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A mathematical model for the respiratory central pattern generator

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Abstract: The respiratory Central Pattern Generator (rCPG) is a neural circuit located in the brainstem, generating the physiological rhythmic breathing pattern of alternating inspiration and expiration. In this work, we propose a mathematical model of the rCPG which incorporates physiological feedback mechanisms. Numerical simulations of a closed-loop model of the rCPG with a lung and gas exchange model confirm the ability of the proposed model to reproduce the behavior of the rCPG in several important physiological regimes.

I. Introduction

The Respiratory Central Pattern Generator (rCPG) is a neural circuit located in the brainstem that autonomously generates a rhythmic breathing pattern without inputs from higher brain regions. This rhythmical pattern of alternating inspiration and expiration is influenced by several physiological feedback mechanisms, including the partial pressure of carbon dioxide in the blood, and can also be consciously controlled [2, 3]. Like many aspects of neurophysiology, the behavior of the rCPG is challenging to investigate *in vivo* and is not yet fully understood. A mathematical model can provide insights into the functioning of the rCPG and offers the possibility of predicting the patient's behavior. Existing models are either very simple and do not include feedback mechanisms [4] or complex, attempting to describe neuroanatomy [5]. In this work, we propose a low-dimensional mathematical model of the rCPG that generates a physiological breathing pattern and reacts to the partial pressure of carbon dioxide in the blood. An increase of this partial pressure causes an increase of ventilation by leading to increased respiratory frequency and amplitude and the begin of active expiration, as illustrated by numerical simulations.

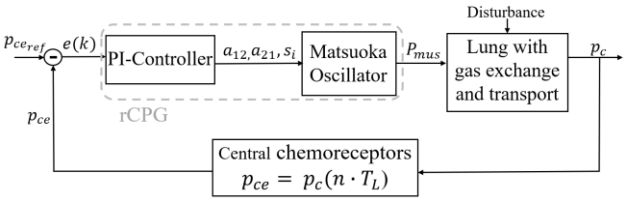

Figure 1: The developed closed-loop model of respiration, including the rCPG model and a flexible lung model with gas exchange and transport.

II. Material and methods

Fig. 1 shows the structure of the developed closed-loop model of the respiration, inspired by Molkov et al. [5]. It encompasses two main parts: A lung model with gas exchange and transport and a model of the rCPG including the Matsuoka oscillator [4] and a PI controller, which adjusts the parameters of the Matsuoka oscillator based on the current partial pressure of carbon dioxide in the blood.

II.I. A model of the respiratory CPG

Many mathematical models have been proposed for Central Pattern Generators (CPGs). The Matsuoka oscillator [4] is a CPG model without periodic external stimulus. It is a continuous-time and continuous-variable model of n mutually inhibiting neurons and is defined by

$$\frac{dx_i}{dt} = \frac{-x_i - \sum_{i=1}^{n} a_{ij} y_j + s_i - b f_i}{T_r}, \quad (1)$$

$$y_i = max\{0, x_i\}, \quad (2)$$

$$\frac{df_i}{dt} = \frac{-f_i + y_i}{T_a}, \quad (3)$$

where $x_i(t)$ is the membrane potential of neuron i, $y_i(t)$ the firing rate, and s_i a constant, external input. The weights a_{ij} from neuron i to neuron j are zero for $i = j$. $f_i(t)$ models an adaption effect, and b determines the steady-state firing rate for constant input. Lastly, T_r and T_a are time constants of the system.

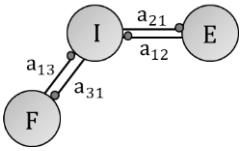

Figure 2: The structure of the chosen CPG model. The inspiratory I (i=1), expiratory E (i=2) and interneuron F (i=3) are connected via mutually inhibitory connections.

In our model of the rCPG, a Matsuoka oscillator with three neurons (shown in Fig. 2) was chosen to represent the rhythm generating part of the rCPG. It was chosen because of its simplicity and its flexibility, admitting both internal and external inputs. We performed a numerical analysis of the dependency of the respiratory rate and the output amplitude on different parameters of the non-linear oscillator. The results (not shown here) indicate that the respiratory rate can be adjusted by changing all weights a_{ij}

simultaneously. The overall amplitude of the oscillation is controllable via the external inputs s_i, and the expiratory amplitude is controllable by adjusting a_{21}.

II.II. Lung model

For respiratory mechanics, gas exchange and gas transport, we use the model of Ben-Tal [1], which describes the lung as a single, flexible container. As opposed to [1], where no model of the rCPG is included, we use the output of our rCPG model to represent the pressure generated by the respiratory muscles. Assuming a constant metabolic rate, the partial pressure of carbon dioxide was reinitialized to a value of 46mmHg at the beginning of every heartbeat [1]. The simulated end-tidal partial pressure of carbon dioxide is fed back into the rCPG model as a physiological feedback signal.

