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Double-wavelet approach to studying the modulation properties of nonstationary multimode dynamics

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Abstract

On the basis of double-wavelet analysis, the paper proposes a method to study interactions in the form of frequency and amplitude modulation in nonstationary multimode data series. Special emphasis is given to the problem of quantifying the strength of modulation for a fast signal by a coexisting slower dynamics and to its physiological interpretation. Application of the approach is demonstrated for a number of model systems, including a model that generates chaotic dynamics. The approach is then applied to proximal tubular pressure data from rat nephrons in order to estimate the degree to which the myogenic dynamics of the afferent arteriole is modulated by the slower tubulo-glomerular dynamics. Our analysis reveals a significantly stronger interaction between the two mechanisms in spontaneously hypertensive rats than in normotensive rats.

Keywords: rhythmic activity, modulation, nonstationarity, wavelet, kidney autoregulation

1. Introduction

Biological time series often demonstrate the coexistence of several different oscillatory components. It is well known, for instance, that one can observe at least five characteristic rhythmic phenomena in measurements of human heart rates (Stefanovska and Bračič 1999) or blood flow and pressure variations (Hoffman *et al* 1990, Holstein-Rathlou *et al* 1995). Similarly, measurements of physiological tremor (Beuter and Edwards 1999), brain activity

(Tuckwell, 1988) and hormonal secretion (Sturis *et al* 1994) typically give evidence of several simultaneous oscillatory mechanisms. The same picture is revealed at the cellular level, e.g. with different types of nerve cells exhibiting complex patterns of fast and slow rhythms in their bursting dynamics (Braun *et al* 1980) and with pancreatic β-cells displaying simultaneous oscillations of electrophysiological and metabolic origin (Goldbeter 1996). The variability of many physiological processes may differ from the healthy to the diseased state (Wolf *et al* 1978). Hence, the problem consists in extracting a few significant components from a multitude of interacting dynamic processes, and quantifying the interaction between the selected modes. This requires the development of new statistical tools and, in many cases, of procedures to fine tune the parameters of these tools (Kantz and Schreiber 1997, Grossmann and Morlet 1984, Daubechies 1992, Tass *et al* 1998).

Multimode dynamics could, in principle, be the result of a purely linear superposition of independent oscillatory components. In most cases of biological interest, however, some kind of coupling is likely to exist between the various processes, causing them to adjust their dynamics relative to one another. This will typically lead to the universal phenomenon of synchronization (Pikovsky *et al* 2001, Mosekilde *et al* 2002). Our efforts in the present paper are concerned with the problem of characterizing such interaction processes in situations where an obvious synchronization cannot be observed. Such situations arise, for instance, if the coupling is relatively weak as measured by the rigidity of the internal dynamics of the interacting oscillators, if the frequencies of the oscillators are too different and/or if the system is influenced by too many disturbing factors to allow it to settle down into a particular state of synchronization.

In this paper we aimed to analyze the modulation process in multimode renal dynamics. First, we examine the limitations of the double-wavelet approach (Sosnovtseva *et al* 2004) by applying it to a number of model systems. Then, we quantify the *degree* to which the myogenic oscillations of the afferent arterioles in rat kidneys are modulated by the slower oscillations mediated by the tubulo-glomerular feedback mechanism. The experimental data to be analyzed consist of time series for the proximal tubular pressure in normal and hypertensive rats. In these time series, the myogenic oscillations are nearly invisible to the naked eye. Statistical analysis over a set of recordings reveals a considerable modulation of both the frequency and the amplitude of the myogenic oscillations by the tubulo-glomerular oscillations. Moreover, we find that this modulation is stronger for spontaneously hypertensive rats than for normotensive rats.

2. Double-wavelet technique: possibilities and limitations

2.1. Method

During the last few decades, wavelet transformation has become an important tool in the spectral analysis of experimental data (Grossmann and Morlet 1984, Daubechies 1992). Unlike the classical Fourier technique, wavelet transformation provides a means to follow the time evolution of particular spectral peaks. If we need to know only the periodicities that are revealed in a time series, then the classical methods can be successfully applied. However, if we are interested in the temporal dynamics of the rhythmic components, then the wavelets have a clear advantage. In this way, wavelet analysis has been widely applied to reveal time-frequency information in cardiovascular related signals (Bračič *et al* 2000).

To study the modulation features of a fast oscillatory mode by a slower variable we propose to use the instantaneous frequencies $f_{\text{fast}}(t)$ and amplitudes $a_{\text{fast}}(t)$ of the fast rhythm, extracted via wavelet analysis, as input signals for a second wavelet transformation as described by Sosnovtseva *et al* (2004). The obtained wavelet spectra will contain information about all components involved in the modulation process. Hence, we can follow the time evolution of characteristics such as the depth and frequency of modulation. In other words, the approach that we will refer to as *double-wavelet analysis* allows us to quantify the nonstationary temporal dynamics of a modulated signal, i.e., to detect all modes involved in the modulation, estimate the depth of modulation for each mode and determine how the modulation properties change during the experimental observation period.

