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Synchronization of Cardiorhythm by Weak External Forcing

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We study the possibility to synchronize cardiorhythm of a human by periodic and aperiodic sequences of light and sound pulses. Aperiodic forcing is defined by variation of RR intervals of another subject. Phase locking between cardiorhythm and *weak* external forcing is detected on finite time intervals. We observe the 1 : 1 synchronization for periodic forcing and *n* : *m* synchronization for aperiodic one.

Keywords: Self-sustained systems, Forced synchronization, Cardiorhythm, Phase synchronization, Effective synchronization

1 INTRODUCTION

One of the brightest examples of self-organization in nature is synchronization. The latter is often understood as coordination in time of processes in coupled or forced self-oscillatory systems being a manifestation of their nonlinear and dissipative properties [1–3].

In systems with irregular dynamics one can find a large variety of forms of synchronization. In a series of papers [4–6] synchronization is associated with complete or almost complete coincidence of states of interacting systems. In systems with dynamical chaos born as a result of period-doubling bifurcations synchronization displays itself as locking of their "basic" frequencies, the latter term meaning some frequency typical for the given system which is related with one of the spectrum peaks.

In [7] for the interacting (or forced) systems instantaneous phases $\Phi_1(t)$ and $\Phi_2(t)$ were introduced using the concept of analytic signal [8]. In these terms if the oscillations of subsystems are synchronous the difference of their instantaneous phases obeys the following expression:

$$|(m\Phi_1(t) - n\Phi_2(t)) - C| < \epsilon_1, \qquad (1)$$

where ϵ_1 is some small constant ($\epsilon_1 < 2\pi$), i.e., phase difference oscillates around some average value $C = \langle m\Phi_1(t) - n\Phi_2(t)\rangle$.

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In reality noise is unremovable and influences synchronization. In [9] Stratonovich studied in detail the behavior of self-sustained periodic oscillators forced harmonically in the presence of Gaussian white noise. He has shown that due to noise phase difference between the forcing and response fluctuates and from time to time "jumps" by 2π, the latter meaning that relation (1) is valid only during finite time intervals. With this, for the noise-affected systems the notion of "effective synchronization" [10] is often used being associated with the decrease of frequency and phase fluctuations. To detect synchronization in the presence of noise in [11,12] it was suggested to use the so-called effective diffusion [9].

In fact, synchronization in the above sense means the increase of coherence between the processes in coupled subsystems. Note, that synchronization phenomena are possible only in self-sustained systems. However, a similar effect can take place in systems whose oscillations are induced by noise. As shown in [13] coupling between such systems can lead to the increase of coherence between their oscillations. A stochastic system can be also synchronized by external forcing [14]. Moreover, the phenomena similar to those discovered in self-sustained systems are observed in biological systems. For instance, [15] reports about synchronization between respiration and electrocardiogramme of a human. In [16] it is demonstrated that encephalogrammes measured from different parts of the human brain can be synchronous. On the other hand, intrinsic processes of an organism can be synchronized by external forcing. Neiman *et al.* [17] have shown that weak external noisy forcing can synchronize an ensemble of neural electrosensitive cells of a fish. In [18] it was shown that periodic variation of glucose concentration in the blood of a human leads to synchronous variation of insulin concentration. In [19] synchronization of cardiorhythm by respiration is observed in pregnant women who were suggested to breath periodically with frequency close to 1 Hz.

All these results testify to the principal role of synchronization in the processes occurring in biological systems. However, the above works report about mutual synchronization between different subsystems of the same organism or about synchronization by rather strong forcing applied directly to the mechanisms governing oscillations. The question remains open if it is possible to synchronize the main rhythms of an organism by means of *weak indirect* non-invasive forcing. The aim of the present work is to demonstrate the possibility to synchronize cardiorhythm of a human by either periodic or irregular sequence of sound and light pulses.

2 METHODS OF EXPERIMENTS

The problem is to reveal the response of cardiovascular system of a human to external forcing of the simplest shape. For this purpose the external forcing is chosen to be the sequence of rectangular pulses, whose duration is small comparing to the interval between them. For convenience (not to take into account individual peculiarities of the shape of P, Q, R, S, T peaks of different people) the system's response was presented as the sequence of pulses (R peaks).

