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QUANTITATIVE ANALYSIS OF CARDIORESPIRATORY SYNCHRONIZATION IN INFANTS

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We investigate the phase synchronization of heartbeat and respiration in a group of healthy infants. Having presented and compared two quantitative measures of synchronization, we conclude that one of these measures — the conditional probability index — allows reliable detection of synchronous epochs of different order $n:m$ and, thus, makes possible an automatic processing of large data sets. In our analysis of experimental time series, we have found numerous epochs of phase synchronization. It turned out that the average degree of synchronization varies with the age of the newborns.

1. Introduction

Generation of rhythms is an inherent property of many physiological systems, of which breathing and heartbeat are the obvious examples. Patterns of autonomic neural regulation of human respiratory and cardiovascular systems are imprinted on these rhythms, therefore their analysis may give insight into the functioning and interaction of these systems.

Both respiratory and cardiac rhythms have been extensively examined with regard to their ability to detect pathological conditions. Different tools of linear and nonlinear univariate time series analysis have been used in numerous attempts to quantify the state of either cardiovascular or respiratory systems and to reveal malfunction [Akselrod *et al.*, 1981; Kluge *et al.*, 1988; Schechtman *et al.*, 1989, 1990; Goldberger & Rigney, 1991; Kurths *et al.*, 1995; Patzak *et al.*, 1996, 1997; Persson, 1997].

Nevertheless, the separate analysis of both rhythms does not seem to be sufficient. Indeed, it is well known that cardiovascular and respiratory systems are not independent. Normally, their interaction is rather weak, its most pronounced manifestation being called respiratory sinus arrhythmia (RSA) [Ludwig, 1847; Saul *et al.*, 1989]. In physical terms, RSA can be regarded as the modulation of heart rate by a respiratory related signal; it has been characterized and analyzed in many studies [Kim & Khoo, 1997; Loula *et al.*, 1997; Koh *et al.*, 1998]. On the other hand, in certain conditions there is apparently a very tight coupling between the circulatory and the respiratory systems. An example is Cheyne–Stokes respiration [Guyton *et al.*, 1956] that is a definite sign of a severe pathology.[1] Appearance of this phenomenon is supposed to be

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[1]This effect can be viewed as a complex modulation of the respiratory activity, so that there are epochs where there is no breathing at all. The Cheyne–Stokes respiration occurs in such situations as intoxication, chronic hypoxemia (low blood oxygen level), and diffuse brain damage.

related to the change of certain parameters of the circulatory system [Guyton *et al.*, 1956; Glass & Mackey, 1988]. Thus, the interdependence of oscillatory activity of respiratory and cardiovascular systems may be physiologically relevant. Therefore, the joint analysis of the two rhythms may provide additional physiological information and may be useful for early detection of malfunctioning.

Coordinated activity of respiratory and cardiovascular systems has been addressed in early work by Hildebrandt, Kenner, Pessenhofer, Raschke, and others [Hinderling, 1967; Engel *et al.*, 1968; Pessenhofer & Kenner, 1975; Kenner *et al.*, 1976; Raschke, 1981, 1987, 1991; Raschke & Hildebrandt, 1987]. In these papers, different *ad hoc* methods have been used and an indication of the $n:1$ synchronization between heartbeat and respiration has been found. For example, Raschke and Hildebrandt [1987] have computed the histograms of ratios of the periods of respiratory and cardiac cycles and found peaks around integers three and four. Synchronization between these systems has been also accessed by analysis of other signals, such as blood pressure and respiration. Koepchen and Thurau [1958] discussed a central neural mechanism for fixed ratio synchronization between blood pressure and respiration. Synchronization between the 0.1 Hz component of blood pressure oscillation and respiration was described by Golenhofen and Hildebrandt [1958].

Recently, several groups addressed different aspects of cardiorespiratory interaction [Hoyer *et al.*, 1997; Schiek *et al.*, 1998; Seidel & Herzel, 1998]. In particular, the concept of phase synchronization was used for this goal [Schäfer *et al.*, 1998, 1999; Toledo *et al.*, 1998]. As a result, different $n:m$ synchronous regimes have been revealed by means of a graphic tool called "cardiorespiratory synchrogram" (CRS), and an attempt was made to assess the cardiorespiratory synchronization quantitatively [Toledo *et al.*, 1998; Rosenblum *et al.*, 2000a, 2000b]. Nevertheless, until now, only a small group of adults (young athletes, normal healthy and heart transplant subjects) have been examined, and it is not clear yet whether synchronization is a typical feature of cardiorespiratory interaction. For example, there are no studies of synchronization phenomena in infants.