To learn about the modulation process we need to estimate the frequency and depth of modulation. The procedure for detection of the modulation frequency is described by Sosnovtseva *et al* (2004). Let us focus on the depth of modulation. For amplitude modulation, $M = \Delta A/A$ where $\Delta A = (A_{\max} - A_{\min})/2$ and A is the mean value. For frequency modulation, $M = \Delta\omega/\Omega$, where $\Delta\omega = (\omega_{\max} - \omega_{\min})/2$ and Ω is the modulation frequency. For nonstationary processes, $A(t)$ and $\Omega(t)$ are determined via a single-wavelet technique while $\Delta A(t)$ and $\Delta\omega(t)$ are determined via the double-wavelet technique.

We begin by illustrating the application possibilities and limitations of the double-wavelet method. For this purpose we consider the classical expressions for an amplitude, and a frequency-modulated signal, expressed, respectively, by means of the two harmonic functions:

$$x(t) = A(1 + m\sin(\Omega t + \varphi))\sin(\omega t + \varphi_0), \tag{1}$$

and

$$x(t) = A\sin[\omega t + m\sin(\Omega t + \varphi)) + \varphi_0)]. \tag{2}$$

We will take $A \in [1; 10]$, $m \in [0; 1]$ and $\omega = 2\pi \cdot 0.15$. Ω changes from $2\pi \cdot 0.03$ to $2\pi \cdot 0.02$. The phase variables φ and φ_0 assume random, but constant values.

Using our double-wavelet technique on time series generated by (1) and (2), it is possible to clearly distinguish two modes, associated with the frequencies Ω and ω to extract the instantaneous amplitude (figure 1(a)) and the frequency (figure 2(a)) of the fast (modulated) mode and, by considering these variables as new signals, to estimate the modulation characteristics.

When performing such an analysis, a number of features of the method are revealed.

(i) Wavelets have some averaging effects that occur because the properties of a signal at the fixed time moment are studied within some 'window' defined by the wavelet function (we use here the Morlet function). While the frequency of modulation is correctly estimated, the modulation depth M obtained from the wavelet analysis is approximately half of its true value m since we estimate averaged characteristics in a finite-sized 'window'. However, for the amplitude modulation (figure 1(b)) the ratio M/m does not depend on the values of m and A, and there is only a weak dependence on m for the case of frequency modulation (figure 2(b)). Moreover, the values M/m practically coincide in figures 1(b) and 2(b), i.e. the frequency and the amplitude modulations lead to the same averaging effect. The latter means that it is possible to correctly estimate the modulation depths by multiplying the results of the double-wavelet approach by a constant factor about 2.0 that we use in the subsequent analysis. (This factor can show some variations depending on the frequency of modulation and can be corrected if the frequency ratio Ω/ω deviates significantly from the values considered in our examples.)

(ii) In the case of pure amplitude modulation (equation (1)), the method can show spurious effects of a weak frequency modulation. This spurious modulation is approximately five times less in relative value than the actual amplitude modulation (figure 1(c)). By analogy, there may be spurious amplitude variations in the case of only frequency modulation, the latter effect being about ten times less than the true modulation (figure 2(c)). In other

