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Modified Mackey-Glass model of respiration control

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We propose a modification of the Mackey-Glass respiration control model taking into account the activity of the brain respiration center. In contrast to the original Mackey-Glass model, the modified one allows one to obtain complex solutions correspondent to irregularly looking breathing patterns, which are observed in the case of pathological (Cheyne-Stokes) respiration; in addition, it describes the increase of frequency of respiratory motions in the case of pathology.

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In recent years, modeling of different human physiological rhythms and their analysis by methods of nonlinear dynamics have aroused considerable interest. Respiratory rhythm, reflecting one of the most important physiological functions of the human organism, has attracted the attention of researchers as an interesting phenomenon of complex oscillatory behavior in a living system and because of its relevance to practical medicine.

One of the types of pathological breathing, known as Cheyne-Stokes, or periodical, respiration, indicates severe, life-threatening pathology. It is also observed in healthy subjects in specific conditions (insufficiency of oxygen, e.g. high in the mountains). One of the reasons for the appearance of Cheyne-Stokes respiration is, apparently, violation of blood circulation giving an increase of duration of travel of blood from the lungs to the brain. The respiration is called periodic because of the alternation of short periods of deep and more frequent (as compared to the normal case) breathing with its complete cessation, termed apnoe. Correspondingly, the level of carbon dioxide in the blood oscillates, too. Both the envelope of breathing patterns and the number of breaths in each pattern are irregular [1–3], as is illustrated by Fig. 1 redrawn from [1].

As is known [2,4], the respiratory rhythm originates in a special center located in the brain stem. This central generator can work autonomously, without afferent signals, but normally it is influenced by several feedback loops. The control variables are levels of CO_2 and O_2 and the pH of the blood, and mechanical variables (level of lung stretch, stiffness of the muscles incorporated into respiration, and so on) measured by corresponding receptors in the structure surrounding the lungs. The chemical parameters are analyzed by special anatomic structures in the brain stem, which are called hemoreceptors. The finite time of blood flow determines the delay in a closed-loop control.

In regulation of breathing both the amplitude (depth) and the frequency of oscillation of brain respiration centers are changed. By doing so, the control system chooses some optimal values of these parameters.

The human respiratory system was modeled in a number of works [5]. A simple dynamical model of breathing control was proposed by Mackey and Glass [6]. In their work the human respiration control system was considered a closed-loop control system with time delay. It was shown that an increase of time delay leads to an excitation of oscillations of the level of carbon dioxide in the blood and of lung ventilation. The Mackey-Glass model does not take into account the activity of the central rhythm generator.

In the present paper we modify the Mackey-Glass model including considering the brain respiratory center. The simulation of the modified model gives solutions correspondent to normal and pathological respiration, such as the Cheyne-Stokes respiration. It is interesting that this model explains the increase of frequency of breathing in a pathological case.

Mackey and Glass considered the following control scheme. Carbon dioxide is produced in body tissues with constant speed (for the steady-state case) and is removed via lung ventilation. The ventilation V is defined as the volume of air passed through the lungs during a single breath times the frequency of respiration [7]. It is a monotonously increasing function of the level of CO_2 in the blood at some previous moment of time. Denoting the partial pressure of CO_2 in the blood as x, they approximated the dependence of V on x by

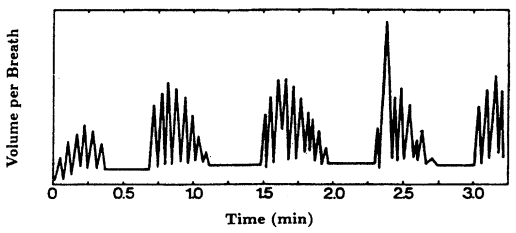

FIG. 1. Experimental record of pathological breathing taken from [1] (see also [6]).

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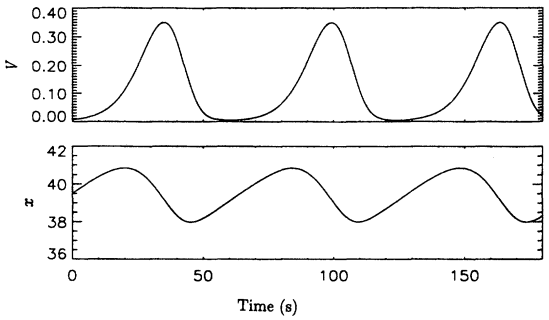

FIG. 2. Solution of the Mackey-Glass equation. V is the ventilation of lungs, liters per second, and x is level of CO_2 in the blood, mm of mercury column. Parameter values are given in the text.

$$V=V_m\frac{x_\tau^n}{\Theta^n+x_\tau^n}, \tag{1}$$

where V_m, Θ, and n are parameters, $x_\tau=x(t-\tau)$. As the velocity of CO_2 removal is proportional to the product of x and V, then

$$\frac{dx}{dt}=\lambda-\alpha xV, \tag{2}$$

where α is some coefficient. Based on the physiological data they chose the following parameters values: $\Theta=40\times(73/7)^{1/n}$, $V_m=4/3$ liters per second, $\alpha=0.0214$ l^{-1}, $\tau=15$ s, $\lambda=0.1$ mm of mercury column per second. The parameter n was changed during simulation.

