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Oxygen therapy for management of periodic breathing : A theoretical approach

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ABSTRACT

A generalized framework for the generation of Periodic Breathing (PB), caused by delay variation, hypocapnia and sleep along with its management with oxygen therapy is presented. For this, a minimal model of respiratory regulation with cardiovascular component and two delays is proposed. This model is linearized and analyzed for stability by the proposed algorithms using Lyapunov–Krasovskii functional. Oscillation in this model is produced by the increase of delays, an increase of chemoreceptor gains (hypocapnia) and a decrease in minute ventilation (sleep induced PB). For delay variation, it is established that both the delays are responsible for oscillation in the system. However, maximum tolerable delay limit for the peripheral chemoreceptors is lower (0.3 min) compared to the central chemoreceptors (5.2 min). Stability analysis shows that application of additional oxygen is capable of suppressing the oscillation in the system by increasing the tolerable delay limit. Hypocapnia caused by hyperventilation is modeled by increased chemoreceptor gain. 50% increase in chemoreceptor gain along with 46% decrease in lung carbon dioxide storage makes the system oscillatory, which increases average minute ventilation by 19.42%. Application of additional oxygen makes the system stable. For sleep induced PB, it is shown that lowering minute ventilation causes oscillation in the system. A parameter is introduced to limit the minute ventilation in sleep, and its upper limit is calculated (8.7% drop in minute ventilation) for producing oscillation in the system. Application of higher oxygen makes the system stable by compensating for the reduction. Finally, two simulation studies are presented, showing the delay limits in hyperventilation and sleep condition. In these conditions, as the gains increase or minute ventilation decreases, tolerable delay limits become smaller.

1. Introduction

In the respiratory regulation model, Periodic Breathing(PB) is classified as the oscillatory behavior of the system, caused by the failure of the feedback mechanism. PB may originate from different sources, but mathematically it is generalized as delay and parameter variation. Clinically, PB is observed in Congestive Heart Failure (CHF) [1] or Central Sleep Apnea (CSA) [2]. Although these diseases are complicated to model, they can be represented by delay and parameter variations. Here, three conditions for the genesis of PB are considered, i.e. higher delay, hypocapnia caused by hyperventilation (increased chemoreceptor gain) and sleep (lower minute ventilation due to lack of wakefulness drive).

Circulatory delay exerted from traveling of blood from the lungs to the chemoreceptor sites is one of the sources of oscillation [3–5]. Guyton [6] has induced PB in dogs by inserting a tube between the heart and cerebral circulation and thereby increasing the transit time. Supplying additional oxygen improves cardiac function, thereby making the system stable [7]. Apart from delay, hypocapnia and hyperventilation is another source of PB [1]. Hyperventilation is caused by increased chemoreceptors gain, leading to hypocapnia [8]. Clinical studies have shown that left ventricular diastolic volume is higher in CHF patients with PB [9]. This causes pulmonary congestion and reduces gas storage capacity in the lungs, thereby making the system oscillatory. Additional oxygen supply increases the oxygen level in the left ventricle and reduces reflex activation of the chemoreceptors, making the system stable [10]. Sleep plays a significant role in the development of PB. This is caused by the reduction of ventilatory drive, which results in insufficient oxygenation of the body. Khoo, Gottschalk and Pack [11] postulated that lack of wakefulness drive plays a central role in the development of PB during sleep along with lower metabolism and chemoreceptor gains. Here, PB in sleep is modeled by lowering the minute ventilation along with metabolic oxy-

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gen consumption and carbon dioxide production. Additional oxygen compensates for the lower ventilation and thereby stabilizing the system. In clinical practice, supplying additional oxygen to CSA patients [12] has been helpful to stabilize PB and improves the sleep quality in CHF-CSR patients [13].

In the literature, models of respiratory regulation homeostasis are formulated by the mass conservation laws for different compartments, i.e. for each compartment(alveolar, brain etc.), the rate of change of gas content inside a compartment is dependent upon gas produced/consumed and transferred via blood/air flow. Models describing respiratory regulation are divided into two groups [14], i.e. comprehensive model and minimal model. In this work, a minimal model of the regulation system is developed from the Khoo et al. [15] model, to analyze the cause of PB in these conditions, along with the effect of additional oxygen to suppress the oscillation. The Khoo et al. [15] model employed three compartments (alveolar, brain and tissue) in a five dimensional model. Batzel and Tran [16] reduced this model into three dimensions, by assuming tissue oxygen and carbon dioxide partial pressure as constant. Using similar assumption and model order reduction technique, a minimal model is developed here to describe the PB condition. Although the proposed modeling approach has certain similarity with the Batzel and Tran [16] model, three major modifications are incorporated into the model to address the current problem. Those modifications are listed below.

- The proposed modeling approach incorporates local vasodilation model of cardiovascular system [17], which is necessary for analyzing the effect of additional oxygen in oxygen therapy condition.
- Since, metabolism varies during awake to sleep transition [11], the proposed modeling approach is equipped with variable metabolism.
- As both the chemoreceptors determine the performance of the system [15], delay to the peripheral and central chemoreceptors are considered separately.