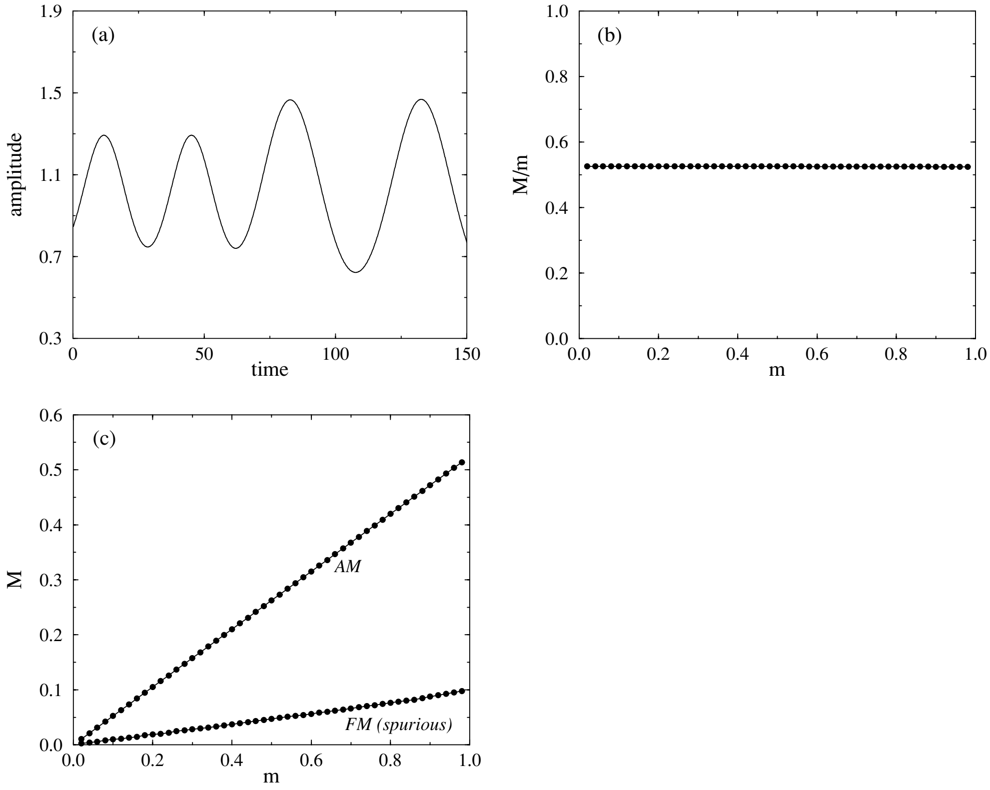

Figure 1. Analysis of amplitude modulation (AM) using the signal (1). (a) The instantaneous amplitude of the fast oscillatory mode extracted by means of wavelets; (b) the ratio M/m versus the parameter m; (c) the dependence of M on m demonstrates the spurious effect of the frequency modulation (FM). Here, $A = 1$.

words, if we deal with pure frequency or amplitude modulation we can expect to see additionally (weak) spurious modulations. Therefore, if both types of modulation are revealed in a data analysis, we must check whether their depths are comparable with the possible spurious effects.

(iii) The results of the double-wavelet approach are fairly insensitive to additive noise (fluctuations). We have added different types of noise to $x(t)$ (a $1/f$-like process modeling a slow nonstationarity and a normally distributed random process with intensities $[10^{-4}; 10^{-2}]$) and have observed that the obtained quantities for all practical purposes coincide with those presented in figures 1(b), (c) and 2(b), (c).

To demonstrate the applications of our approach to the case of more complex dynamics we have considered the model of an electronic oscillator described by the following mathematical model (Anishchenko 1995):

$$\begin{aligned}\dot{x} &= kx + y - xz - bx^3,\\ \dot{y} &= -x,\\ \dot{z} &= -gz + gx(x + |x|)/2.\end{aligned} \tag{3}$$

Choosing different values for the control parameters k, g and b, it is possible to obtain a variety of dynamical regimes, including periodic and chaotic dynamics (Anishchenko 1995).