Here we discuss the methods that allow to quantify the strength of synchronization from bivariate data. We present the results of a quantitative analysis of cardiorespiratory interaction in a group of 25 healthy newborn babies and address the age dependence of cardiorespiratory synchronization.

2. Quantification of Phase Synchronization

The notion of phase synchronization implies the appearance of some interrelation between suitably introduced phases of two (or many) self-sustained oscillators whereas the amplitudes can be generally uncorrelated; for the introduction to the concept and the references see the tutorial paper in this issue [Pikovsky *et al.*, 2000]. Here we briefly summarize the facts needed in the following for quantification of the synchronization from noisy data.

For two weakly interacting periodic oscillators one can obtain in the first approximation the equations for the phase dynamics:

$$\frac{d\phi_1}{dt} = \omega_1 + \varepsilon g_1(\phi_1, \phi_2)\,, \quad \frac{d\phi_2}{dt} = \omega_2 + \varepsilon g_2(\phi_2, \phi_1)\,, \tag{1}$$

where the phases $\phi_{1,2}$ are defined not on the $[0, 2\pi]$ circle but on the whole real line, the coupling terms $g_{1,2}$ are 2π-periodic in both arguments, and ε is the coupling coefficient. For a general case of $n:m$ locking one can introduce the *generalized phase difference*, or relative phase

$$\varphi_{n,m}(t) = n\phi_1(t) - m\phi_2(t) \tag{2}$$

and obtain for it the equation

$$\frac{d\varphi_{n,m}}{dt} = n\omega_1 - m\omega_2 + \varepsilon G(\phi_1, \phi_2)\,, \tag{3}$$

where $G(\cdot,\cdot)$ is 2π-periodic in both arguments. As it is well known, Eq. (3) admits solutions of two kinds: the relative phase is either unbounded or bounded. The first case corresponds to the quasiperiodic motion with two incommensurate frequencies, whereas a solution of the second type corresponds to phase locking

$$|n\phi_1(t) - m\phi_2(t) - \delta| < \text{const}\,, \tag{4}$$

where δ is some (average) phase shift. We emphasize, that in the synchronous state the relative phase generally oscillates around a constant value; these oscillations vanish only if the coupling depends on the relative phase: $G(\phi_1, \phi_2) = G(n\phi_1 - m\phi_2)$ [Pikovsky *et al.*, 2000].

Noise is inevitable in live systems, and we must take its influence on the phase locking into account. As known [Stratonovich, 1963], noise causes the fluctuations of the relative phase and (sometimes) rapid 2π jumps of $\varphi_{n,m}$ (phase slips). Chaotic systems exhibit qualitatively similar phase dynamics [Rosenblum *et al.*, 1996], so that in the following we do not discuss whether the system we analyze is noisy or chaotic and noisy.

To introduce the quantitative measures of synchronization we consider first the simple case: let the oscillation of the relative phase in the locked state vanish and no noise be present. Then the relative phase is constant, $\varphi_{n,m}(t) = \delta$, if synchronization occurs, and $\varphi_{n,m}(t) \sim (n\omega_1 - m\omega_2)t$, if the motion is quasiperiodic. Respectively, the distribution of the cyclic relative phase $\varphi_{n,m}(t) \bmod 2\pi$ is either a δ-function, or broad. Now we can consider the influence of a weak noise: the distribution becomes smeared, but remains, nevertheless, unimodal [Stratonovich, 1963]. To characterize this distribution, we compute the intensity of its first Fourier mode

$$\gamma_{n,m}^2 = \langle \cos \varphi_{n,m}(t) \rangle^2 + \langle \sin \varphi_{n,m}(t) \rangle^2 , \quad (5)$$

where the brackets denote the average over time [Rosenblum *et al.*, 2000a, 2000b]. The synchronization index γ varies from 0 (no synchronization) to 1 (synchronization in the noise-free case). Due to the noise, γ does not attain unity any more, nevertheless it remains almost 1 in the middle of the synchronization region and continuously decreases with the loss of synchronization.

The situations gets more complicated if in the synchronous regime the relative phase oscillates, so that the general condition (4) must be taken into account. If this oscillation is not negligible then the distribution of $\varphi_{n,m}(t) \bmod 2\pi$ is not unimodal and narrow any more, even in the absence of noise, and the noise makes it practically uniform. This is especially essential if the interaction is not very weak, or if synchronization occurs via modulating (parametric) action of one oscillator on the second one [Schäfer *et al.*, 1999; Rosenblum *et al.*, 2000a, 2000b]. Therefore, the synchronization index γ can be rather small even if the synchronization does occur, and we need another measure of locking. Such a measure can be obtained by means of the stroboscopic approach.

