Reversible Transitions between Synchronization States of the Cardiorespiratory System

A. Stefanovska,[1] H. Haken,[2] P. V. E. McClintock,[3] M. Hožič,[1] F. Bajrović,[4] and S. Ribarič[4]

[1]*Group of Nonlinear Dynamics and Synergetics, Faculty of Electrical Engineering, University of Ljubljana, Tržaška 25, 1000 Ljubljana, Slovenia*

[2]*Center of Synergetics, Institute of Theoretical Physics 1, University of Stuttgart, Pfaffenwaldring 57, 70550 Stuttgart, Germany*

[3]*Department of Physics, University of Lancaster, Lancaster LA1 4YB, United Kingdom*

[4]*Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Zaloška 4, 1000 Ljubljana, Slovenia*

(Received 30 June 2000)

Phase synchronization between cardiac and respiratory oscillations is investigated during anesthesia in rats. Synchrograms and time evolution of synchronization indices are used to show that the system passes reversibly through a sequence of different phase-synchronized states as the anesthesia level changes, indicating that it can undergo phase transitionlike phenomena. It appears that the synchronization state may be used to characterize the depth of anesthesia.

PACS numbers: 87.19.Hh, 05.45.Tp, 05.45.Xt, 87.19.Uv

Whenever two or more oscillatory processes are weakly coupled, there exists the possibility of their becoming synchronized. It is a scenario that is ubiquitous in nature, including living systems where rhythmic processes take place on widely differing time scales, ranging from milliseconds for single cell activity up to years for ecological changes.

Living systems are becoming increasingly accessible to mathematical modeling using the methods of dynamical systems theory. However, they are inherently nonstationary, being characterized by many oscillatory processes whose frequencies also change in time. The fact that they are quasiperiodic (with several characteristic frequencies) and nonstationary makes them difficult to study since, strictly, most of the methods for linear and nonlinear time series analysis require stationarity. The recently proposed concept of phase-synchronization analysis of noisy nonstationary bivariate data [1,2] provides a promising method for reconstructing their dynamics.

In this Letter we use the concept of synchronization to analyze interactions between cardiac and respiratory oscillations during general anesthesia in rats. Under resting conditions, the cardiovascular-respiratory system has been shown to be characterized by oscillatory processes on multiple time scales in both humans [3] and rats [4]. It has long been recognized that heart and respiratory activity interact, leading, e.g., to frequency modulation of the heart rate by respiration, known as respiratory arrhythmia [5]. The adjustment of the rhythms of the two oscillators may be expected to give rise to synchronization.

Early studies of the dynamics of coordinated activity between the respiratory and cardiovascular systems [6,7] assumed they behaved as almost periodic oscillators. Histograms of ratios of their periods were analyzed and, for example, an n:1 synchronization between the cardiac and respiratory rhythms was found in healthy subjects during sleep [7]. Entrainment was also found to occur in anesthetized rabbits [6] and humans [8]. It was proposed that synchronization (or, as named, frequency and phase coordination) establishes a system of economical coaction and thus favors the functional economy of the organism [7]. In another study, however, only weak coupling between cardiac and respiratory rhythms was found and it was concluded that the two rhythms are generally not phase locked [9].

The development of nonlinear methods has brought new attention to this problem [10]. Recently, using the concept of synchronization analysis in chaotic, noisy, and nonstationary oscillators, episodes of phase synchronization between cardiac and respiratory oscillations were observed in resting humans [11]. Cardiorespiratory synchronization during paced respiration [12] and heart synchronization to external stimuli [13] were also demonstrated. It appears that the degree of synchronization at rest differs in athletes (synchronization periods $\sim$1000 s [11]) and nonathletes ($\sim$100 s [14]), and is inversely related to the extent of frequency modulation of the heart rate. Therefore, we may expect that a better understanding of phase and frequency relations among the oscillatory processes involved in blood circulation may lead to deeper insight into the state of the system, with corresponding diagnostic possibilities.