Literature shows, analysis of the feedback scheme of the linearized model is done using analytical methods, i.e. Nyquist criteria [15], Direct method [16,18], τ decomposition [19–21]. These methods have given insights into the causes of the occurrence of PB, i.e. loop gain and phase lag [15], chemoreceptors gain and wakefulness to sleep transitions [11], delay [22], lower minute ventilation [16,18]. All these conditions are generalized as delay / parameter variations and incorporated into the current model for the generation of PB. For analyzing the causes of PB and treatment with oxygen therapy, these conditions are analyzed for stability using Lyapunov–Krasovskii (LK) functional method. As the proposed model is a nonlinear time delay model and the analysis methodology for such systems are limited [23], stability analysis is done on the linearized (Taylor series) model. Analysis of linear time delay system with multiple delays using LK functional is a well-established area [23], which requires feasibility testing of Linear Matrix Inequality. Delay variation does not change the linearized model, but parameter variation causes the linearized model to vary. For this reason, two algorithms are proposed to assess the stability of such systems under delay and parameter variation. Higher circulatory delay, hypocapnia caused by hyperventilation and PB during sleep conditions are realized in the proposed respiratory model and these two algorithms are applied to guarantee the stability of the linearized model in these conditions. Additional oxygen is also treated as a parameter, whose variation is analyzed to suppress the oscillation in the system.

2. Mathematical model

The respiratory system component is considered as a compartmental model, and cardiovascular part is modeled as function of alveolar gases. Modeling of each of these systems is discussed separately.

2.1. Respiratory system

Proposed respiratory model is derived from the model developed by Khoo et al. [15] using model order reduction. The detailed procedure for deriving this model is described in Appendix B. The Khoo et al. [15] model is a five dimensional model, and it is reduced to three dimensional model using model order reduction (matched DC gain method). State variables considered in the original model are alveolar carbon dioxide ($P_{A_{CO_2}}$), alveolar oxygen ($P_{A_{O_2}}$), brain carbon dioxide ($P_{B_{CO_2}}$), tissue carbon dioxide ($P_{T_{CO_2}}$) and tissue oxygen ($P_{T_{O_2}}$) partial pressure. The proposed model considers alveolar oxygen and carbon dioxide partial pressure, along with brain carbon dioxide partial pressure (responsible for central chemoreceptor excitation). Air flow from the external environment is assumed to be continuous and described as minute ventilation.

Alveolar compartment. It is assumed that alveolar compartment is continuously ventilated and perfused by air and blood flow respectively. Hence, the rate of change of carbon dioxide pressure inside alveolar compartment consists of the metabolic carbon dioxide production from the tissues, and carbon dioxide removed during ventilation. The rate of change of carbon dioxide pressure due to metabolism, as perceived inside alveolar compartment is defined as $[(M_{T_{CO_2}} R_Q)/(C_{T_{CO_2}} R_{Q_T})]$. Ventilation part, responsible for removal of carbon dioxide from lungs compartment, is defined as $[R_{VA}(P_{I_{CO_2}} - P_{A_{CO_2}})/V_{A_{CO_2}}]$. Combination of these two components give the rate of change of carbon dioxide partial pressure in the alveolar compartment as,

$$\frac{dP_{A_{CO_2}}(t)}{dt} = \frac{M_{T_{CO_2}} R_Q}{C_{T_{CO_2}} R_{Q_T}} + \frac{R_{VA}\left(P_{I_{CO_2}} - P_{A_{CO_2}}(t)\right)}{V_{A_{CO_2}}} \tag{1}$$

The parameter values for the model are defined in Table B.2. Similar to this, the rate of change of alveolar oxygen partial pressure become,

$$\frac{dP_{A_{O_2}}(t)}{dt} = -\frac{M_{T_{O_2}} R_Q}{C_{T_{O_2}} R_{Q_T}} + \frac{R_{VA}\left(P_{I_{O_2}} - P_{A_{O_2}}(t)\right)}{V_{A_{O_2}}} \tag{2}$$

Here, the metabolic oxygen consumption ($M_{T_{O_2}}$) term assumes negative sign, showing oxygen consumption.

Brain compartment. The rate of change of brain carbon dioxide partial pressure consists of two quantity. One part is due to the brain metabolism, and the other part is due to brain blood flow. The CO_2 production due to metabolism is defined as $[M_{B_{CO_2}}/C_{B_{CO_2}}]$ and the CO_2 transportation due to blood flow is defined as, $[R_{Q_B}(P_{A_{CO_2}}(t - \tau_b) - P_{B_{CO_2}}(t))/V_{B_{CO_2}}]$. τ_b is the delay from alveolar to lungs compartment. Hence, the equation for brain carbon dioxide partial pressure becomes,

$$\frac{dP_{B_{CO_2}}(t)}{dt} = \frac{M_{B_{CO_2}}}{C_{B_{CO_2}}} + \frac{R_{Q_B}\left(P_{A_{CO_2}}(t - \tau_b) - P_{B_{CO_2}}(t)\right)}{V_{B_{CO_2}}} \tag{3}$$

Control of ventilation. Eqs. (1)–(3) define the respiratory plant model. The actuation signal of minute ventilation is generated by the respiratory center, based on gas content perceived by the chemoreceptors. Peripheral receptors respond to arterial oxygen and carbon dioxide partial pressure after transport delay τ_p,