delay, which typically assumes a value of 12-18 *sec*, will be considered a bifurcation parameter in our analysis. Another important parameter is the strength $\alpha$ of the feedback regulation. This parameter takes a value of about 12 for normotensive rats, increasing to about 18 for hypertensive rats [9]. For a more detailed explanation of the model and the parameters, see Ref. [10].

Both experimental investigations and our simulations [8] reveal one of the most important features of the single-nephron model, namely the presence of two different time scales in the pressure and flow variations. Considering the model equations (3) we can identify the two time scales in terms of (i) a low-frequency (TGF-mediated) oscillation with a period $T_h \cong 2.2T$ arising from the delay in the tubuloglomerular feedback, and (ii) somewhat faster oscillations with a period $T_v \approx T_h/5$ associated with the inherent myogenic adjustment.

To determine $T_h$ and $T_v$ in our numerical simulations we have used the mean return times of the trajectory to appropriately chosen Poincaré sections

$$T_v =< T_{ret} |_{.v_r=0} >, \text{and} T_h =< T_{ret}|_{.X_2=0} > . \quad (2)$$

From these return times it is easy to calculate the

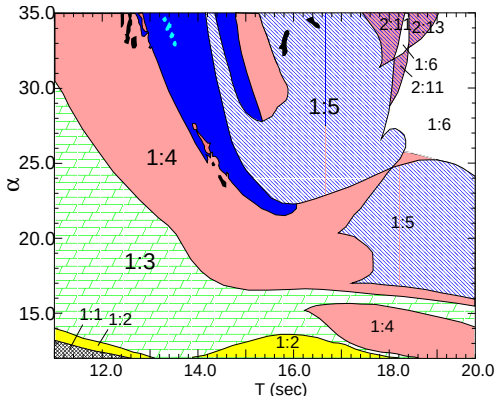


**Figure 4:** Two-mode oscillatory behavior in the single nephron model. Black colored regions correspond to a chaotic solution.

intra-nephron rotation number (i.e., the rotation number associated with the two-mode behavior of the individual nephron)

$$r_{vh} = T_v/T_h. \quad (3)$$

This measure will be used to characterize the various forms of frequency locking between the two modes. With varying feedback delay $T$ and varying slope $\alpha$ of the open loop feedback curve, Fig. 4 shows how the two oscillatory modes can adjust their dynamics and attain states with different rational relations $(n : m)$ between the periods. The regions of high resonances $(1 : 4,\ 1 : 5,$ and $1 : 6)$ are seen to exist in the physiologically interesting range of the delay time $T \in [12\ sec, 20\ sec]$.

While the transitions between the different locking regimes always involve bifurcations, bifurcations may also occur within the individual regime. A period-doubling transition, for instance, does not necessarily change $r_{vh}$, and the intra-nephron rotation number may remain constant through a complete period-doubling cascade and into the chaotic regime. This is illustrated in Fig. 5 where we have plotted $r_{vh}$ as a function of the feedback gain $\alpha$ for different time delays $T_2 = 13.5\ sec$ (black circles) and $T = 15.0\ sec$ (open circles). Phase projections $(P_t, r)$ from the various regimes are shown as inserts. Inspection of the figure clearly shows that $r_{vh}$ remains constant under the transition from regular $1 : 4$ oscillations (black circles for $\alpha = 25.0$) to chaos (for $\alpha = 28.0$), see inserts 1 and 2. With further evolution of the chaotic attractor (insert 3), the $1 : 4$ mode locking is destroyed. In the interval around $\alpha = 31.5$ we observe $2 : 9$ mode locking. A similar transition is observed for $T = 15\ sec$ (open circles). Periodic $1 : 5$ oscillations ($\alpha = 27.0$) evolve into a chaotic attractor

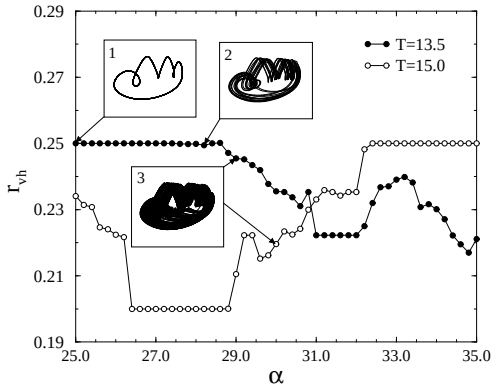


**Figure 5:** Internal rotation number as a function of the parameter $\alpha$ calculated from the single-nephron model. Inserts represent phase projections of typical regimes.

($\alpha = 28.5$), but the rotation number maintains a constant value. For fully developed chaos, the $1:5$ locking again breaks down.