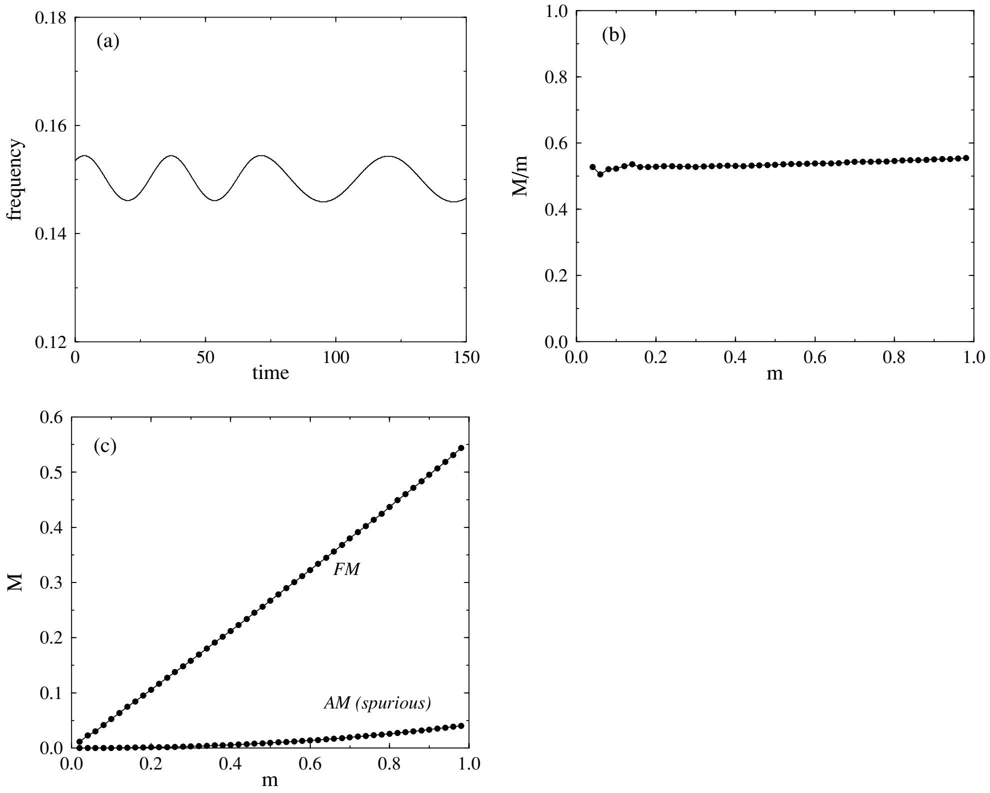

Figure 2. Analysis of frequency modulation using signal (2). (a) The instantaneous frequency of the fast oscillatory mode extracted by means of wavelets; (b) the ratio M/m versus the parameter m; (c) the dependence of M on m shows the spurious effect of the amplitude modulation.

In particular, system (3) can produce a regime of self-modulated oscillations. This autonomous regime is characterized by slow oscillations for the variable z and fast oscillations for variables x and y (Sosnovtseva *et al* 2002b). To illustrate the double-wavelet technique for nonstationary data, we have chosen the case of self-modulated oscillations in a regime of transient chaos (figure 3). The dynamics of the fast variable of model (3) suggests modulation by the slow rhythm (figure 3). The amplitude and the frequency of the fast oscillatory mode are changed in time with the period of slow dynamics.

For the considered regime, the instantaneous frequency of the fast mode extracted from the slow variable z is shown in figure 4(a). For part of the oscillatory period the frequency of the fast mode here takes values that are close to prominent harmonics of the slow rhythm, and the wavelet analysis can fail to distinguish between them. However, even missing some points, we are able to estimate the frequency of modulation and the modulation depth by performing the wavelet transform for the extracted temporal dependence (figure 4(a)). Here, $M_{\rm f}$ takes the value ≈ 1.1 reflecting a strong frequency modulation (or self-modulation)[5]. Analysis of the instantaneous amplitude with the double-wavelet approach gives the value $M_{\rm a} \approx 0.95$, i.e., we also deal with the case of strong amplitude modulation. The frequencies of modulation practically coincide with the instantaneous frequency of the slow mode

[5] Hereafter we use the notation $M_{\rm f}$ and $M_{\rm a}$ for the depths of frequency and amplitude modulation, respectively, as estimated using the wavelets.

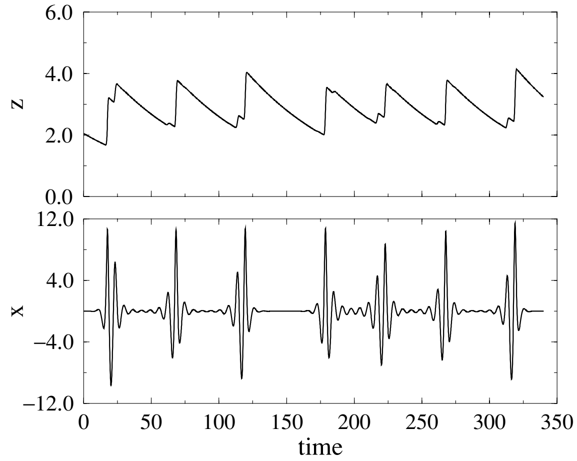

Figure 3. Time plots for the slow (z) and fast (x) variables in model (3). Here, $k = 2.903\,28$, $g = 0.012\,505$ and $b = 5 \times 10^{-5}$.