Here we investigate phase synchronization during the state of anesthesia in rats, which in practice can be studied under more precisely controlled conditions than are usually possible for humans. It has been shown that the dynamics of the cardiovascular-respiratory system in rats [4] possesses similar features to those observed in humans, despite the cardiac and respiratory rhythms in rats being approximately 4 times faster than in humans. Moreover, during anesthesia in rats, respiration need not be assisted. This is an important point, as paced respiration has already been shown to influence the state of cardiorespiratory synchronization [12].

The electric activity of the heart (EKG) and excursions of the thorax, which are proportional to respiratory activity [15], were noninvasively recorded (Fig. 1) while the breathing remained spontaneous and unassisted. Using a 16 bit A/D converter, each time series was digitized at

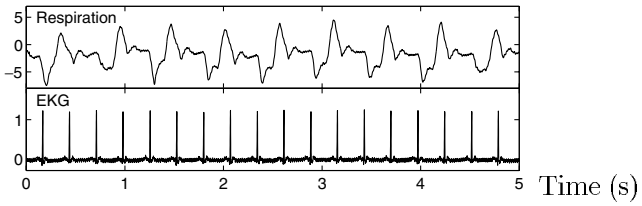

FIG. 1. Extracts from typical respiratory and EKG signals recorded from a rat in anesthesia. The y axes are in arbitrary units.

a sampling rate of 2000 Hz and recorded over the entire duration of anesthesia (~120 min). Recording started 5–10 min after anesthetic drugs [16] were injected and ended 5–10 min after the first signs of recovered reflex responses, detected by a skin pinch test [17], were observed. Five rats were recorded in the same way. On each animal the recording was repeated after one week, using the same anesthetics and concentrations. The synchronization analysis presented below revealed the same pattern in all animals and was well reproduced in the second recording in each case.

The instantaneous cardiac, f_h, and respiratory, f_r, frequencies and their ratio were first calculated. To calculate the instantaneous frequency the marker events method was used. The times of R peaks in the EKG signal and maxima of inspiration were taken as markers. Peaks were detected automatically and also manually checked. One oscillatory cycle was determined as the interval between two consecutive peaks in each time series, at times t_k and t_{k+1}. The instantaneous frequency was taken to be $f(t) = \frac{1}{t_{k+1}-t_k}$, and set constant within one cycle. In this paper, we use the same method to calculate the relative cyclic phase.

Both frequencies were found to undergo dramatic changes during the anesthesia (Fig. 2). During the first ~25 min, f_h decreases from 4 to 3.2 Hz; it then increases and decreases again and, after ~70 min, varies randomly between 3.5 and 4.5 Hz. The f_r slowly decreases from 2 to ~0.8 Hz until at ~40 min, it begins to increase again; it returns to its initial value of 2 Hz at ~70 min, at which point it becomes highly variable, between 1 and 4 Hz. Consequently, f_h/f_r first increases, from 2 to 5, then decreases back to 2 (top graph in Fig. 3), and as the effect of the anesthetic drugs vanishes it becomes highly variable, spanning a wide amplitude range, between 1 and 4.

The instantaneous cyclic relative phase between cardiac and respiratory activity was then calculated. This quantity has been discussed in several recent papers [1,2,11,18] but, briefly, the underlying idea is as follows. Classically, synchronization of two periodic nonidentical oscillators is understood as an adjustment of their rhythms, or locking (entrainment) of their phases, $\varphi_{n,m} = n\phi_1 - m\phi_2 =$ const, where ϕ_1 and ϕ_2 are phases (here defined on the whole real line and not on the circle $[0, 2\pi]$), n and m are integers, and $\varphi_{n,m}$ is the generalized phase difference, or relative phase. In this simplest case, the condition for phase locking is equivalent to the notion of frequency

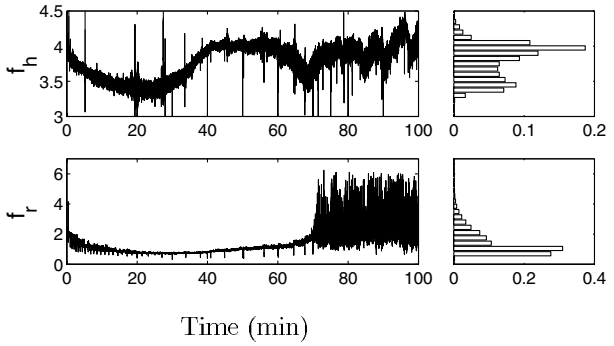

FIG. 2. Evolution of the instantaneous cardiac and respiratory frequencies during the period of anesthesia. The right-hand column shows the corresponding distributions.