Consider again Eq. (3). For convenience we treat now the cyclic phases $\tilde{\phi}_{1,2} = \phi_{1,2} \bmod 2\pi$. Let us fix the value of the phase of, say, first oscillator at some constant value θ, and observe the phase of the second oscillator for each time t_i when $\tilde{\phi}_1 = \theta$:

$$\eta_i = \tilde{\phi}_2(t)|_{\tilde{\phi}_1(t)=\theta} \, . \quad (6)$$

This is nothing else than the construction of the Poincaré secant surface that reduces Eq. (3) to the well-known circle map. In case of 1:1 phase locking it has a fixed point, so that $\eta_i = \text{const}$; due to the presence of a weak noise the values of η_i are scattered around this constant value. The distribution of η_i can be characterized in a similar way as above by computing the intensity of its first Fourier mode. To improve the statistics, we average over different values of θ. Numerically, it can be done if we introduce a binning for the phase of the first oscillator, compute the estimate of the index for the lth bin as

$$\Lambda_l^2 = M_l^{-2} \left(\sum_{i=1}^{M_l} \cos \eta_i \right)^2 + M_l^{-2} \left(\sum_{i=1}^{M_l} \sin \eta_i \right)^2 , \quad (7)$$

where $l = 1, \ldots, N$, and M_l is the number of points in the corresponding Poincaré section, and average Λ_l over all N bins in order to get a synchronization index

$$\lambda = N^{-1} \sum_{l=1}^{N} \Lambda_l \, . \quad (8)$$

The last step is to generalize the index λ for the case of $n:m$ locking. When the integers n and m are *a priori* known, we expect to observe nm points in the Poincaré section. To focus on any of them alone, we rescale the phases, $\phi_1 \to \phi_1/m$, $\phi_2 \to \phi_1/n$, and use the above described approach in order to obtain the $n:m$ locking index; this rescaling is equivalent to "making" the frequencies of two oscillators equal and thus reducing the problem to the 1:1 case.

According to its definition, $\lambda_{n,m}$ measures the conditional probability for $\tilde{\phi}_2$ to have a certain value provided $\tilde{\phi}_1$ is in a certain bin [Tass *et al.*, 1998], see Fig. 1. One can see, that if the oscillation of the relative phase vanishes, then the indices $\lambda_{n,m}$ and $\gamma_{n,m}$ coincide. In practice, the integers n and m are chosen by trial and error.

We emphasize that appearance of a certain interdependence between phases indicates, strictly speaking, only the presence of coupling between systems, but does not necessarily imply that they are synchronized. Indeed, if the coupling is not sufficient in order to induce synchronization, but

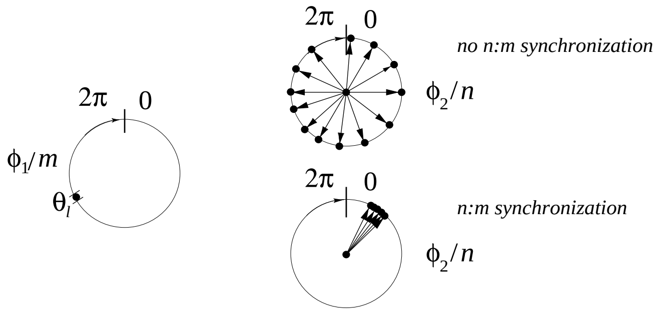

Fig. 1. Synchronization index based on the conditional probability. Phase of the second oscillator ϕ_2 rescaled by n and wrapped onto the circle $[0, 2\pi]$ is observed stroboscopically, i.e. when phase of the first oscillator $\phi_1/m \bmod 2\pi$ is found in the certain bin θ_l of the interval $[0, 2\pi]$. If there is no $n:m$ synchronization then the stroboscopically observed ϕ_2 is scattered over the circle, otherwise it groups around some value. The sum of the vectors pointing to the position of the phase on the circle provides a quantitative measure of synchronization.

close to this threshold value, the distribution of the relative phase is also unimodal.

3. Experimental Data and Preprocessing

We measured the electrocardiograms (ECG) using a bipolar limb lead (Biomonitor 501, Meßgerätewerk Zwönitz, Germany) and obtained thoracic respiration with the inductive plethysmographic method (Respitrace, Studley Data Systems, Oxford, UK) in 25 newborn infants. Measurements were performed on each of the first five days of life, then every week and later monthly up to the sixth month of life.

