Basics of mathematical modeling of pulmonary ventilation mechanics and gas exchange

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Abstract. The human cardiovascular-respiratory system is a complex system which exhibits the properties of a control system of the regulator type. The gas exchange combines many processes that occur in the brain, lungs, vasculature, and body tissues. This paper deals with a simple model that provides a linearized description of pulmonary ventilation mechanics. Some equations describing the introduction to chemical regulation of lung ventilation are derived.

Keywords: human respiratory system, pulmonary ventilation, gas exchange, mathematical modeling

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1 Introduction

The concept of physiological regulation dates back to the ancient Greeks (about 500 BC), when the human body was considered as a small copy of the universe where its four basic elements (air, water, fire and earth) were represented by blood, phlegm, yellow bile and black bile, respectively [1]. Interaction between pairs of these elements gave four irreducible characteristics: humidity, heat, dryness and coldness. It was considered that the establishment of the harmonic balance between these elements and characteristics led to the proper functioning of various organs of the body. In the second century, Greek physicist Galen integrated existing traditional knowledge and theoretically promoted physiology in a way that had been accepted until the end of the 16th century. Similar concepts had been developed in ancient China by Taoists starting from the third century BC. In their teachings the universe was made up of five elements: wood, fire, metal, earth and water. It had been considered that their interaction was dual. It is productive in a case when one element enhances the effect of other, otherwise is limiting or destructive, so the health preservation is in direct relation with their harmonic balance.

Although many famous physiologists, such as Boyle, Lavoisier and Pelüger, introduced the concept of regulation, it remained quite unclear until the end of the 19th century, when the French physiologist Claude Bernard proposed the concept of self-regulation, starting from the assumption that in the higher evolution level organisms cells "swim" in the blood or lymph. Regardless of disturbances in the whole organism physiology, he claimed that such environment was fairly stable. This stable environment was achieved and maintained by the organism itself. Later, the physiologist W. B. Cannon revised Bernard's ideas and illustrated new concept describing different physiological processes (sufficient intake of food and water in accordance with the information received from the thirst and hunger sensor, the role of the kidney in water excess regulation, preservation of acid-base blood balance).

In the forties of the 20th century, Wiener funded the approach of modeling the nonlinear dynamics of the physiological system, which modern development is the result of joint work of physiologists, mathematicians and engineers, forming a new discipline known nowadays as biomedical engineering.

Mathematical modeling of human respiratory system has been studied in literature with different approaches [1]-[19]. For example, lung mechanics modeling is studied in [10], [11] while gas exchange modeling can be found in [12], [13], [16]. There are examples of controller design for regulation of respiratory system in [11], [14], [15], and virtual laboratories developed to simulate the respiratory and cardiovascular system [6], [7]. This paper deals with a simple model that provides a linearized description of pulmonary ventilation mechanics and provides some equations describing the basics of chemical regulation of lung ventilation. Processes related to the lung ventilation are discussed, which is the basis for the consideration of other respiratory functions and physiology of certain respiratory disorders [5].

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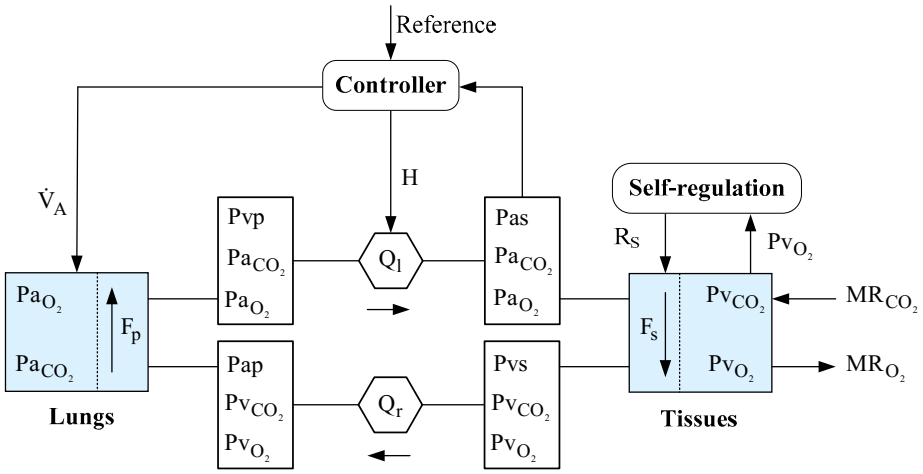