Each experiment had two stages. First, ECG of a subject in rest state was registered from I, II and III standard leads during 10 min with the sampling frequency 180 Hz from which RR intervals T_i defining cardiorhythm (time intervals between the two successive R peaks, Fig. 1(a)) were extracted in the absence of external forcing. Second, ECG (and the corresponding RR intervals) of the subject under external forcing was registered also during 10 min.

External forcing was realized as follows. With the help of a computer a sequence of sound and light pulses was generated with duration $\tau = 0.1$ s (Fig. 1(b)), the time intervals between them being fixed in case of periodic forcing and varied in case of aperiodic forcing. Sound was generated by the speaker of a computer, and the light pulse looked as a red square appearing on the screen.

The forcing was either periodic with the period close to the average RR of the same subject at rest

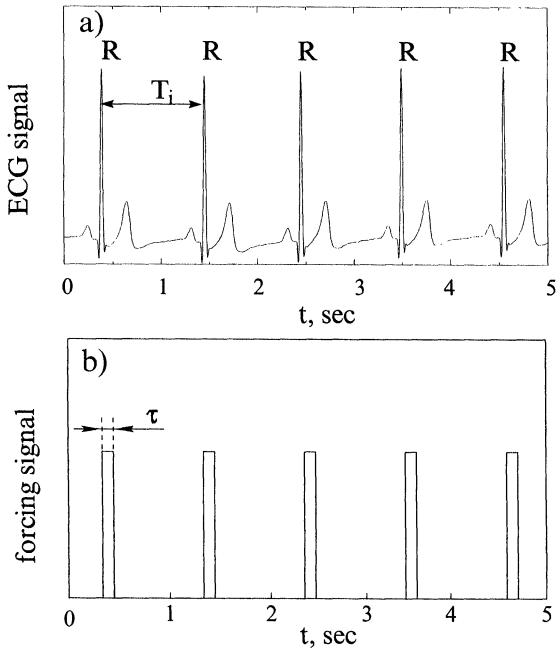


FIGURE 1 (a) Typical human electrocardiogramme; (b) Forcing signal.

conditions, or aperiodic with instantaneous periods coinciding with the RR intervals of another subject. In the course of examination the patients looked at the screen of the computer sitting in the armchair. The intensity of external forcing was chosen to be small not to cause noticeable changes in the work of cardiovascular system (CVS), namely, marked speeding up of heart rhythm, the increase of stroke volume and blood pressure. From this point of view the applied forcing can be considered as weak.

3 EXPERIMENTAL RESULTS

As a result, for every subject two signals were obtained, namely, the RR sequences in rest state and under forcing. The third signal of interest was the forcing signal itself. Our task was to establish the degree of synchronism between the forcing signal and the signal of response of CVS. With this, the signal, measured from a patient at rest was used to evaluate the reliability of results.

Detection of phase locking in oscillators with complex (irregular) dynamics requires definition of instantaneous phase. In case when phase portrait of the system under study has obviously band structure the phase can be introduced via the times t_i of trajectory return to some secant surface (Poincare secant) as it was suggested, e.g. in [7].

$$\Phi(t) = 2\pi\frac{t - t_i}{t_{i+1} - t_i} + 2\pi i, \quad t_i < t < t_{i+1}, \quad i = 1, 2, \ldots \tag{2}$$

The phase portrait reconstructed from ECG by delay technique [20] has a band structure. By the way of construction the RR intervals are return times as well as the current intervals between the fronts of the pulses of the forcing signal. Thus, in our experiments we can define the phase using (2).

Since we deal with real systems which are unavoidably polluted by noise we can expect the phenomenon of phase locking on only finite times, i.e., effective synchronization. In such a regime instantaneous phase difference between signals is bounded and during a certain time interval varies slightly, the latter corresponding to the phase locking. However, it is known that in systems with irregular dynamics the behavior of phase difference can contain alternating segments of phase locking and the segments during which the phase difference changes rather quickly [21]. In this case the time intervals when the locking takes place will be seen as so-called "plateaus".

We can evaluate the degree of synchronism by computing the average duration of "plateaus" on the dependence $(n/m)\Phi_1(t) - \Phi_2(t)$ (were $n:m$ is the ratio of basic frequencies in the spectra of signals under comparison) which characterizes the average time of phase locking and is somehow equivalent to the estimation of effective diffusion.