Data acquisition began 30–60 min after feeding, in the evening hours between 8 p.m. to 11 p.m., and took approximately 1 h. Data were stored on a DAT multichannel recorder (DAT, DTR-1800, biologic, France) for further analysis. The data were offline digitized with a computer based monitoring system (XmAD, ftp://sunsite.unc.edu/pub/Linux/science/lab/) with a sampling rate of 1000 Hz.

An artifact free, 10 min long segment of each measurement was chosen for further analysis. R-waves were detected with the precision of 1 ms by means of a convolution technique applied to a high pass filtered ECG (20 ms moving average) and a typical QRS-template. Instantaneous phase of the ECG was estimated as

$$\phi_h(t) = 2\pi k + 2\pi \frac{t - t_k}{t_{k+1} - t_k}\,, \qquad (9)$$

where t_k are the times of appearance of a kth R-peak.

The respiratory signal was filtered with a high-pass (3 sec length moving average) and a low-pass (50 ms length moving average) filter prior to a resampling at 100 Hz. Instantaneous phases of the respiratory signal were computed by means of the analytic signal approach [Gabor, 1946; Panter, 1965] based on the Hilbert transform; technical implementation of that technique is discussed, e.g. in [Rosenblum & Kurths, 1998; Schäfer *et al.*, 1999]. The instantaneous phases of the respiratory signal were smoothed with the help of a second order Savitzky–Golay filter [Press *et al.*, 1992] of length 1000. Synchronization indices γ and λ were calculated in a sliding window of length 2000 points; the window was moved step by step.

4. Results

We have analyzed 221 records. A typical data set along with the computed synchronization indices is shown in Fig. 2. For visualization of entrainment between heartbeat and respiration we used the phase stroboscope, or synchrogram technique [Schäfer *et al.*, 1999]. Briefly, it can be explained in the following way. The phase of the respiration ϕ_r is observed stroboscopically at the instants t_k of occurrence of the kth R-peak in the ECG. Afterwards, $\phi_r(t_k)$ is plotted versus t_k. In the noise-free case of $n:1$ synchronization (n heartbeats within each respiratory cycle), we would observe n distinct values within one respiratory cycle so that such a plot would exhibit n horizontal lines. In our plots n colors are used in a cyclical order, so that the lines are clearly seen. Noise smears these lines, and some bands are expected to be observed instead. To look for $n:m$ locking one has to use the wrapping of the respiratory phase into $[0, 2\pi m]$ interval, i.e. consider m adjacent oscillations as one cycle, and plot

$$\psi_m(t_k) = \frac{1}{2\pi}(\phi_r(t_k) \bmod 2\pi m) \qquad (10)$$

versus t_k.

We have found a considerable number of epochs, where synchronization of different order $n:m$ occurs; these results are summarized in Table 1. To analyze the efficiency of two indices $\gamma_{n,m}$ and $\lambda_{n,m}$, we compared their values for the epochs where synchronization can be detected by visual inspection of cardiorespiratory synchrograms and by