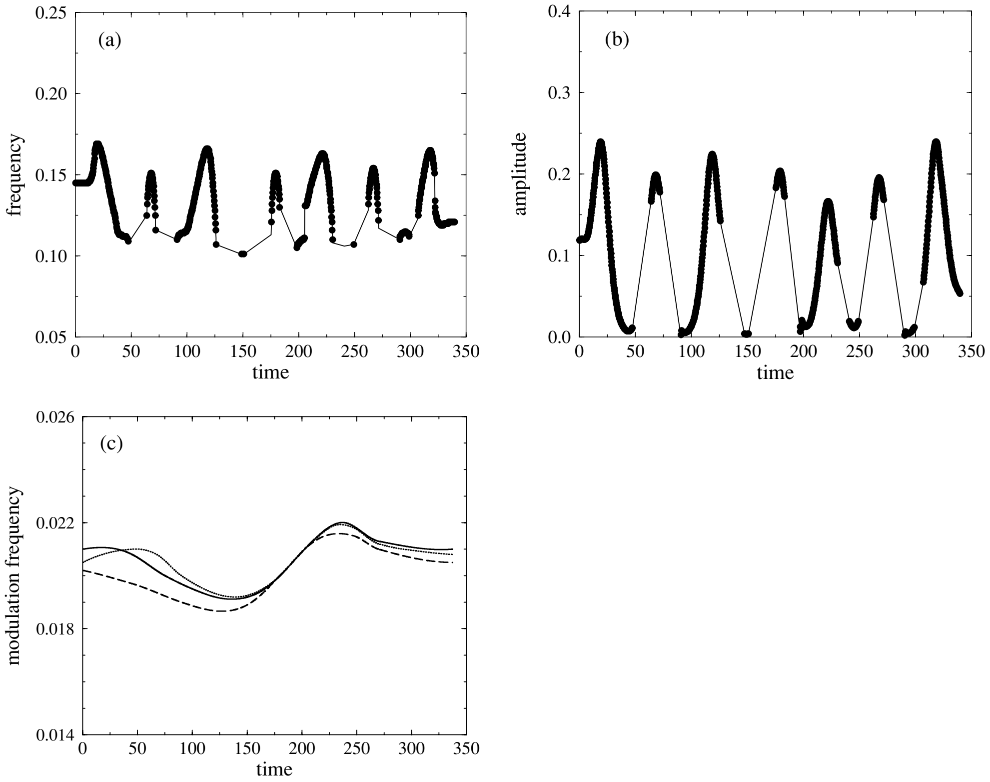

Figure 4. Instantaneous frequency (a) and amplitude (b) of the fast mode as extracted from the time series of the slow variable (z) of model (3) for the case of self-modulated oscillations in the regime of transient chaos. Missing points can be interpolated. This approach is not crucial to correctly estimate the modulation properties, however. (c) The instantaneous modulation frequencies for amplitude (dashed) and frequency (dotted) modulation. The solid curve represents the instantaneous frequency of the slow dynamics.

(figure 4(c)), and the obtained values of the modulation depth correspond to the expected values, which can be approximately estimated from the time series of the fast variable x depicted in figure 3. Hence, we can state that the approach allows us to correctly estimate the properties of modulation in the case of complex multimode dynamics. Besides, we can be sure that the presence of a slow nonstationarity in the data ($1/f$-like processes) does not have an essential influence on the estimated characteristics.

3. Application to experimental data

In this section we consider applications of the double-wavelet technique to study the features of bimodal oscillations in nephron dynamics. The nephron may be considered as the functional unit of the kidney. Experimental studies (Holstein-Rathlou and Leyssac 1986, Yip *et al* 1993) have shown that the nephron can produce self-sustained bimodal oscillations in its tubular pressure and flow with typical periods of 30–40 s (slow mode) and 5–10 s (fast mode). While for normal rats these oscillations are typically regular, highly irregular dynamics are observed for so-called spontaneously hypertensive rats with a genetic form of high blood pressure (hypertension).

In order to protect its function in the face of a varying blood pressure, the individual nephron disposes of a number of mechanisms to control the incoming blood flow. The glomerular filtration rate and renal blood flow are regulated at the level of the single nephron by an intrinsic action of afferent arterioles, known as the myogenic mechanism, and by a signal conducted to the afferent arterioles in response to changes in the tubular electrolyte concentration at the macula densa. The second mechanism is the tubulo-glomerular feedback (TGF). If the salt concentration in this fluid becomes too high, specialized cells (macula densa cells) near the terminal part of the loop Henle elicit a signal that causes the smooth muscle cells at the downstream end of the afferent arteriole to contract. Hence, the incoming blood flow is reduced, and so is the glomerular filtration rate and finally the salt concentration in the tubular fluid at the macula densa. Only a few attempts have been made to examine the interplay between the mechanisms responsible for the bimodal autoregulation (Chon Ki *et al* 1994, Sosnovtseva *et al* 2002a). In this work we consider how the degree of modulation of the fast mode by a slower rhythm can be related to normal and hypertensive states of renal dynamics.

3.1. Individual recording analysis

Examples of the tubular pressure data for a normotensive and a hypertensive rat are given in figure 5. Figure 6 shows how the modulation frequencies are changed in time. Black circles in this figure mark the temporal dependence of the instantaneous frequency of the slow oscillatory mode, and white circles are related to the instantaneous modulation frequency. For a normal rat (figure 6(a)) the latter fluctuates around the slow rhythm; however, the deviations from the slow mode do not exceed 0.01 Hz. For a hypertensive rat (figure 6(b)), the modulation frequency is also close to the slow rhythm, although the dynamics are more nonstationary. The observed delay between the two dependences in figure 6(b) is probably connected with some averaging effect: to estimate the characteristics at a given time we use a kind of ‘sliding window’ with the width of the wavelet ‘mother’ function at the chosen frequency, i.e. we consider both some previous and some future dynamics. Due to this averaging, changes in the modulation characteristics may be obtained earlier (or, in some cases, later) than they occur in the slow rhythm. Hence, we cannot exactly reproduce the latter rhythm; however, the qualitative similarity is obvious.