We conclude that besides being regular or chaotic, the self-sustained pressure variations in the individual nephron can be classified as being synchronous or asynchronous with respect to the ratio between the two time scales that characterize the fast (arteriolar) mode and the slow (TGF mediated) mode, respectively. As we shall see, this complexity in behavior may play an essential role in the synchronization between a pair of interacting nephrons.

## 3 Entrainment of oscillatory modes for interacting nephrons

### 3.1 Experimental results

Using anatomical criteria, neighboring nephrons having a high likelihood of deriving their afferent arterioles from the same interlobular artery were identified [11]. In these nephrons 29 out of 33 pairs (i.e., 80 %) were found to have synchronized oscillations. In contrast, nephron pairs not fulfilling these criteria only showed synchronous oscillations in one case out of 23 investigated pairs (i.e., 4 %). This observation shows that synchronized oscillations are preferentially found in nephrons originating from the same interlobular artery. Figure 6 displays the tubular pressure variations in pairs of neighboring nephrons for a normotensive rat (a) and for hypertensive rats (b-d). Oscillations presented in Figs. 6 (b,c and d) are significantly more irregular than the oscillations displayed in (a). One can visually observe a certain degree of synchronization between the interacting nephrons. It is difficult, though, to separately estimate the degree of adjustment for the myogenic oscillations and for the TGF mediated oscillations without special tools.

To study multimode interactive dynamics in coupled systems we propose to use the wavelet based coherence measure $\Gamma_\Delta$ (in analogy with the classical coherence function). Let $E_\psi[xx](f,t)$ and $E_\psi[yy](f,t)$ be the energy densities of signals $x(t)$ and $y(t)$. Let also in some range of frequencies $\Delta$ each of the processes $x(t)$ and $y(t)$ have a clearly expressed rhythm (e.g., the range of slow or fast oscillations for the two nephrons). In this case synchronization means that the corresponding frequencies for $x(t)$ and $y(t)$ will be locked (coincide). Such a situation corresponds to the value $\Gamma_\Delta = 1$ for the function:

$$\Gamma^2_\Delta(t) = \frac{\max_{f\in\Delta}\left[E_\psi[xy](f,t)\right]^2}{\max_{f\in\Delta}\left[E_\psi[xx](f,t)\right]\cdot\max_{f\in\Delta}\left[E_\psi[yy](f,t)\right]}$$

Here, $E_\psi[xy](f,t)$ is the mutual energy density $E_\psi[xy](f,t) = \mid T_\psi[xy](f,t)\cdot T^*_\psi[yx](f,t) \mid$. $\Gamma_\Delta(t)$ is a function of time that allows us to follow the evolution of the interactive dynamics of the two processes in the chosen frequency range $\Delta$. The more synchronous the rhythms of these processes are, the closer $\Gamma_\Delta(t)$ will be to 1.

Figures 8 and 9 demonstrate different degrees of coherence for the considered modes. For periodic oscillations (a), both the slow and fast modes of the interacting nephrons are perfectly locked during the observation time. For a system with complex oscillations subjected to noise one can speak about a certain degree of synchronization if the periods of locking is significant compared with the characteristic periods of oscillations. Fully incoherent behavior with respect to both oscillatory modes can be observed in (b). In many cases we can diagnose syn-

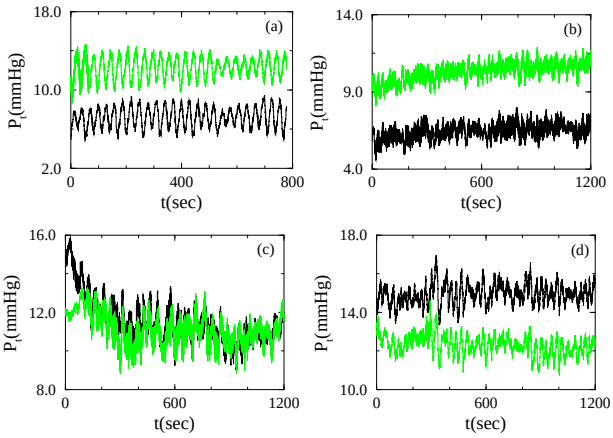


**Figure 6:** Examples of the tubular pressure variation that one can observe in adjacent nephrons (a) for normotensive and (b-d) for hypertensive rats.