To be sure that the existence of above plateaus is not caused by accidental correlations between the signals under study, the similar dependence was calculated for the forcing signal and the signal measured from the same individual at rest (before forcing). But in the latter case the phase difference was found between these signals taken with such

time shift v against each other that the dependence $(n/m)\Phi_1(t) - \Phi_2(t+v)$ had the plateaus of maximal durations. A segment of the plot was considered to be a plateau if it did not contain trend and the absolute value of deviation of every point from the average did not exceed $\pi/2$.

Thus, if as a result of forcing the duration of every "plateau" and their total duration exceed their possible maximal "accidental" values we can speak about external synchronization of cardiorhythm, or the phenomenon of cardiorhythm instantaneous phase locking by external signal.

From the classical oscillations theory it is known that for finite amplitudes of forcing there should exist a synchronization region of finite width. Therefore, to study the 1 : 1 synchronization of cardiorhythm, i.e., the case when $m = n = 1$, the frequency of pulses of external periodic forcing was chosen to be either equal to the average heart rate (AHR) of a patient, or differing from AHR by $\pm 25\%$.

A typical result for the case without frequency detuning, i.e., when the frequency of forcing signal equals precisely to the AHR of the patient is shown in Fig. 2(a). Here curve 1 reflects the coherence between the forcing signal and the patient's ECG for zero detuning, curve 2 characterizes accidental correlations between the forcing signal and the original signal when $n : m = 1 : 1$, $v = 0$.

As seen from the plots, the phase locking is detected during the time intervals $t \geq 150$ s, even in this case being reliably higher than the time of accidental correlations ($t \approx 60$ s). Note that the times of accidental correlations between the external forcing and ECG of the patient in the absence of forcing are relatively large. This is due to the fact that by the way of construction the frequency of forcing signal is equal to the average frequency of the original signal.

Synchronization of ECG by external forcing with 3% frequency detuning from AHR is illustrated in Fig. 2(b). A typical plot for phase difference between the forcing signal and ECG of the patient versus time are given by curve 1. Curves 3 and 2 show the accidental correlations between forcing and ECG of a patient without forcing for $n : m = 1 : 1$, $v = 0$ and for optimal values n, m and v, respectively. As seen from the plots, on the time dependence of instantaneous phase between the signal and response (curve 1) there are synchronization plateaus whose average duration exceeds 50 s. With this, maximal duration of accidental correlations even under special fitting of experimental realizations does not exceed 20 s!. Thus, the increase of the frequency of external forcing by 3% caused the authentic increase of AHR of a patient also by approximately 3%, i.e., the effect of frequency locking is realized. A similar picture takes place for other values of frequency detuning between forcing and heart rate. Phase and frequency locking is detected on finite times, the latter being in agreement with the idea of effective synchronization.

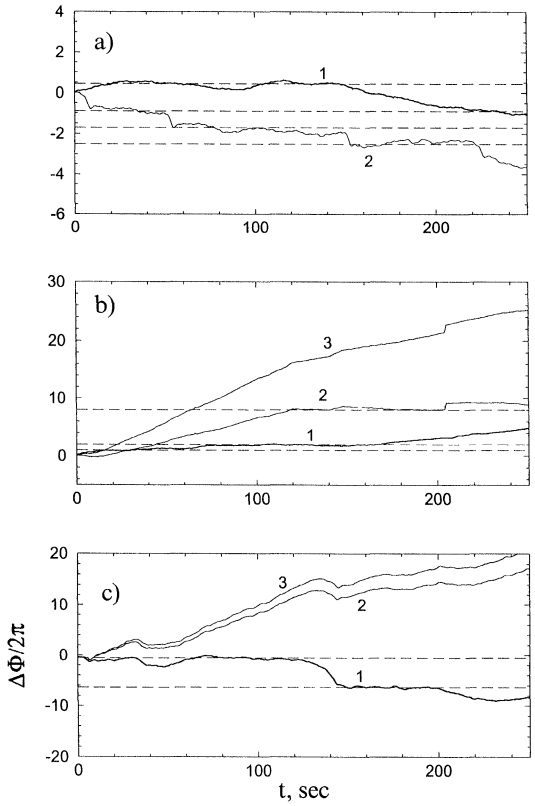


FIGURE 2 Instantaneous phase difference versus time. (a) Periodic forcing without frequency detuning; (b) periodic forcing with 3% frequency detuning; (c) irregular forcing governed by the RR intervals of another individual.