For positive x Eqs. (1) and (2) have one singular point, $x=x^*$, which is the root of the equation $\lambda(\Theta^n+x_\tau^n)=\alpha V_m x_\tau^{n+1}$. For the above set of parameters, $x^*=40$ mm of mercury column. Stability of this singular point can be studied by use of the D-partition technique [8]. As a result, one obtains that the singular point $x=x^*$ is oscillatory unstable if $V^*\leqslant Sx^*$ and

$$\tau>\tau_{cr}=\frac{\arccos[-V^*/(Sx^*)]}{\alpha\sqrt{S^2x^{*2}-V^{*2}}}, \tag{3}$$

where $V^*=V|_{x_\tau=x^*}$, $S=(dV/dx_\tau)|_{x_\tau=x^*}$. Close to the stability boundary the period of oscillation is

$$T=2\pi\tau/\arccos[-V^*/(Sx^*)].$$

If $V^*\ll Sx^*$, which is valid for the above parameter values, then the condition (3) can be reduced to the form of $S>S_{cr}$, where $S_{cr}=\pi/(2\alpha\tau x^*)$. The latter is equivalent to the condition $n>n_{cr}$. For the presented values of the parameters, $n_{cr}\approx 46.59$ and the period of oscillations close to the stability boundary is approximately equal to 4τ. The results of integration of Eqs. (1) and (2) for $n=62.62$ are shown in Fig. 2. The solution obtained reminds one of the envelope of lung ventilation for Cheyne-Stokes respiration [6]. However, contrary to the experimental data, this solution is periodic.

Let us now take into account the rhythm of the central generator. This rhythm defines the frequency f of separate breaths. During each breath cycle the air flow through the lungs increases from zero to some maximal value with inspiration and decreases back to zero during expiration [2]. Hence, for the constant level of CO_2, the instantaneous ventilation V_I is a non-negative function periodic with period $1/f$. We suppose that it can be modeled as

$$V_I=V(1+\cos 2\pi ft).$$

Averaging of this function over time gives a slowly varying function V like the one presented in Fig. 2. Respectively, instead of Eqs. (1) and (2) we consider the following equation:

$$\frac{dx}{dt}=\lambda-\alpha xV_m\cdot\frac{x_\tau^n}{\Theta^n+x_\tau^n}(1+\cos 2\pi ft). \tag{4}$$

The dependence of the respiration rate on the level of CO_2 is not known exactly. Experimental studies show that, until the tidal volume (the volume of air entering the lungs during a single breath) is less than about half the vital capacity, ventilation increases at the expense of depth of breathing while the frequency remains nearly constant [9]. In order to describe the frequency control feedback loop, we suppose that frequency of the central generator f weakly depends on the level of CO_2 at some previous moment of time, and that the purpose of this control is to maintain the constant level of CO_2 in the blood, $x=x^*$. We also assume that this depen-

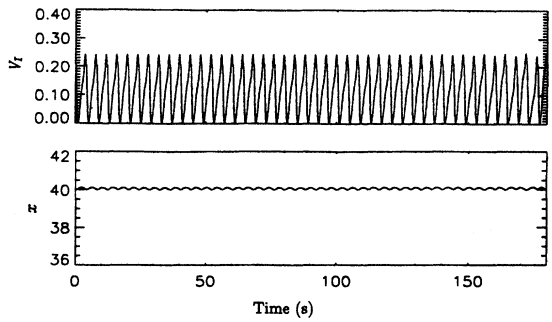

FIG. 3. Solution of Eqs. (4) and (5) for the value of time delay $\tau=3$ s ($\tau<\tau_{cr}$) and $\nu=0.0009$ Hz (mm Hg)$^{-1}$. This solution corresponds to respiration in the healthy state. V_I is the instantaneous ventilation of lungs, liters per second.