locking $nf_1 = mf_2$, where $f_{1,2} = \langle \dot{\phi}_{1,2} \rangle$ and the brackets mean time averaging. If n periods of the first oscillator have exactly the same duration as m periods of the second one, the rhythms are n:m entrained.

Recently, the concept of synchronization was generalized to chaotic systems [19] and synchronizationlike

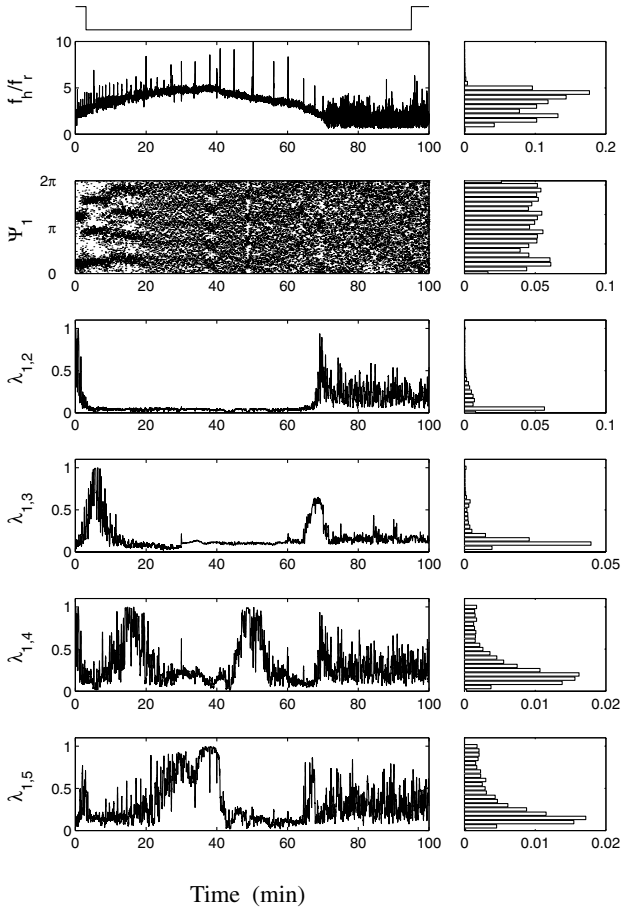

FIG. 3. Evolution of phase-synchronization measures during anesthesia. Top to bottom: frequency ratio, cardiorespiratory synchrogram, and 1:2, 1:3, 1:4 and 1:5 synchronization indices, respectively. Occurrence of 1:n synchronization is demonstrated both by the appearance of n plateaus in Ψ_1 and by $\lambda_{1,n}$ approaching unity. The reflex responsiveness from the skin pinch test [17] is given at the top.

phenomena have also been reported in purely stochastic systems, where the noise controls a characteristic time scale [20]. For noisy, chaotic systems and/or systems with modulated natural frequencies a weaker condition of phase synchronization, $|\varphi_{n,m}| = |n\phi_1 - m\phi_2 - \delta| < \text{const}$, where δ is some (average) phase shift, was introduced [1,2]. Accordingly, synchronization is understood as the appearance of peaks in the distribution of cyclic relative phase $\Psi_{n,m} = \varphi_{n,m} \bmod 2\pi$ and interpreted as the existence of a preferred stable value of phase difference between two oscillators. In such a case, the n:m phase locking is manifested as a time variation of $\Psi_{n,m}$ around a horizontal plateau.