Fig. 1. Block diagram of cardiovascular-respiratory system model

2 Breathing process

The main role of breathing is to provide oxygen (O_2), which is required for the tissue metabolism, and to remove metabolic byproducts, such as carbon dioxide (CO_2), from the tissues. The complete gas exchange is achieved by passive diffusion through the blood/gas barrier between capillaries and alveoli. This requires, in the case of varying load conditions, maintaining the appropriate pressure gradient through the barrier, which is achieved by changing the rate at which fresh air enters the alveoli. As a result of this exchange, blood that leaves the lungs through pulmonary veins contains high concentration of O_2, and low concentration of CO_2. The opposite process of exchange is carried out in tissues where O_2 is used and CO_2 is produced as a byproduct in the metabolism activities.

Note that there are four main functional parts of the breathing process:

1. pulmonary ventilation, which includes the air flow between the atmosphere and lung alveoli in both directions;
2. diffusion of O_2 and CO_2 between the alveoli and blood;
3. transport of O_2 and CO_2 through blood and body fluids to the cells and back;
4. regulation of ventilation and other aspects of breathing.

Only processes related to the ventilation of the lungs will be discussed in this paper.

One of the models which describe the human cardiovascular-respiratory system is shown in Fig. 1 and is represented by a system of 13 differential equations [2]-[4]. This model consists of two circuits connected in series (systemic and pulmonary) and two pumps (left and right ventricle). A number of symbols for parameters used in this model and further in this paper is given in Table 1 [2].

2.1 Air movement into and out of the lungs, and processes which cause it

Recall that the lungs can be stretched and shrunk in two ways:

- lowering and raising of the diaphragm when the chest cavity is prolonged or shortened, and
- raising and lowering of the ribs which increases and decreases the size of the chest cavity.

Under normal conditions breathing is done, almost completely, by the movements of the diaphragm. During the inspiratory for a period of 2 seconds, the contraction of the diaphragm pulls the bottom surface of the lungs downwards, when 0.5 liters of air enter the lungs. The same amount of the inhaled air leaves the lungs during the expiratory in 2 to 3 seconds. Otherwise, the lungs are elastic structure that would, in the absence of force that keeps them in the inflated state, collapse as an air balloon and eliminate all the air through the windpipe. As between the lungs and the chest wall there are no anatomical joints (except of the hilar area), lungs, surrounded only by a thin layer of pleural fluid, "float" in the chest cavity.

Table 1. Parameters of cardiovascular-respiratory system model

Symbol	Description	Unit
$\dot{V}_A$	alveolar ventilation rate	l_{BTPS}/min
Pa_{CO_2}	partial pressure of CO_2 in arterial blood	mmHg
Pa_{O_2}	partial pressure of O_2 in arterial blood	mmHg
Pv_{CO_2}	partial pressure of CO_2 in mixed venous blood	mmHg
Pv_{O_2}	partial pressure of O_2 in mixed venous blood	mmHg
MR_{CO_2}	metabolic CO_2 production rate	l_{STPD}/min
MR_{O_2}	metabolic O_2 production rate	l_{STPD}/min
F_p	blood flow perfusing the lung compartment	l/min
F_s	blood flow perfusing the tissue compartment	l/min
H	heart rate	min^{-1}
R_s	peripheral resistance in the systemic circuit	mmHg·min/l
Q_l	left cardiac output	l/min
Q_r	right cardiac output	l/min
Pas	arterial mean blood pressure: systemic circuit	mmHg
Pap	arterial mean blood pressure: pulmonary circuit	mmHg
Pvs	venous mean blood pressure: systemic circuit	mmHg
Pvp	venous mean blood pressure: pulmonary circuit	mmHg

Note. Metabolic gas production rate is expressed in STPD (***S****tandard* ***T****emperature* ***P****ressure* ***D****ry*, at 273°K and 760 mmHg) unit. Ventilation rate is expressed in BTPS (***B****ody* ***T****emperature* ***P****ressure* ***S****aturated*, at 310°K and 47 mmHg) unit.