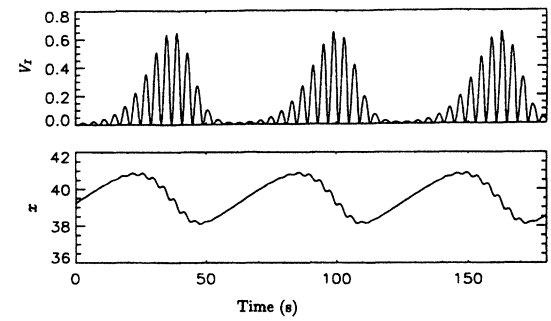

FIG. 4. Solution of the model in the absence of frequency feedback loop; $\tau=15$ s. The frequency of respiration is practically the same as in the healthy state (approximately one breath per 4 s).

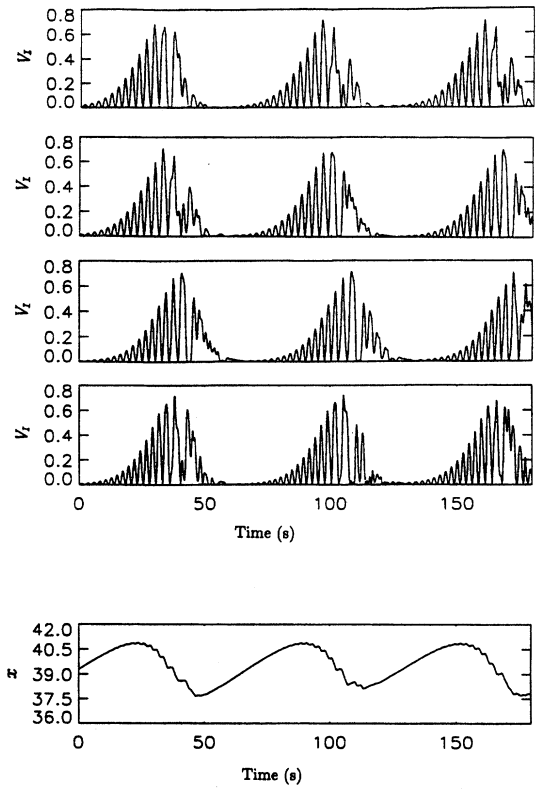

FIG. 5. Several three-minute irregular breathing patterns generated by the model (a). The lowest from these four plots corresponds to oscillation of the CO_2 level x (b). Parameter values are $\tau=15$ s and $\nu=0.0009$ Hz (mm Hg)$^{-1}$.

dence can be linearized in the neighborhood of x^*. It means that we consider small modulations of the frequency of the central generator:

$$f=f_0+\nu(x_\tau-x^*), \tag{5}$$

where $\nu \ll 1$ is parameter of modulation, and the frequency of

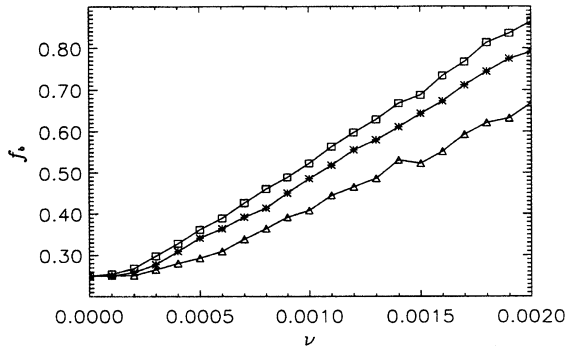

FIG. 6. Dependence of the mean respiration frequency f_b, Hz, on the coefficient in the frequency control feedback loop ν, Hz (mm Hg)$^{-1}$ for $\tau=12$ s (triangles), $\tau=15$ s (asterisks), and $\tau=18$ s (rectangles).

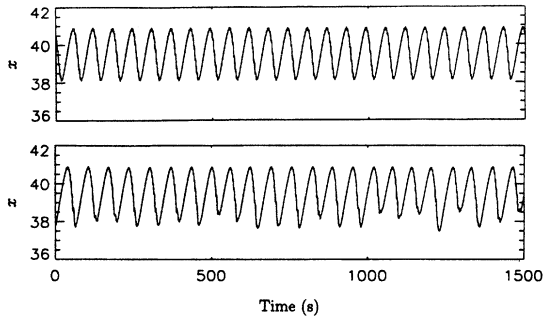

FIG. 7. Oscillations of the level of CO_2 in the blood in the case of absence (upper plot, $\nu=0$) and presence ($\nu=0.0009$) of modulation.

normal respiration f_0 is approximately one breath per 4 s. As shown below, this small modulation leads, nevertheless, to a nontrivial effect.