In analyzing synchronization, the integers n and m should both be determined. In the case of two interacting noisy oscillatory processes, n and m change in time. One possibility (similar to an earlier proposed method of entrainment analysis [6]), known as the phase stroboscope, or synchrogram, is to fix the value of m and observe changes of n in time [11]. Accordingly, the cardiorespiratory synchrogram is constructed by plotting the normalized relative phase of a heartbeat within m respiratory cycles, $\Psi_m = \frac{1}{2\pi}(\phi_r(t_k) \bmod 2\pi m)$, where t_k is the time of kth heartbeat and ϕ_r is the instantaneous phase of respiration.

Here we focus on phase synchronization for $m = 1$ since, for most of the time, an integer value of the instantaneous frequency ratio was observed. We calculated the normalized relative phase, Ψ_1, directly from the measured data, exploiting the fact that both signals contain sharp peaks that clearly mark the instantaneous cycles (see Fig. 1). Each successive peak was marked as an equivalence of one oscillatory cycle, corresponding to which a 2π increment was added. The instantaneous phase is then

$$\phi(t) = 2\pi \frac{t - t_k}{t_{k+1} - t_k} + 2\pi k, \qquad t_k \le t < t_{k+1}, \quad (1)$$

where t_k is time of kth marker event. Defined in this way the phase is a monotonically increasing piecewise-linear function of time defined on the real line.

Usually, the first step in searching an n:m locking is to look for horizontal plateaus in Ψ_1, revealing the value of n in cases when synchronization exists. The distribution of $\Psi_{n,m}(t)$ is then a δ function, smeared in the presence of noise. For strongly nonlinear oscillators it can be nonuniform even in the absence of noise [2]. To characterize the strength of synchronization we therefore need a robust quantitative measure. Since in noisy systems phase synchronization can be understood in a statistical sense as the existence of preferred values of generalized phase difference, measures based on quantifying the distribution of phases

$$\eta = \phi_2 \bmod 2\pi n|_{\phi_1 \bmod 2\pi m = \theta} \quad (2)$$

were proposed. We will use an index based on conditional probability which was introduced in [18] and was shown to facilitate reliable detection of synchronous epochs of different order n:m [21]. Accordingly, the phase of the second oscillator is observed at fixed values of the phase of the first oscillator, θ. The interval of each phase ϕ_1 and ϕ_2, $[0, 2\pi m]$ and $[0, 2\pi n]$, respectively, is divided into N bins. The values of $\phi_1 \bmod 2\pi m$ that belong to bin l are denoted as θ_l, while the number of points inside this bin is denoted as M_l, and, by using Eq. (2), M_l values of $\eta_{j,l}$, $j = 1, \ldots, M_l$, are calculated.

If there is no synchronization between the oscillators, a uniform distribution of $\eta_{j,l}$ can be expected on the interval $[0, 2\pi n]$, or else it clusters around a certain value resulting in a unimodal distribution. Hence, the distribution is quantified as $r_l(t_k) = \frac{1}{M_l(t_k)} \sum_{i=1}^{M_l(t_k)} e^{i\phi_2(t_j)}$ for each j when $\phi_1(t_j)$ belongs to the lth bin and $t_k - t_p/2 \le t_j < t_k + t_p/2$. $M_l(t_k)$ is the number of points in this bin at the kth instant. An average over 10 periods, t_p, of the slower oscillator was used [18]. Where the phases are completely locked, or completely unlocked we obtain $|r_l(t_k)| = 1$ or $|r_l(t_k)| = 0$, respectively.

To improve reliability, we also calculate the average over all bins and obtain the index of synchronization $\lambda_{n,m}(t_k) = \frac{1}{N} \sum_{l=1}^{N} |r_l(t_k)|$. Accordingly, $\lambda_{n,m}$ is a measure of the conditional probability that ϕ_2 has a certain value within lth bin when ϕ_1 belongs to this bin.

Some typical results are shown in Fig. 3. The synchrogram, $\Psi_1(t)$, indicates immediately that several phase-synchronization states occur during anesthesia. This is confirmed by time evolutions of the synchronization indices, $\lambda_{1,n}$, which were obtained using a sliding window with $t_p = 8$ s. Three distinct stages during anesthesia may be distinguished from the evolutions of f_h/f_r, Ψ_1, $\lambda_{1,2}$, $\lambda_{1,3}$, $\lambda_{1,4}$, and $\lambda_{1,5}$. Stage 1, 0–40 min from the start of recording, may be defined as the interval during which the frequency ratio increases. Stage 2 of the recording (40–70 min) is where the frequency ratio decreases again. Stage 3 consists of the interval (70–100 min) in which the frequency ratio is hugely variable around a steady value. These same three stages were observed in all recordings, which lasted between 70 and 130 min (until the rat started to run freely).