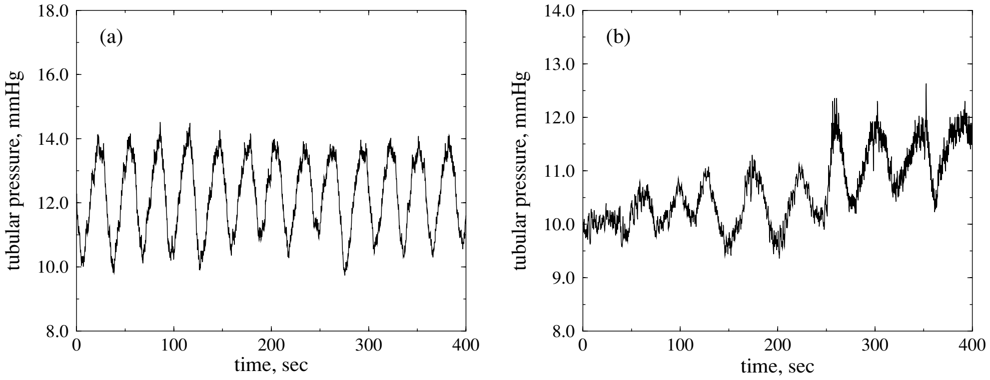

Figure 5. Experimental recordings of the proximal tubular pressure in a single nephron of a rat kidney for a normotensive (a) and a spontaneously hypertensive (b) rat.

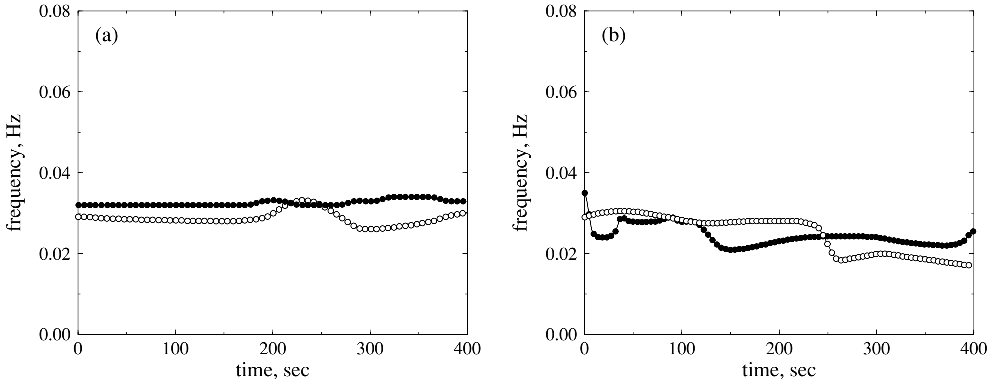

Figure 6. Results of the double-wavelet analysis of the time series shown in figure 5. (a) and (b) correspond to the case of frequency modulation for a normotensive and a hypertensive rat, respectively. Black circles mark the instantaneous frequency of the slow rhythm, and white circles indicate the instantaneous modulation frequency.

The depth of modulation also changes with time (figure 7). However, some averaged quantity can be used to characterize the dynamics. For the normotensive rat $M_{\mathrm{f}} \approx 0.35$, while for the hypertensive rat $M_{\mathrm{f}} \approx 1.1$. These results allow us to state that we observe a significant frequency modulation. Analogous studies can be performed for the instantaneous amplitudes of the fast mode. In this way, we obtained the values $M_{\mathrm{a}} \approx 0.33$ and $M_{\mathrm{a}} \approx 0.55$ (for the normotensive and the hypertensive rat, respectively), i.e., the effect of amplitude modulation is less expressed than the frequency modulation from the viewpoint of absolute values of modulation depths. This observation may provide an important testing criterion for alternative models of the interaction between the two modes.

3.2. Statistical approach

Let us now discuss the results obtained for a series of experiments. We used 76 recordings, among which 34 were from normotensive rats and 42 were from hypertensive rats. Animal preparation and experimental procedure are described by Holstein-Rathlou *et al* (Holstein-Rathlou and Leyssac 1986, Holstein-Rathlou *et al* 1995).