Pleural pressure (P_{pl}) is the pressure of fluid in the narrow space that lies between the pulmonary pleura and thoracic pleura and is slightly negative in relation to atmospheric pressure, i.e. it varies from -5 cm to -7.5 cm of the water column. Alveolar pressure (P_A) is the pressure which exists inside of the pulmonary alveoli. When the glottis is open and there is no airflow into or out of the lungs, the pressure in all parts of the respiratory tree is equal to the atmospheric pressure. This is a reference pressure in the airways and is defined with 0 cm of water column. Alveolar pressure decreases to -1 cm of water column during normal inspiratory, and increases to +1 cm of water column during expiratory. As the physiology of breathing deals with a mixture of gases (mostly oxygen, nitrogen and carbon dioxide), the diffusion size of each of them is directly proportional to the pressure that gas itself causes, and is designated as the partial pressure of the gas.

The ultimate goal of breathing is to maintain tissue concentrations of O_2, CO_2 and hydrogen ions H^+ at the appropriate level. Excess of CO_2 and H^+ ions in the blood mainly acts directly on the respiratory center in the medulla oblongata.

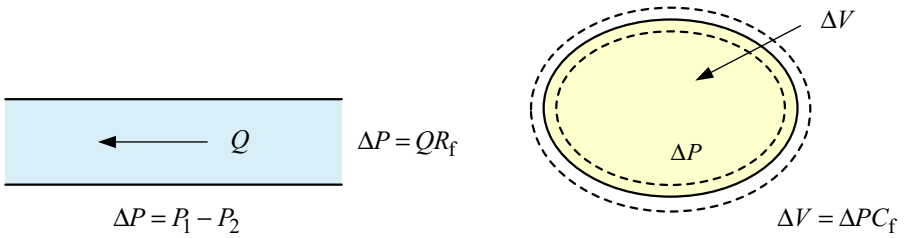

Fig. 2. "Resistance" and "compliance" in fluid systems

3 Mathematical modeling of human respiratory system

3.1 Generalized system properties

It is well known that the formation of structural or gray-box model of an arbitrary system is based on the use of mathematical expressions that describe three generalized properties of the system [1]:

- resistive property: $\psi = R\,\varsigma$, (1)
- storage property: $\psi = \frac{1}{C}\int_0^t \varsigma\,\mathrm{d}t$, (2)
- inertance property: $\psi = L\,\frac{\mathrm{d}\varsigma}{\mathrm{d}t}$. (3)

In previous relations ψ and ζ denote two variables (generalized effort and generalized flow) and R, C and L denote three parameters (generalized resistance, generalized compliance and generalized inductance).

In relation (1) the generalized Ohm's law can be recognized (ψ - voltage and ζ - current), or Poiseuille's law defining that the flow of fluid (Q [1/min]) through a rigid tube is proportional to pressure difference (ΔP [mmHg]) at the ends of the tube (Fig. 2). At the same time the hydro-dynamic resistance of the fluid R_f [mmHg·min/l] is directly proportional to fluid viscosity and tube length, and inversely proportional to its cross-section.

In the electrical systems, the concept of capacitance is introduced via property of storage. It is defined as the amount of electrical charge stored in the capacitor per unit voltage that exists at its ends. In mechanical systems, property of storage is equal to compliance (of a spring or balloon filled with fluid, for example), Fig. 2. In case of such fluid system compliance C_f [l/mmHg] defines the volume ΔV of the balloon for which it is expanded or contracted per unit change of applied pressure ΔP. The elasticity of the material that the balloon is made of primarily affects its compliance (more rigid material - smaller balloon compliance and vice versa).Thus, the storage element allows the accumulation of static or potential energy.

The third property, inertance property, is related to the storage of kinetic energy, so the generalized Newton's law can be recognized in equation (3). Recall that in addition to the inductance in electrical systems, the mass and the moment of inertia in mechanical systems, there is no analogy in thermal and chemical systems since they are not capable of storing kinetic energy.