During stage 1 all four states of synchronization, 1:2, 1:3, 1:4, and 1:5, are clearly present and gradually switch one into the other. The 1:2 phase-locked state seems to be observed for as long as a reflex response (tested by skin pinch test [17]) can still be obtained (depicted at the top of the figure). Approximately at the time when the reflex disappears, the transition to 1:3 phase locking starts, which then changes into 1:4 locking, followed by 1:5 locking. One possible explanation is that nerve conductivity decreases during this initial state of anesthesia, and this causes changes of the overall nervous control of the cardiorespiratory system, which then results in a series of phase-synchronized states.

As the effect of the drugs starts to decline, the phase-synchronization states switch back in reverse order. The strength of phase synchronization is slightly weaker on the way out of anesthesia than during entry. Shortly before the

end of anesthesia (stage 3), phase synchronization becomes very weak.

In conclusion, we have shown that the cardiac and respiratory systems possess dynamical properties and couplings that can synchronize their oscillations in a hierarchy of different phase-locked states. Kinetic phase transition phenomena between these states are reminiscent of those seen and analyzed in detail for physical systems such as lasers [22]. During the course of anesthesia, the transitions are found to occur in a reproducible sequence, suggesting that the state of synchronization may provide a potentially useful measure of the depth of anesthesia at any moment. Given the similarities in cardiorespiratory dynamics, in f_h/f_r, and in other characteristic frequency ratios for humans and rats [3,4], it seems plausible that similar results may also apply to humans.

This study was supported by the Slovenian Ministry of Science and Technology, and the Slovenian-German Scientific-Research Project Collaboration. A. S. was partially supported by the Royal Society of London. We thank P. A. Tass for valuable comments on the manuscript.

[1] A. S. Pikovsky, M. G. Rosenblum, and J. Kurths, Europhys. Lett. **34**, 165 (1996); M. G. Rosenblum, A. S. Pikovsky, and J. Kurths, Phys. Rev. Lett. **76**, 1804 (1996); M. G. Rosenblum, A. S. Pikovsky, and J. Kurths, *ibid.* **78**, 4193 (1997); A. S. Pikovsky, M. G. Rosenblum, G. V. Osipov, and J. Kurths, Physica (Amsterdam) **104D**, 219 (1997).

[2] M. G. Rosenblum, A. S. Pikovsky, C. Schäfer, P. Tass, and J. Kurths, in *Handbook of Biological Physics,* edited by S. Gielen and F. Moss [Elsevier Science, New York (to be published)].

[3] P. Ch. Ivanov, L. A. N. Amaral, A. L. Goldberger, S. Havlin, M. G. Rosenblum, Z. Struzik, and H. E. Stanley, Nature (London) **399**, 461 (1999); A. Stefanovska and M. Bračič, Contemp. Phys. **40**, 31 (1999); M. Bračič, P. V. E. McClintock, and A. Stefanovska, in *Stochastic and Chaotic Dynamics in the Lakes,* edited by D. S. Broomhead, E. A. Luchinskaya, P. V. E. McClintock, and T. Mullin (AIP, New York, 2000), pp. 146–153.

[4] F. Bajrović, M. Čenčur, M. Hožič, S. Ribarič, and A. Stefanovska, Eur. J. Phys. **439**, R158 (2000).

[5] S. Hales, *Statistical Essays II, Haemastatisticks* (Innings Manby, London, 1773); C. Ludwig, Arch. Anat. Phys. **13**, 242 (1847); C. T. M. Davies and J. M. M. Neilson, J. Appl. Phys. **22**, 947 (1967); J. A. Hirsch and B. Bishop, Am. J. Phys. **241**, H620 (1981).