We simulated Eqs. (4) and (5) using the above parameter values from the works of Mackey-Glass, taking $f_0=1/4$ Hz and changing the parameter ν from Eq. (5) [10]. For $\tau<\tau_{cr}$ and ν varying from zero until at least 0.005 we obtained a result correspondent to normal breathing: ventilation is periodical in time and the level of CO_2 in the blood is practically constant and equal to x^* (Fig. 3). For $\tau>\tau_{cr}$ and $\nu=0$ (no modulation) we observed a quasiperiodic regime with the basic frequencies f_0 and $1/4\tau$ (Fig. 4). We note that

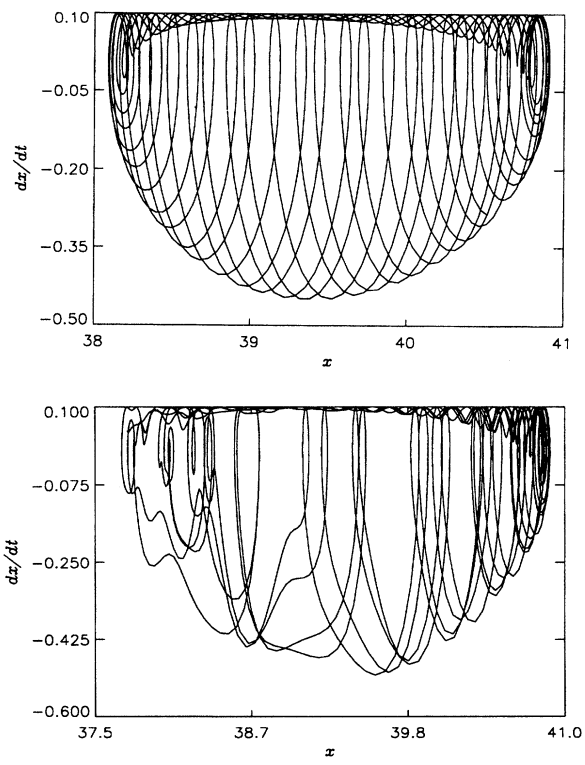

FIG. 8. One of the projections of the attractor of the system [Eqs. (4) and (5)] in the case of absence (upper plot, $\nu=0$) and presence ($\nu=0.0009$) of modulation.

the respiration frequency corresponds to the healthy case. For $\tau > \tau_{cr}$ and $\nu > 0$ we observed irregularly looking breathing patterns, typical for the case of Cheyne-Stokes respiration (Fig. 5).

Let us note that high-frequency oscillation of the variable V_I practically does not manifest itself in variation of x, as Eqs. (2) and (4) resemble the equation of the detector (demodulator). From Fig. 5 we can see that frequency of respiratory motions is approximately two times higher than in the normal case. This fact cannot be explained only by modulation of the frequency of the central generator, described by Eq. (5). Really, with the chosen parameter values, this variation is of the order of several percent only. Apparently, the detected considerable increase of frequency is caused by a combination of nonlinearity, time delay, and modulation. In order to show it, we calculated the averaged frequency of breathing $f_b = 1/T_b$ as a function of ν, where T_b is the mean interval between two successive breaths, for different values of time delay τ. This dependence is shown in Fig. 6. From this picture we can see that f_b/f_0 depends both on modulation and time delay, increasing with an increase of each of these parameters.

The found solution for $\tau = 15$ s and $\nu = 0.0009$ Hz $(\text{mm Hg})^{-1}$ seems to be chaotic [as one can suppose from the time plot (Fig. 7) and a projection of the attractor of the system, Eqs. (4) and (5) (Fig. 8)], although it can be quasiperiodic. It would be interesting to find out whether the Cheyne-Stokes respiration is really a chaotic or regular process (in any case it is certainly disturbed by noise), but because of the high noise level in measurements it is hardly possible to answer this question by means of analysis of experimental data [3]. It is very complicated and time consuming to obtain an exact answer to similar questions from simulated data. At the same time, it is not essential for the purpose of the presented study.

In summary, we have considered and investigated numerically a modification of the Mackey-Glass respiration control model. As a result we observed breathing patterns which are similar to the experimental data presented in the literature. An account of the frequency feedback loop allows us to describe in pathological respiration not only irregularity but also an increase of frequency of breathing, which is observed in reality.

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[10] The equation was solved by use of the implicit Adams method. The delayed values of x were stored with the time step $\tau/100$ and linearly interpolated in between, if required by the solver. Integration started from initial conditions correspondent to the steady solution $x = x^*$; transient was omitted.