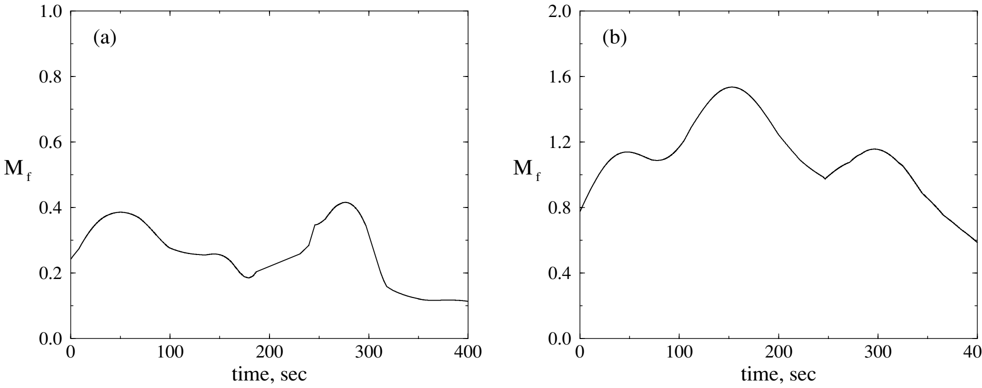

Figure 7. Time dependences of the depth of frequency modulation for a normotensive (a) and a hypertensive (b) rat. Note the significant difference in modulation depth between the two strains.

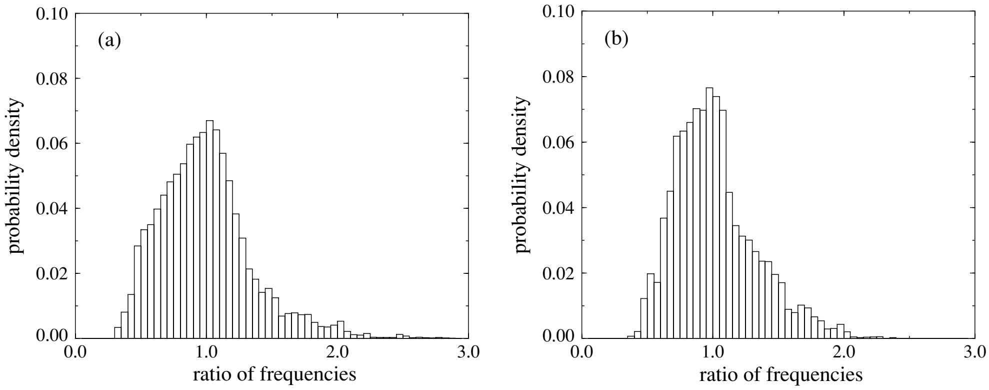

Figure 8. Distributions of the ratio of instantaneous frequencies as obtained from 76 experimental tubular pressure recordings. (a) Ratio of the frequency of amplitude modulation and (b) of the frequency of frequency modulation to the frequency of the slow TGF mode.

Figure 8 presents histograms of the *instantaneous* ratio of the modulation frequency to the TGF frequency at each moment of time over all recordings. It is clearly seen that there is a maximum around a ratio of unity. The width of the histogram may be related to different sources of variation in the system that are not normally distributed (the blood pressure, for example). To perform statistical analyses for different rat strains, it is useful to estimate a time-averaged ratio for each recording. Figure 9 shows slight deviations around 1 that indicate a strong correlation between slow and fast modes. These results fit the data of blood flow recordings for the efferent arteriole (Marsh *et al* 2005) and are consistent with the hypothesis of TGF modulation of the myogenic oscillations.

Figure 10(a) illustrates the distribution of depths of frequency and amplitude modulation for hypertensive (black circles) and normotensive (white circles) rats. Inspection of the figure clearly shows that there is a well-defined line of distinction between the two strains for both the amplitude and the frequency modulation, although the latter effect is more clearly expressed. Over all data the mean values of the modulation depth with standard error of the mean are $M_a = 0.49 \pm 0.02$ and $M_f = 1.08 \pm 0.06$ as indicated by the dashed lines in figure 10(a). It is clearly seen that the depth of modulation, and, hence, the nonlinear interaction

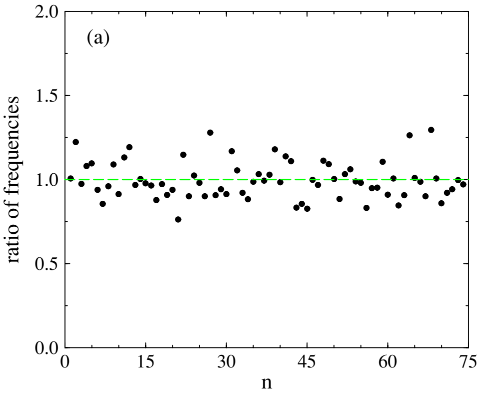

Figure 9. Time-averaged ratio of frequencies from experiments at tubular pressure versus the recording's number in the case of (a) amplitude modulation and (b) frequency modulation.