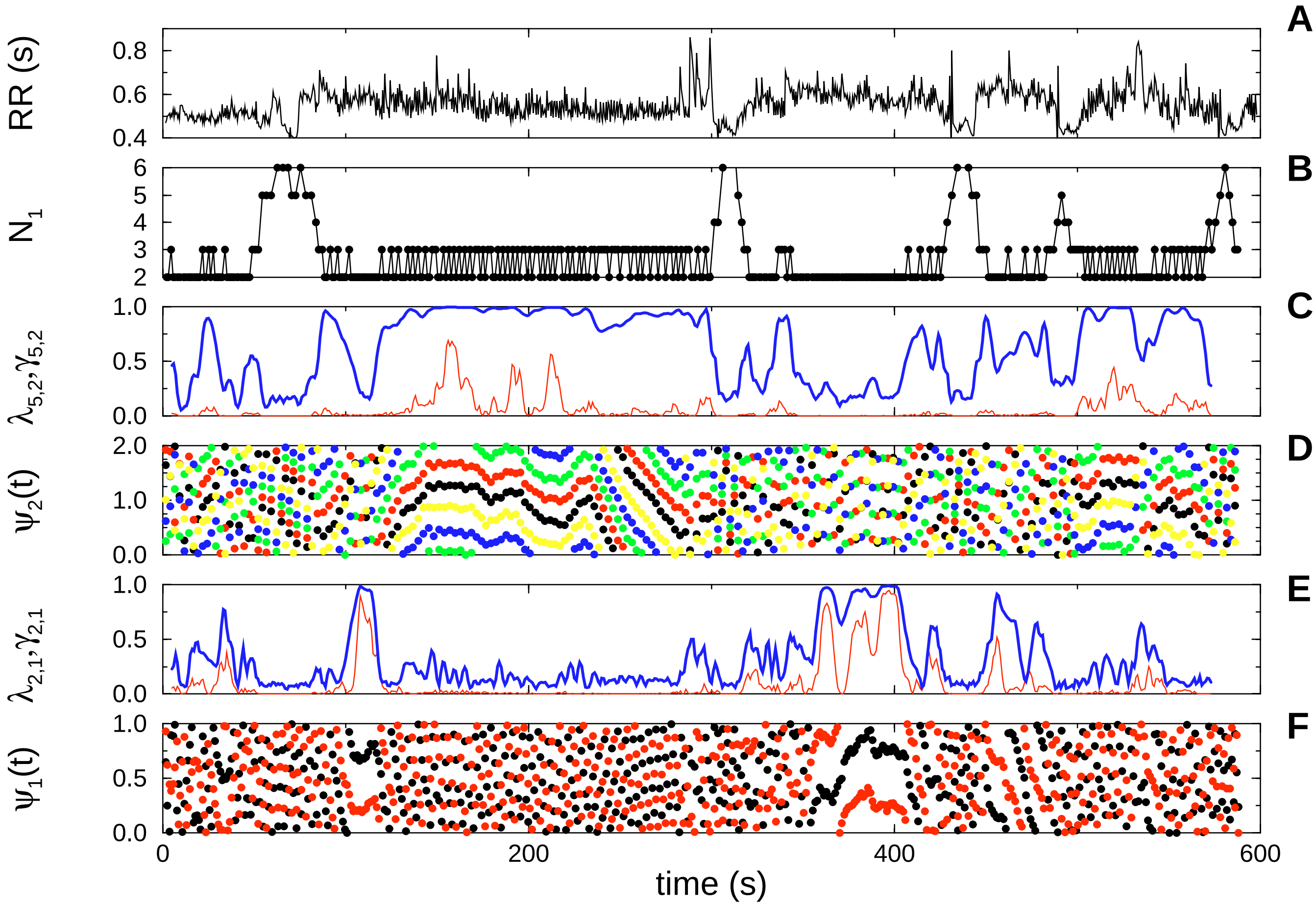

Fig. 2. An example of occurrence of 2:1 and 5:2 synchronization. A: R–R (interbeat) intervals. B: Number of heartbeats per respiratory cycle. C and E: Quantitative measures of $n:m$ synchronization: conditional probability index $\lambda_{n,m}$ (blue) and index $\gamma_{n,m}$ based on computation of the Fourier mode of the distribution of relative phase (red). D and F: Cardiorespiratory synchrograms demonstrating alternating epochs of 2:1 and 5:2 synchronization.

Table 1. The number of epochs of $n:m$ synchronization found in 221 data sets. The rows correspond to the number n of cardiac cycles, whereas the columns correspond to the number m of cycles of respiration. Only the epochs that lasted longer than 20 seconds are counted; synchronization is identified if the conditional probability index $\lambda_{n,m} \geq 0.95$.

	resp. cycle (m)		
R–R cycle (n)	1	2	3
2	3		
3	25	7	
4	39		6
5	15	52	19
7		85	85
8			94
9		82	

counting the number of heartbeats N_1 within each respiratory cycle. We find that the index $\gamma_{n,m}$ is less sensitive than the conditional probability index $\lambda_{n,m}$; this becomes especially essential with the increase of the order of synchronization. So, comparing Figs. 2C and 2D we see that the index $\gamma_{n,m}$ indicates synchronization of order 2:1 but fails to detect the epochs of 5:2 synchronization. Inspection of another data set (Fig. 3), where 4:1 synchronization appears for almost all 10 minutes, shows that the index $\gamma_{n,m}$ drops strongly if a phase slip occurs (the slips can be easily seen in Fig. 3B). Summarizing the comparison of two quantitative measures of synchronization in Table 2, we conclude that reliable detection of synchronous epochs can be achieved by means of the conditional probability index $\lambda_{n,m}$.