3.2 A simplified linear model of pulmonary ventilation mechanics

For the modeling of pulmonary ventilation, an analogous electrical circuit is formed, Fig. 3 [1]. Note that airways are divided into two categories: the first are longer (central), and the second are shorter (peripheral), and are characterized by mechanical resistances R_c and R_p, respectively. Since the chest cavity expands in accordance with alveolar ventilation, i.e. the amount of fresh air that arrives in the alveoli where gas exchange occurs, this is represented by lungs compliance (C_L) and chest wall (C_W) compliance connected in series in electrical scheme in Fig. 3.

A part of the inhaled air during inspiratory, however, never reaches the area where gas exchange takes place, but fulfills the respiratory tract (nose, pharynx and trachea) in an area that is known in the literature as the anatomical dead space [5]. At the young male adult, this space occupies a volume of about 150 [ml]. In certain cases, some alveoli only partially or not at all perform their function, since the blood poorly or not at all flows through capillaries in that area of the lungs. If alveolar dead space is added to anatomical dead space, the physiological dead space is obtained, or in other words a kind of physiological shunt is obtained. Thus, in the case of a disease that leads to obstruction of the peripheral airways (when R_p increases) or to enhance stiff-

ness of the lungs or chest wall (when C_L or C_W decreases), physiological dead space can take up 10 times the value of the anatomical dead space. Hence, shunt compliance C_S is in parallel with C_L and C_W in an analogous electrical circuit in Fig. 3.

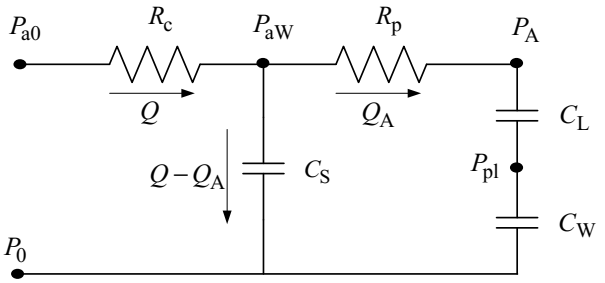

Fig. 3. Electrical circuit of respiratory mechanics

Let us now define pressure at different locations in a simplified linearized model of the lungs, as follows: P_{a0} at the entrance of the airway, P_{aW} at the central airway, P_A in the alveoli and P_{pl} in the pleural space. These pressures are defined in relation to the ambient pressure P_0, which is usually set to zero. Assume that the air flow at the entrance of the respiratory system is Q and that it is necessary to determine the mathematical relation between P_{a0} and Q. Equations which describe dynamical behavior of the considered system are

$$R_p Q_A(t) + \left(\frac{1}{C_L} + \frac{1}{C_W}\right)\int Q_A(t)\,dt = \frac{1}{C_S}\int \left(Q(t) - Q_A(t)\right)dt \quad (4)$$

$$P_{a0}(t) = R_c Q(t) + \frac{1}{C_S}\int \left(Q(t) - Q_A(t)\right)dt\,, \quad (5)$$

from which, eliminating Q_A, is obtained:

$$\frac{d^2P_{a0}(t)}{dt^2} + \frac{1}{R_p C_T}\frac{dP_{a0}(t)}{dt} = R_c\frac{d^2Q(t)}{dt^2} + \left(\frac{1}{C_S} + \frac{R_c}{R_p C_T}\right)\frac{dQ(t)}{dt} + \frac{1}{R_p C_S}\left(\frac{1}{C_L} + \frac{1}{C_W}\right)Q(t) \quad (6)$$

where $$\frac{1}{C_T} = \frac{1}{C_L} + \frac{1}{C_W} + \frac{1}{C_S}\,. \quad (7)$$