[6] H. Passenhofer and T. Kenner, Pflügers Archiv. **355**, 77 (1975); T. Kenner, H. Passenhofer, and G. Schwaberger, *ibid.* **363**, 263 (1976).

[7] G. Hildebrandt, in *Temporal Disorder in Human Oscillatory System,* edited by L. Rensing, U. an der Heiden, and M. C. Mackey (Springer, Berlin, 1987), pp. 160–174; F. Raschke, *ibid.,* pp. 152–158; F. Raschke, in *Rhythms in Physiological Systems,* edited by H. Haken and H. P. Koepchen (Springer, Berlin, 1991), pp. 155–164.

[8] D. C. Galletly and P. D. Larsen, Br. J. Anaesth. **79**, 35 (1997).

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

[10] D. Hoyer, O. Hader, and U. Zwiener, IEEE Eng. Med. Biol. **16**, 97 (1997); M. Schiek, F. R. Drepper, R. Engbert, H.-H. Abel, and K. Suder, in *Nonlinear Analysis of Physiological Data,* edited by H. Kantz, J. Kurths, and G. Mayer-Kress (Springer, Berlin, 1998), pp. 191–209.

[11] C. Schäfer, M. G. Rosenblum, J. Kurths, and H. H. Abel, Nature (London) **293**, 239 (1998); C. Schäfer, M. G. Rosenblum, H. H. Abel, and J. Kurths, Phys. Rev. E **60**, 857 (1999).

[12] H. Seidel and H. P. Herzel, IEEE Eng. Med. Biol. **17**, 54 (1998).

[13] V. S. Anishchenko, A. G. Balanov, N. B. Janson, N. B. Igosheva, and G. V. Bordyugov, in *Stochastic and Chaotic Dynamics in the Lakes,* edited by D. S. Broomhead, E. A. Luchinskaya, P. V. E. McClintock, and T. Mullin (AIP, New York, 2000), pp. 162–167.

[14] M. Bračič Lotrič and A. Stefanovska, Physica (Amsterdam) **283A**, 451 (2000).

[15] A piezoelectric sensor was inserted into a rigid strap which was wrapped around the thorax.

[16] Experiments were performed on adult male Wistar rats under general anesthesia with ketaminhydrochlorid 100 mg/kg b.w. and xylazinhydrochorid 20 mg/kg b.w., administered in a bolus, intraperitoneally. During the recording the animal was placed on a homeothermic operating table that enabled the body temperature to be kept constant at 37 °C.

[17] The depth of anesthesia was assessed at 5-min intervals, starting from the moment at which the drugs were applied, by the animal's response to touch and to painful stimulus with the skin pinch test. The plantar surface of the animal's hind paws was stroked with the tip of a pair of tweezers (touch stimulus) or pinched (pain stimulus). The tests were considered positive if the animal responded by flexing its fingers or withdrawing its limb and were not perturbative to any of the quantities analyzed (see Figs. 2 and 3).

[18] P. Tass, M. G. Rosenblum, J. Weule, J. Kurths, A. S. Pikovsky, J. Volkmann, A. Schnitzler, and H.-J. Freund, Phys. Rev. Lett. **81**, 3291 (1998).

[19] L. M. Pecora and T. L. Carroll, Phys. Rev. Lett. **64**, 821 (1990); L. Kocarev and U. Parlitz, *ibid.* **74**, 5028 (1995); N. F. Rulkov, M. M. Sushchik, L. S. Tsimring, and H. D. I. Abarbanel, Phys. Rev. E **51**, 980 (1995).

[20] A. Neiman, Phys. Rev. E **49**, 3484 (1994); B. Shulgin, A. Neiman, and V. Anishchenko, Phys. Rev. Lett. **75**, 4157 (1995); A. Longtin and D. R. Chialvo, *ibid.* **81**, 4012 (1998).

[21] R. Mrowka, A. Patzak, and M. Rosenblum, Int. J. Bifurcation Chaos Appl. Sci. Eng. (to be published).

[22] H. Haken, *Laser Theory* (Springer, Berlin, 1970); H. Haken, *Synergetics, An Introduction* (Springer, Berlin, 1983).