Next, we investigate how the occurrence of synchronization depends on the postnatal age. We

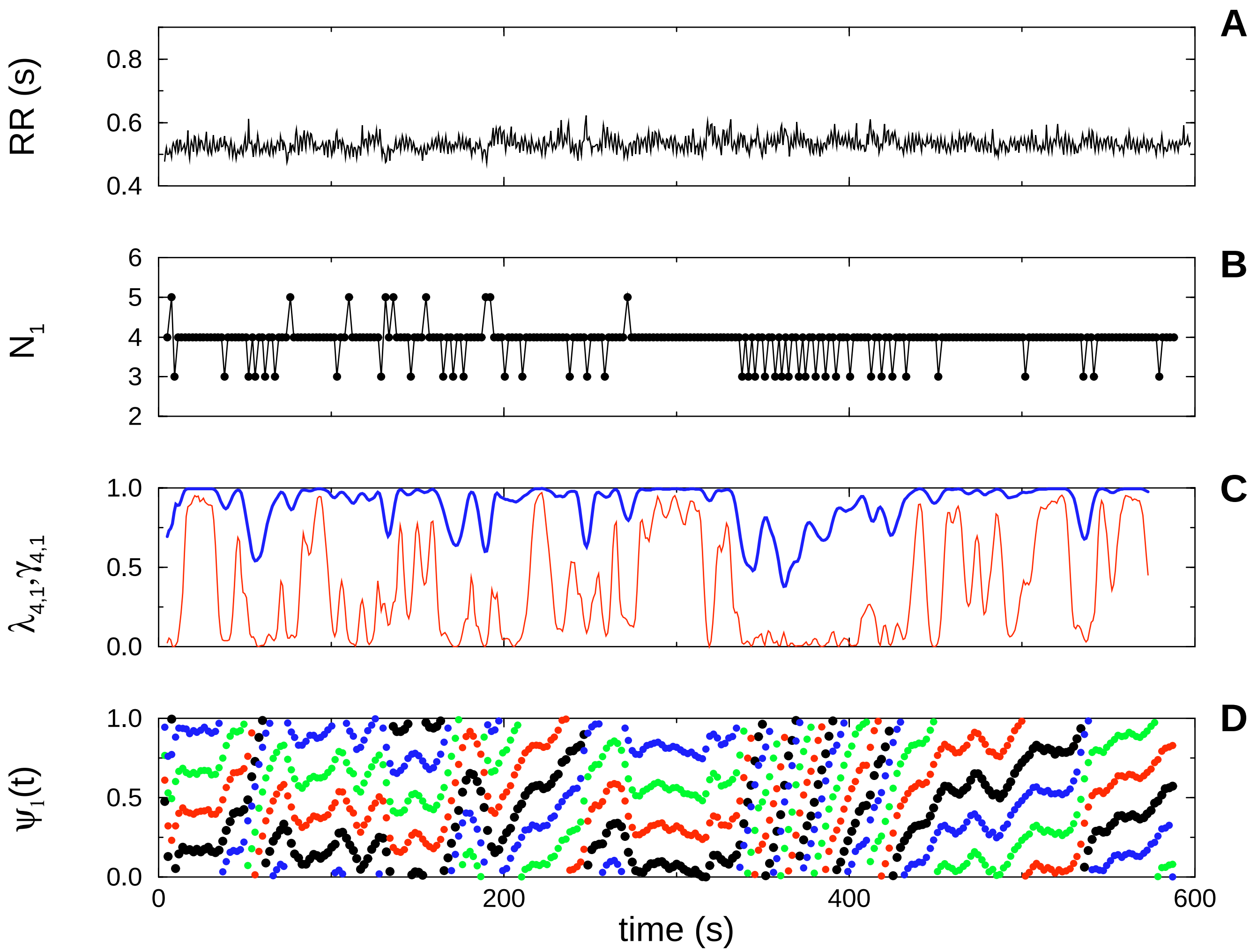

Fig. 3. An example of 4:1 synchronization. A: R–R intervals. B: Number of heartbeats per respiratory cycle. C: Conditional probability index $\lambda_{n,m}$ (blue) and index $\gamma_{n,m}$ (red). D: Cardiorespiratory synchrogram demonstrating long synchronous epochs interrupted by phase slips.