II.III. Controlling the respiratory CPG

To ensure that a rising partial pressure of carbon dioxide leads to increased ventilation by increasing frequency, breath amplitude and expiratory activity, a control scheme for adapting the parameters of the CPG model is required. For simplicity, we decided to use a single control parameter and chose a PI controller for updating the weight a_{12} from the expiratory to the inspiratory neuron once per heartbeat:

$$\Delta a_{12}(\ell) = k_P e(t_\ell) + k_I \int_0^{\ell \cdot T_L} e(\tau) d\tau, \qquad (4)$$

where ℓ denotes the heartbeat index and T_L its length (assumed to be constant), k_P and k_I are controller parameters, and $e(t)$ denotes the deviation of the partial pressure of carbon dioxide from its physiological set point. All other parameters of the Matsuoka oscillator then should be defined as a function of a_{12}, such that the respiratory rate and amplitude, as well as the expiratory amplitude, are controlled in a physiological way. To solve this non-linear tuning problem, we performed additional numerical analyses, assessing the dependency of the respiratory rate, amplitude and expiratory amplitude on two or more parameters (exemplary diagram shown in Fig. 3).

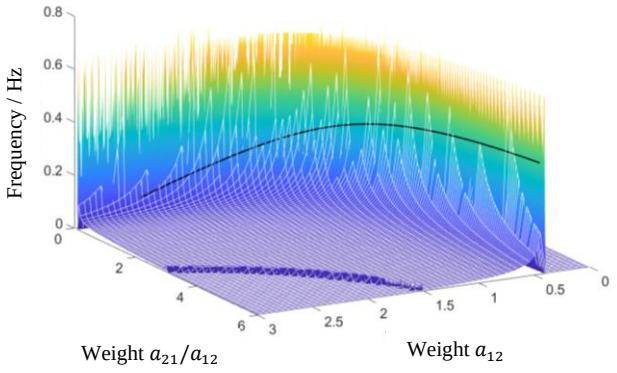

Figure 3: Respiratory frequency as a function of the weights a_{12} and a_{21}. The black line displays a_{21} as an interpolated function of a_{12} along which the frequency depends linearly on a_{12}.

Using physiological values for the respiratory frequency and the muscle pressure's amplitude, and defining these two quantities as a linear function of the weight a_{12}, it was possible to define all other parameters of the CPG model via interpolation of the linear equations in the analyzed data.

III. Results and discussion

All simulations were performed using a 4th-order variable-step Runge-Kutta solver in Matlab R2019a.

A simulation of respiration under resting conditions is shown in Fig. 4. The muscle pressure resembles quiet breathing activity with a breathing frequency of 14 breaths per minute. The partial pressure of carbon dioxide is reinitialized after each heartbeat and stays in the normal physiological range.

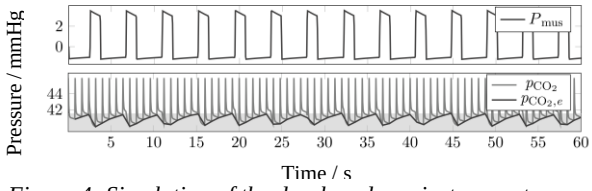

Figure 4: Simulation of the developed respiratory system under resting conditions.

Fig. 5 shows the results of a simulated hypercapnia – an increased partial pressure of carbon dioxide in the blood. We simulated the effect of an increased concentration of 5% of carbon dioxide in the inspired air. The end-tidal partial pressure of carbon dioxide quickly exceeds the normal range and provokes an increase of respiratory rate and amplitude of the muscle pressure as long as the partial pressure remains outside its physiological range. Once the blood partial pressure of CO_2 returns to the normal range, the system converges to a new equilibrium. While the expiratory amplitude is very small at the beginning of the simulation, expiratory and inspiratory amplitudes are nearly equal after 3.5 minutes, demonstrating active expiration.

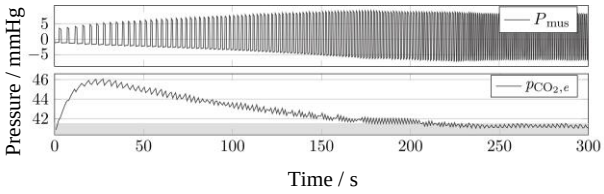

Figure 5: Simulation of hypercapnia induced by an increased concentration of CO_2.

IV. Conclusions

We have proposed a low-dimensional, nonlinear oscillator model of the rCPG that reproduces a physiological breathing pattern and incorporates physiological feedback mechanisms. Numerical simulations indicate its capability to reproduce physiological behavior in several regimes.

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