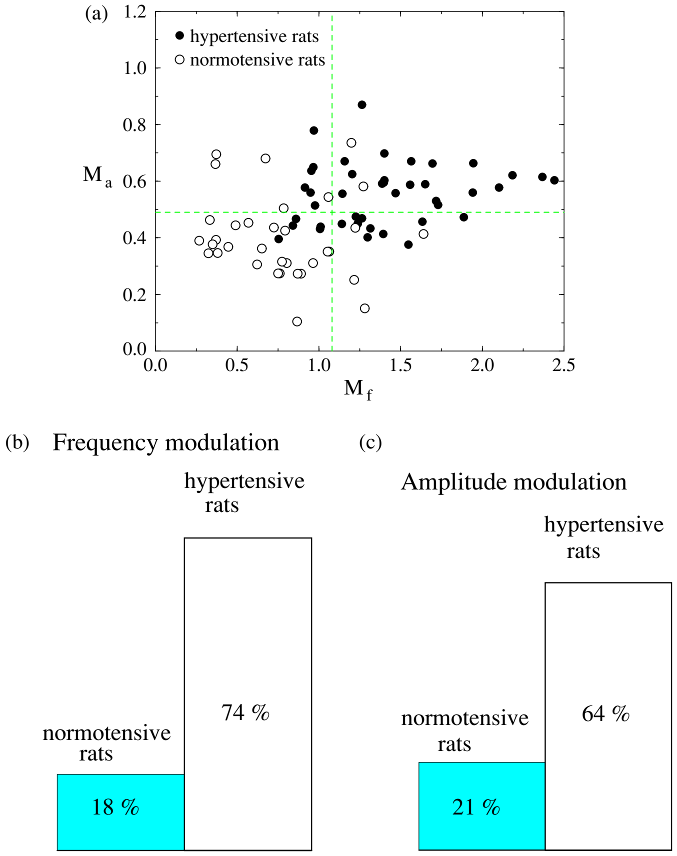

Figure 10. (a) Distribution of depths of frequency and amplitude modulation estimated from recordings of tubular pressure for normotensive rats (34 time series) and hypertensive rats (42 time series). Dashed lines represent the average values of the two modulation depths. (b) and (c) Fraction of nephrons with the depth of frequency and amplitude modulation, respectively, that exceeds the average value over all experimental data of tubular pressure.

between the involved mechanisms, is stronger for hypertensive than for normotensive rats. The mean values are $M_a = 0.40 \pm 0.02$ and $M_f = 0.74 \pm 0.06$ for normotensive rats, while $M_a = 0.55 \pm 0.02$ and $M_f = 1.35 \pm 0.06$ for hypertensive rats. Figures 10(b) and (c) show the distributions of nephrons for the two rat strains according to their depth of frequency (figure 10(b)) and amplitude (figure 10(c)) modulation estimated from tubular pressure recordings. The number of nephrons with a frequency modulation that exceeds the average value is higher for hypertensive rats (75%) than for normotensive rats (18%). For the amplitude variations, we obtained 64% and 21%, respectively. The smaller difference between the amplitude modulations may be connected with the smaller values of M_a in comparison with M_f and, therefore, with the possible existence of spurious effects that influence our estimations for the amplitudes.

On the basis of the above results we suggest that the mechanism of regulation of the afferent arterial blood flow is more complex than previously assumed. In hypertension, the active parts of the blood vessels demonstrate increased variability in their oscillations, i.e. regulation of the flow is associated not only with changes in vascular diameters but also with an accompanying adjustment of the frequency of the vascular oscillations.

4. Discussion

To investigate features of the nonlinear interaction between the modes in the case of nonstationary multimode dynamics we proposed to use a double-wavelet approach that allows us to detect all spectral components involved in the modulation, estimate their contribution and characterize how the modulation properties are changed in response to changes of system parameters. As indicated by the examples of multimode dynamics listed in the introduction, the domain of applicability for the double-wavelet analysis is very broad. The limitations of the approach were examined by means of simple multimode signals and of nonstationary chaotic dynamics. Despite some spurious effects (that are fairly small and can be taken into account), wavelets allow us to correctly estimate the modulation characteristics even in the case of rather complex multimode dynamics.

We have applied the proposed approach to study the modulation properties in bimodal oscillations of the nephrons of the kidney. Following the obtained results, both normotensive and hypertensive rats show frequency modulation.

We showed that there is a clear difference in the depth of modulation between two rat strains. The genetically hypertensive rats typically demonstrate a deeper modulation in both frequencies and amplitudes. The presence of a strong frequency modulation in the dynamics of nephrons allows us to suppose that a more complex mechanism of flow regulation takes place: regulation is provided not only by a change in the diameters of the active parts of the vessels (i.e., changes of amplitudes), but also by an adjustment of the frequency of myogenic oscillations.

Acknowledgments

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