Suppose that patient's lungs are of relatively normal mechanics with the following pulmonary parameters: R_c=1 [$cmH_2O \cdot s/l$], R_p=0.5 [$cmH_2O \cdot s$ /1], C_L=0.2 [l/cmH_2O], C_W=0.2 [l/cmH_2O], C_S=0.005 [l/cmH_2O]. Transfer function of the linear model derived above is

$$\frac{Q(s)}{P_{a0}(s)} = \frac{s^2 + 420s}{s^2 + 620s + 4000}\,. \quad (8)$$

A simple block diagram to simulate the pulmonary ventilation is shown in Fig. 4. Assume that there is a sinusoidal input signal with amplitude of 2.5 [cmH_2O] and natural frequency of 1.57 [rad/s]. This corresponds to the frequency of 0.25 [Hz] or 15 breaths per minute. Thus, it can be assumed that in the real experiment the appropriate ventilator generates a sinusoidal signal which frequency approximately corresponds to the normal breathing frequency when a person is resting. At this relatively low frequency, the waveform of volume V is nearly in phase with P_{a0}, while the air flow Q shows a significant positive phase shift with respect to P_{a0}. This means that at very low frequencies the storage property (compliance) dominates in lung mechanics. If the ventilator frequency increases four times (60 breaths per minute) without changing the input signal amplitude, it is clear that the maximum flow rate would increase as well, and the tidal volume would decrease. Notice that under these conditions the flow Q is even more in phase with P_{a0}, while volume change occurs with a significant delay. Thus, this leads to conclusion that the resistive property begins to dominate at higher frequencies.

Using the described technique, which is based on a forced oscillation method, the dependence of pulmonary resistance and compliance of the breathing frequency is observed, so that at frequencies higher than those that correspond to the breathing of a person who is resting, the lungs become stiffer and provide less resistance. Note that, in order to model lung mechanics more realistically, the influence of the inertia of the fluid in the airways should be considered as well, which means that the inductive element should be added in analogous circuit in Fig. 3.

3.3 Pulmonary gases exchange

Although gases exchange process is done in the lungs, the vasculature and in the tissues (as shown in Fig. 1), exchange of gases in the lungs will be just considered in this paper. Static characteristics of the gas exchanger can be obtained on the basis of mass balance for the CO_2 and O_2, as shown in Fig. 5.

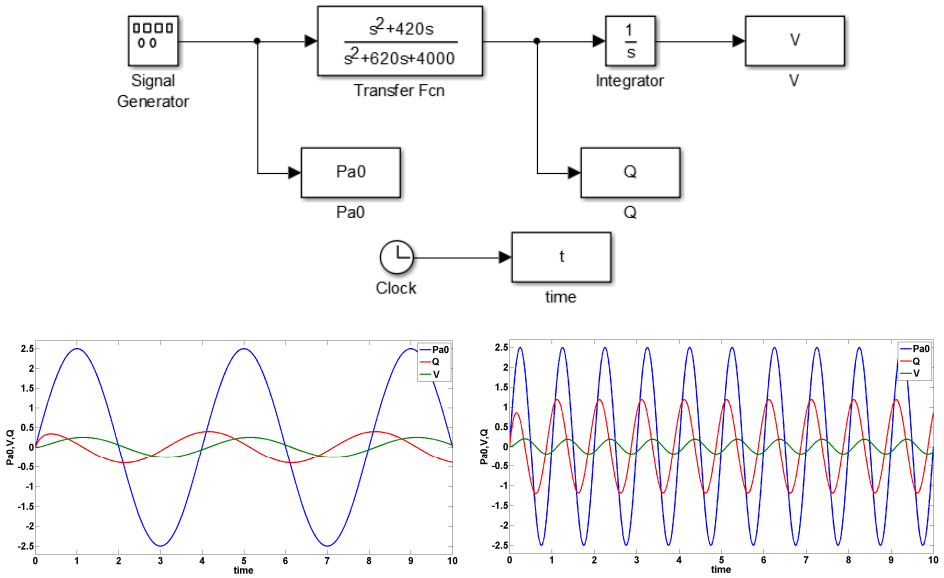

Fig. 4. Block diagram of a linear model of pulmonary ventilation mechanics and simulation results (15 breaths per minute (left); 60 breaths per minute (right))