Table 2. Probability of the synchronization index $\gamma_{n,m}$ to be larger than 0.707 provided that $\lambda_{n,m} > 0.95$. The rows correspond to the number n of cardiac cycles, whereas the columns correspond to the number m of cycles of respiration. The results suggest that the index $\gamma_{n,m}$ may not be used for reliable automatic detection of synchronization.

	resp. cycle (m)		
R–R cycle (n)	1	2	3
3	0.744	0	
4	0.391		0
5	0.0317	0	0
7		0.0008	0
8			0
9		0.0081	

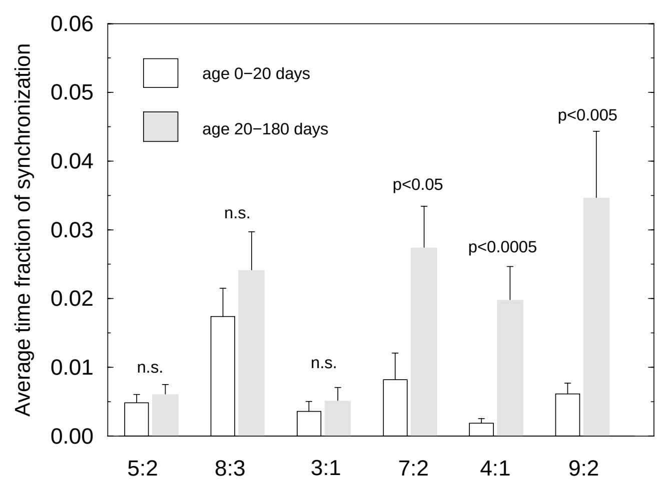

Fig. 4. Average time fraction of $n:m$ synchronization identified by $\lambda_{n,m} > 0.95$ within first 20 days of life and for the age 20–180 days. The error bars indicate the standard error of mean.

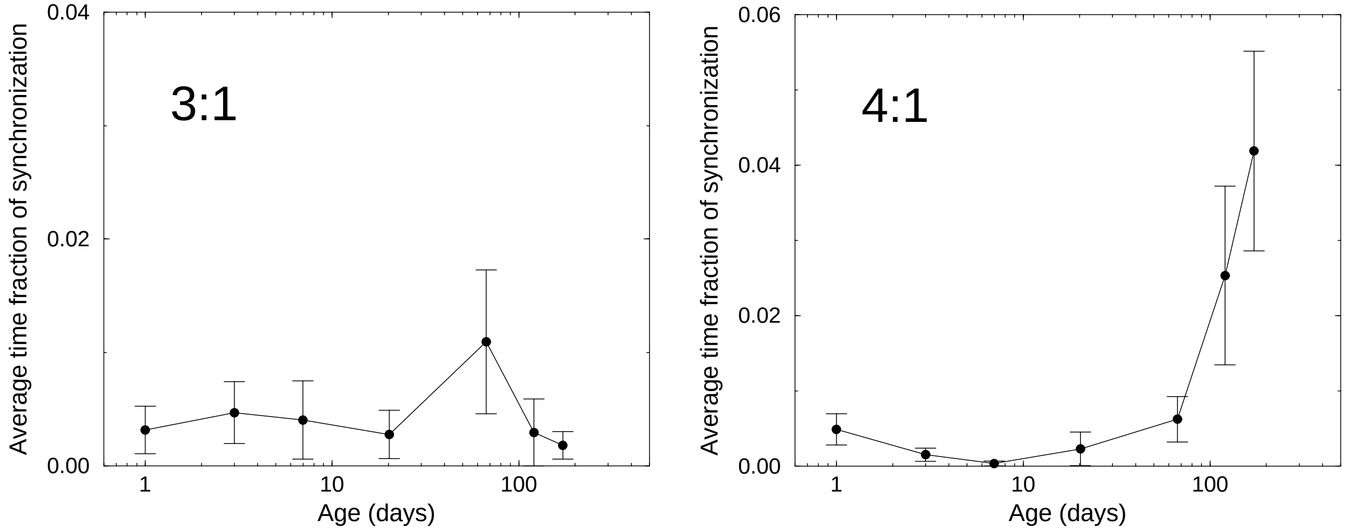

Fig. 5. Average time fraction of 3:1 and 4:1 synchronization as a function of the postnatal age. The error bars indicate the standard error of mean.

have found that the average time fraction of the 7:2, 4:1, and 9:2 synchronization is significantly smaller in the first three weeks of life compared to the fractions at the age from three weeks up to six months. In contrast, the average time fraction of a 5:2, 8:3, and 3:1 synchronization did not show any statistically significant age dependency. These results are summarized in Fig. 4. The detailed age development of the average time fraction for 3:1 and 4:1 synchronization is shown in Fig. 5.

Furthermore, from Fig. 4 it becomes clear that the time fraction where synchronization occurs is small compared to the fraction of nonsynchronized periods. However, in some cases long epochs of synchronization were observed (cf. Fig 3).

5. Discussion and Outlook

The exact physiological mechanisms responsible for cardiorespiratory synchronization are so far poorly understood. There are several levels where the interaction occurs.