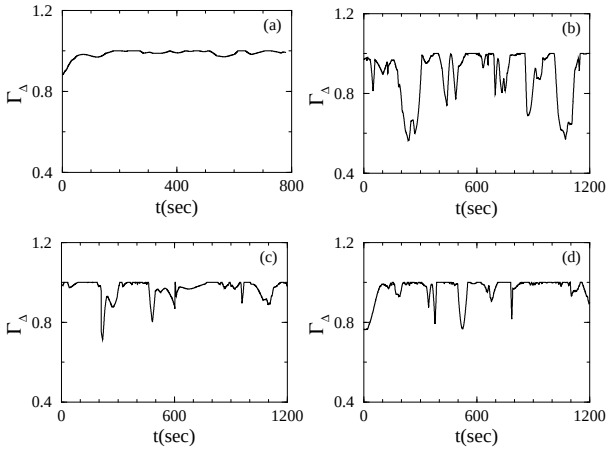


**Figure 7:** Mutual wavelet analysis for the slow oscillations of the two time-series presented in Fig. 6: (a) synchronous behavior, (b) nonsynchronous dynamics, (c) and (d) synchronous behavior but during limited time intervals.

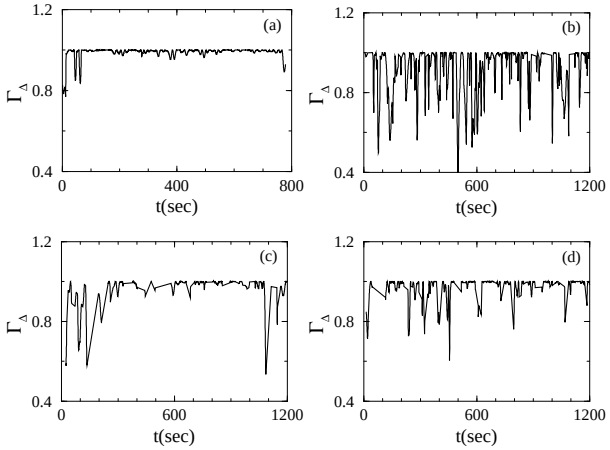


**Figure 8:** Mutual wavelet analysis for the fast oscillations extracted from time-series presented in Fig. 6. (a) and (c) illustrate synchronous behavior, (b) and (d) nonsynchronus dynamics.

chronization of the slow motions (c,d) for relatively long time intervals where the frequencies remain almost equal. The fast motions, on the other hand, can demonstrate different coherence properties between nephrons. The oscillations can be locked during long periods of time together with the slow oscillations (c). We define this type of synchronization as full synchronization since all time scales of the system are locked. Another case (d) is when the fast oscillations are incoherent while the slow oscillations are synchronized during the considered time interval. We refer to this phenomenon as partial synchronization.

### 3.2 Simulation results

Neighboring nephrons can influence each other's blood supply either through vascularly propagated electrical (or electrochemical) signals or through a hemodynamic coupling arising via a direct redistribution of the blood flow between the coupled nephrons. In the present work we shall focus our attention on the vascularly propagated coupling, assuming the hemodynamic coupling to be negligible. In the single-nephron model the equilibrium pressure in the afferent arteriole depends on the current radius $r$ and on the activation level $\Psi$ of the smooth muscles surrounding the arteriole and controlling its diameter. The muscular activation arises at the juxtaglomerular apparatus and travels upstream along the afferent arteriole in a damped fashion. When it reaches the branching point with the arteriole from the neighboring nephron, part of the signal may propagate down that arteriole and start to contribute to its TGF response. The coupling is considered nearly instantaneous since the time it takes for the vascular signal to reach the other nephron is very small relative to the period of the TGF-oscillations. It has been observed [11] that the signal decreases nearly exponentially as it propagates. In the model, the vascularly propagated coupling is represented by adding a contribution of the activation level in one nephron to the activation level in the neighboring nephron:

$$\Psi^*_{1,2} = \Psi_{1,2} + \gamma\Psi_{2,1} \tag{4}$$

with $\gamma$ being the coupling parameter and $\Psi_{1,2}$ the uncoupled activation levels of the two nephrons as determined by their respective Henle flows. By virtue of the two-mode dynamics of the individual nephron, a number of new and interesting results appear.

The individual oscillatory system has two modes that can be locked with each other. However, an interaction between functional units can break their mutual adjustment. It is also plausible that a coupling can act in different manners on the fast and slow oscillations. For the interacting systems we introduce two rotation numbers as follows:

$$r_v = T_{v1}/T_{v2}, \quad r_h = T_{h1}/T_{h2}. \tag{5}$$

To provide more information, the variation of the phase difference is calculated separately for the slow $h$ and for the fast $v$ oscillations.