The results of experiments with an arbitrarily selected person subjected to periodic forcing whose frequency differed from the average heart rate at rest by $\pm 25\%$ are summarized in Fig. 3. Here the ratio of number of forcing pulses to the number of heart beats during 250 s versus detuning between AHR at rest and forcing frequency is plotted. One can see that for the values of detuning $\approx \pm 5\%$ this dependence has a plateau which corresponds to the region of frequency locking. The latter result is in a good agreement with the classical case of synchronization of self-oscillations in the presence of noise.

We conducted 19 experiments on the synchronization of cardiorhythm by periodic forcing with small (not exceeding $\pm 5\%$) detuning. In 16 cases the phase locking phenomenon was found. With this, average times of phase locking varied in the interval 40–150 s and in all cases authentically exceeded the maximal time of accidental correlations.

In terms of oscillations theory the results considered above can be related to the 1 : 1 synchronization. Taking into account the fact that the concept of chaotic synchronization proved to be fruitful in application to the study of phase locking phenomenon in systems with deterministic chaos [21] and even in stochastic systems [11], it is interesting to study the cardiorhythm synchronization

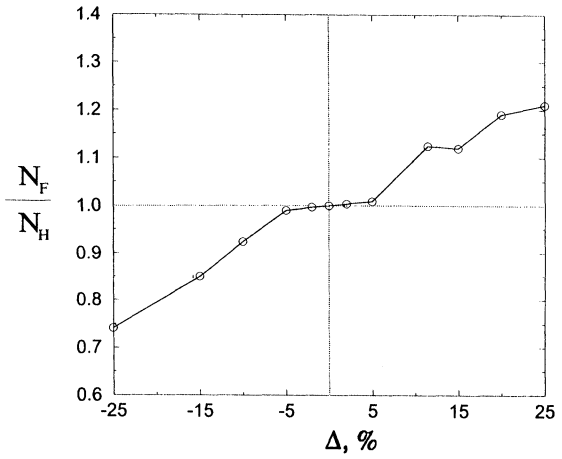


FIGURE 3 Ratio of number of external forcing pulses to the number of heart beats during 250 s versus frequency detuning between forcing and response.

when the patient is forced by aperiodic forcing. In our experiments we forced a subject by the signal defined by the sequence of RR intervals of another subject. Since the average heart rates of two different people do not coincide in general, we expect synchronization of $n:m$ type.

A typical result is shown in Fig. 2(c). Curve 1 shows the instantaneous phase difference for the case when $n:m = 7:6$. As seen from the plot, the effect of phase locking again takes place during the times not less than 50 s, the latter authentically exceeding the times of accidental correlations. Comparing this plot with the curves 3 and 2 (having the same meaning than in Fig. 2(b)) which reflect the accidental correlations between the forcing and original signals, one can see that the total duration of phase locking authentically exceeds 20% of time of signal registration being much larger than the maximal time of accidental correlations ($< 10\%$ of time of signal registration).

Twenty experiments were performed on the study of synchronization of cardiorhythm by aperiodic signals. The effect of synchronization was authentically detected in 19 cases.

Locking of AHR by external signal under small detuning provides an additional argument towards the hypothesis that human CVS can be perceived from the viewpoint of nonlinear dynamics as self-sustained system and demonstrate the forced synchronization phenomenon. However, we are far from a simplified understanding of the problem. Besides further investigations capable of proving the generality of the results obtained, there is a series of questions to be answered to, e.g., concerning physiological mechanisms responsible for synchronization of heart rhythm by sound and light.

4 CONCLUSION AND OUTLOOK

The fact that CVS exhibits properties typical for self-sustained systems opens new perspectives in the study of CVS of human and animals from the viewpoint of oscillations theory. In particular, it would be interesting to study how synchronization

exhibits itself when the intensity of forcing is increased, when the forcing signals with different structure are applied, when the respiration is taken into account, etc. We plan to continue the research in the directions listed above and hope that the reported results will turn to be interesting and useful not only from the viewpoint of fundamental knowledge of the properties of CVS, but also for application in medical practice.

To summarize, we have shown that by means of weak non-invasive forcing one can synchronize cardiorhythm of a human. Synchronousness was defined as the locking between the signals of forcing and response and detected as the presence of a plateau on the plot of phase difference versus time. In about 90% of the undertaken experiments we observed the appearance of plateaus with duration being authentically larger than accidental plateaus existing without forcing. Their total duration also increased. Based on the above observations we can make a conclusion that weak external forcing in the form of either periodic or aperiodic sequence of sound and light pulses is able to synchronize cardiorhythm.

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