First, the frequency of the primary pacemaker of the heart (sino-atrial node) is modulated by the autonomic neural and hormonal control. It is known that the efferent neural activity incorporates the respiratory related rhythms [Jewett, 1964]. Furthermore, there is a mechanical coupling between the systems. In the examinations of the heart transplant patients, in which the neural autonomic control is abolished, it was found that respiratory modulation effects [Slovut *et al.*, 1998] are still present and synchronization is possible [Toledo *et al.*, 1998]. This interaction is thought to originate from the mechanical stretch of the sinus node caused by variation of the intra-thoracic pressure, which in its turn causes the variation of the atrial filling pressure. This breathing dependent stretch alters the electrical properties of the sino-atrial node membrane, and therefore influences the frequency of the heart excitation.

Secondly, the respiratory rhythm is generated in the cardiorespiratory center of the brain stem [Koshiya & Smith, 1999]. The nerves coming from the arterial baroreceptors provide the brain stem with information regarding blood pressure, and, hence, on heart rhythm. Furthermore, it has been found that the baroreceptor reflex depends on the phase of respiration [Seidel *et al.*, 1997]. These are examples of physiological cross-connection between the "generators" of cardiac and respiratory rhythms which may yield synchronization.

Synchronization of heartbeat and respiration in infants occurs in different ratios $n:m$. The typical change in mean heart rate and respiration frequency [Mrowka *et al.*, 1996] after birth may predispose for certain synchronization ratios. The frequency ratio of heartbeat and respiration, recomputed using the data of Mrowka *et al.* [1996], is shown in Fig. 6. This dependence explains the age development of the average time fraction of 3:1 and 4:1 synchronization illustrated in Fig. 5. Indeed, the average frequency ratio is ≈ 2.5 for the age up to 20 days, ≈ 3 for the age from 40 to 80 days, and ≈ 4 for the

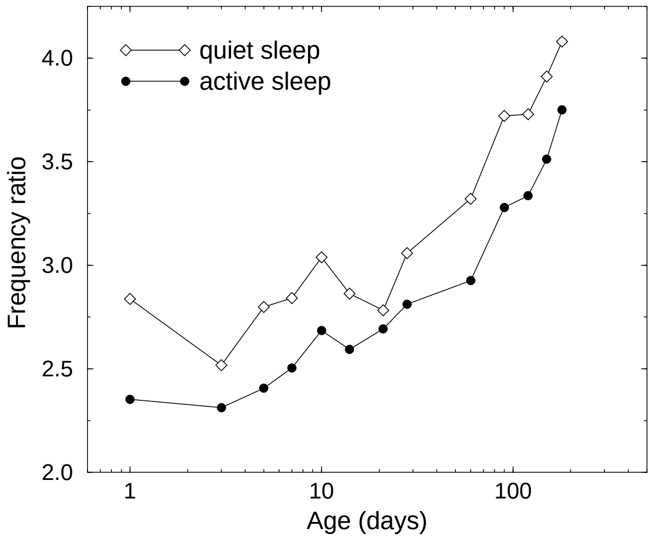

Fig. 6. Average ratio of respiratory frequency and heartrate in dependence on postnatal age shown for different sleep stages. (Recalculated after [Mrowka *et al.*, 1996].)

age after 100 days. Thus, synchronization of order 5:2 is more likely to occur within the first three weeks of life, whereas synchronization of order 4:1 (and with close ratios 7:2 and 9:2) is more probable at the age 20–180 days. On the other hand, analyzing the average occurrence of synchronous epochs shown in Fig. 4, we see that the probability to observe 4:1, 7:2 and 9:2 synchronization is large than the probability to encounter the 5:2 synchronization. Moreover, for any ratio, the probability of synchronization increases with age. Therefore, we conclude that the strength of coupling between respiratory and cardiovascular systems increases with the age of infants.

The duration of epochs of synchronization compared to the nonsynchronous ones is usually rather small,[2] nevertheless in some cases synchronization is a long-lasting effect (see Fig. 3). It is not clear yet whether synchronization is essential for efficient cardiovascular and respiratory control. However, one might speculate that the lack of synchronization might indicate blunted feedback mechanisms or interconnections in pathological conditions, or in individuals at risk. The examination of data originating from different diseased stages may provide understanding of synchronization and its relevance.

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[2]Obviously, the time fraction of synchronization depends on the threshold value of the index that is chosen for the identification of synchronization; the results we present were obtained with a rather high value, $\lambda_{n,m} \geq 0.95$. Additional computations show that this choice is not essential for the analysis of the age dependence of the synchronization occurrence.

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