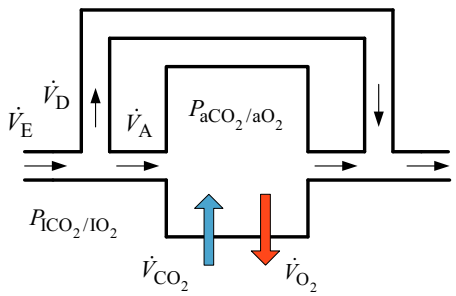

Fig. 5. Stationary model of CO_2 and O_2 exchange

The minute volume of alveolar ventilation is the total volume of fresh air that enters into all areas where gas exchange takes place every minute [5], and according to Fig. 5 it is

$$\dot{V}_A = \dot{V}_E - \dot{V}_D \tag{9}$$

where: $\dot{V}_A$ - alveolar ventilation rate, $\dot{V}_E$ - total ventilation rate, $\dot{V}_D$ - dead space ventilation rate. At normal values of the respiratory volume V_E=500 ml and dead space V_D=150 ml, as well as the breathing frequency of 12 respirations per minute, the rate of alveolar ventilation is $\dot{V}_A = f\left(V_E - V_D\right) = 4.2\ \left[\text{l/min}\right]$.

Note that for $\dot{V}_{CO_2}$ (the rate at which CO_2 comes to the lungs via the pulmonary circulation) the following equation based on the mass balance of CO_2 can be written:

$$\dot{V}_{CO_2} = k\dot{V}_A\left(F_{ACO_2} - F_{ICO_2}\right), \tag{10}$$

where: F_{ACO_2} - concentration of CO_2 in the air that leaves the alveoli, F_{ICO_2} - concentration of CO_2 in the inspiratory, k - constant that enables volume and flow conversion from BTPS units to STPD units using ideal gas equation as follows

$$\frac{V_{STPD}\cdot 760}{273} = \frac{V_{BTPS}\cdot\left(P_B - 47\right)}{310}. \tag{11}$$

Thus, it is obtained

$$k = \frac{V_{STPD}}{V_{BTPS}} = \frac{P_B - 47}{863}, \tag{12}$$

where P_B is barometric preassure under which tha gas excange proces occurs. Its value is 760 [mmHg] at sea level and it decreases with altitude increase.

Corresponding concentrations can be converted in partial pressures using Dalton's law, so

$$P_{\mathrm{ICO}_2} = F_{\mathrm{ICO}_2}\left(P_{\mathrm{B}} - 47\right) \tag{13}$$

$$P_{\mathrm{ACO}_2} = F_{\mathrm{ACO}_2}\left(P_{\mathrm{B}} - 47\right) \tag{14}$$

The so-called metabolic hyperbola for CO_2 and O_2 is obtained from equations (10)-(14) in a form

$$P_{\mathrm{ACO}_2/\mathrm{AO}_2} = P_{\mathrm{ICO}_2/\mathrm{IO}_2} \pm \frac{863 \cdot \dot{V}_{\mathrm{CO}_2/\mathrm{O}_2}}{\dot{V}_{\mathrm{A}}}. \tag{15}$$

In previous equation sign "±" corresponds to the direction of air flow, so metabolic hyperbola for CO_2 is obtained when sign "+" is chosen. Normal value of alveolar pressure P_{ACO_2} is 40 [mmHg], it is between the value in the inhaled air (0 [mmHg]) and the value in venous blood (45 [mmHg]). For alveolar pressure P_{AO_2} normal value is 104 [mmHg], and it lies between the value in the inhaled air (149 [mmHg]) and the value in venous blood (40 [mmHg]). For the purpose of modeling, it can be adopted that the alveolar partial pressure equals to partial pressure of the corresponding gas in arterial blood:

$$P_{\mathrm{aCO}_2/\mathrm{aO}_2} = P_{\mathrm{ACO}_2/\mathrm{AO}_2} \tag{16}$$

although the alveoli/arteria preassure gradient is about 5 [mmHg].

4 Conclusions

In this paper a simple linear model of pulmonary ventilation mechanics is obtained, starting from the conceptual model of the cardiovascular-respiratory system. According the obtained model a simulation is performed. Special attention was paid to a static analysis of gas exchange in the lungs. The purpose of this paper was to describe how to get a simple model of the lung mechanics and gas exchange which can be used as starting point in understanding the basic physiological processes and their dynamics during quiet breathing for both engineering and medical researchers. Based on the model, proper measures could be suggested and taken when different functional respiratory disorders appear. The subject of future research could be a complex physiological control mechanism of cardiovascular system, as well as its interaction with the respiratory control system. This requires adequate identification of both inherently nonlinear dynamic systems.

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