Let us consider the case of $\alpha = 30.0$ corresponding to a weakly developed chaotic attractor in the individual nephron. The coupling strength $\gamma$ and delay time $T_2$ in the second nephron are varied. Two different chaotic states can be recognized as asynchronous and

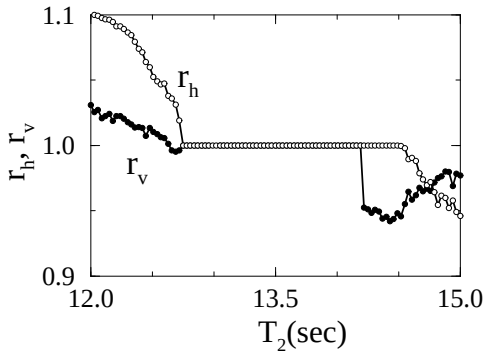


**Figure 9:** Full and partial synchronization of fast and slow motions ($T_1 = 13.5$ *sec*, $\alpha = 30.0$ and $\gamma = 0.06$).

synchronous (Fig. 9). For asynchronous behavior the rotation numbers $r_h$ and $r_v$ change continuously with $T_2$ while inside the synchronization region two cases can be distinguished. To the left, the rotation numbers $r_h$ and $r_v$ are both equal to unity since both slow and fast oscillations are synchronized. To the right ($T_2 > 14.2$ *sec*), while the slow $h$-mode of the chaotic oscillations remain locked, the fast $v$-mode drifts randomly. In this case the synchronization condition is fulfilled only for one of oscillatory modes.

## 4 Conclusions

Based on the analysis of experimental results we showed that the vascular dynamics and the tubuloglomerular feedback mechanism are responsible for two time scales associated with a fast and a slow oscillatory mode in the individual nephron. Both for periodic oscillations observed in normotensive rats and for the chaotic oscillations in hypertensive rats the two modes exhibit resonant behavior as well as nonsynchronous dynamics.

To investigate different types of internephron mode entrainment we developed a mutual wavelet transformation that allows us to easily analyze adjustments between different time scales from nonstationary data. We observed simultaneous (full) locking for the slow and fast oscillations both for normotensive and for hypertensive rats. We also identified a state of partial synchronization where the slow oscillations are synchronized while the fast motion demonstrates noncoherent behavior. Such a situation is typical for hypertensive rats.

Numerical simulations for coupled nephron models demonstrate similar behavior. With varying time delay in the tubuloglomerular feedback and varying strength of the vascular coupling the experimentally observed forms of synchronous behavior were recovered.

**Acknowledgments**

This work was partly supported by INTAS grant (01-2061) and RFBR (01-02-16709). O.S. acknowledges support from INTAS grant (YS 2001/1-23).

## References

[1] W. B. Cannon, "Organization for physiological homeostasis", *Physiol. Rev.* **9**, 399-431 (1929).

[2] L. Glass and M.C. Mackey, *From Clocks to Chaos: The Rhythms of Life* (Princeton University Press, Princeton, 1988).

[3] N.-H. Holstein-Rathlou and P.P. Leyssac, "TGF-mediated oscillations in the proximal intratubular pressure: Differences between spontaneously hypertensive rats and Wistar-Kyoto rats", *Acta Physiol. Scand.* **126**, 333-339 (1986).

[4] N.-H. Holstein-Rathlou and D.J. Marsh, "Renal blood flow regulation and arterial pressure fluctuations: A case study in nonlinear dynamics", *Physiol. Rev.* **74**, 637-681 (1994).

[5] N.-H. Holstein-Rathlou, K.-P. Yip, O.V. Sosnovtseva, and E. Mosekilde, "Synchronization phenomena in nephron-nephron interaction", *Chaos* **11**, 417-426 (2001).

[6] D.E. Postnov, O.V. Sosnovtseva, E. Mosekilde, and N.-H. Holstein-Rathlou, "Cooperative phase dynamics in coupled nephrons", *Int. J. Mod. Phys. B* **15**, 3079-3098 (2001).

[7] I. Daubechies, *Ten Lectures on Wavelets* (S.I.A.M., Philadelphia, 1992).

[8] M. Barfred, E. Mosekilde, and N.-H. Holstein-Rathlou, "Bifurcation analysis of nephron pressure and flow regulation", *Chaos* **6**, 280-287 (1996).

[9] P.P. Leyssac and N.-H. Holstein-Rathlou, "Tubolo-glomerular feedback response: Enhancement in adult spontaneously hypertensive rats and effects of anaesthetics", *Pflügers Arch.* **413**, 267-272 (1989).

[10] M.D. Andersen, N. Carlson, E. Mosekilde and N.-H. Holstein-Rathlou, "Dynamic model of nephron-nephron interaction", in *Membrane Transport and Renal Physiology*, edited by H. Layton and A. Weinstein (Springer, New York, 2001).

[11] Y.-M. Chen, K.-P. Yip, D.J. Marsh, and N.-H. Holstein-Rathlou, "Magnitude of TGF-initiated nephron-nephron interactions is increased in SHR" *Am. J. Physiol.* **269**, F198-F204 (1995).