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MATHEMATICAL MODELLING OF A HUMAN EXTERNAL RESPIRATORY SYSTEM

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This mathematical model of the human external respiratory system is a closed system of algebraic and common differential equations, solved by computer. It includes equations which describe the activity pattern of the respiratory center, the phrenic nerve, the thrust produced by the diaphragm as a function of the lung volume and discharge frequency of the phrenic nerve, as well as certain relations of the lung stretch receptors and chemoreceptors on various lung and blood characteristics, equations for lung biomechanics, pulmonary blood flow, alveolar gas exchange and capillary blood composition equations to determine various air and blood flow and gas exchange parameters, and various gas mixing and arterial and venous blood composition equations, to determine other blood, air and gas mixing characteristics. Data are presented by means of graphs and tables, and some advantages of this model over others are demonstrated by test results.

Abstract

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[Anonymous]

The oxygen consumed in cell respiration is supplied to the tissues of the human body and the carbon dioxide formed, as a result of this process, are removed from the tissues by the human external respiratory system. In this manner, it plays the primary part in regulation of the oxygen conditions and acid-base balance of the body, which, to a great extent, determines the possibilities of adaptation of the body to extreme effects.

In study of the effect of extreme factors connected with space flight on the human external respiratory system, it must be taken into consideration that the basic portion of them (weightlessness, g-forces, changed gaseous living environment) directly affect the controlled link of the system, i.e., the lungs and pulmonary blood circulation. The effect of these factors frequently is not manifested at the level of separate pulmonary units, but only of the organ as a whole, and it most significantly involves the pattern of the processes in the lungs.

It follows from this that a model of external respiration equal to the tasks of space medicine has to consider pulmonary gas exchange as a dynamic process in a system with rhythmically changing blood and gas flows, and the lungs, as the aggregate of a large number of functional units, which work under any permissible conditions. Such a model permits the information content of the external respiration characteristics accessible for measurement under space flight conditions to be increased, predicting their quantitative connection with vitally important parameters of the body, which are not accessible for measurement.

Principles of Synthesis of a Mathematical Model of a Human External Respiratory System

In this work, the human external respiratory system is considered as a closed control circuit, consisting of controlling and controlled links. The controlling link is the bulbar respiratory center and the pneumotaxic center of the pons varolii, as well as the stretch receptors of the lungs and the arterial chemoreceptors, which provide feedback between the controlled and controlling links of the system.

The electrical activity of the phrenic nerve, which provides

*Numbers in the margin indicate pagination in the foreign text.
for contraction of the inspiratory muscles of the diaphragm, is an incoming control action from the respiratory center. The controlled link includes a biomechanical system, which participates in the respiratory motions of the lungs, pulmonary blood circulation and the pulmonary gas exchange system.

At the present time, unified ideas of the mechanism of formation of the respiratory rhythms still have not been put together in science. Therefore, a model of the respiratory center is proposed in this study, which is of a "phenomenological" nature. This model, which does not claim to completeness in reflecting all of the complicated aggregate of connections between the neurons of the respiratory center, permits prediction of the experimentally observed relations between the depth of respiration and the durations of inhalation and exhalation, as well as correct description of the phase nature of the activity of the basic groups of respiratory neurons.

In synthesis of the model, the effects of gravitation and other external forces on the lungs and pulmonary blood circulation were taken into account in detail. The basis of the model of the controlled link of the system is the concept of the lungs as an aggregate of a large number of parallel-connected units, each of which can independently carry out all pulmonary functions. Therefore, the model of functionally uniform lungs, which is at the same time a model of an individual pulmonary unit, permits regional differences in functioning of the lungs to be studied. Blocks of the model of human external respiration, as applied to uniform lungs, are described below. These blocks are included in the model of nonuniform lungs, without significant changes.

**Block Diagram of Model**

The mathematical model of external human respiration is synthesized in the form of a closed system of algebraic and ordinary differential equations, investigation of which was carried out, by means of digital solution by computer. The equations of the model can be divided into the following blocks, shown in Fig. 1.

1. The blocks classified as the control link of the model (they are located inside the dashed rectangle in the figure) include: equations which describe the activity pattern of various neuron pools of the respiratory center and the electrical activity of the phrenic nerve; the dependence of the thrust produced by the diaphragm on lung volume and the frequency of discharges in the phrenic nerve; the dependence of the lung stretch receptor signal on the magnitude and rate of change in pulmonary volume; the characteristics of the chemoreceptors which express the relation of "chemical drive" (the primary exciting effect on the respiratory center neurons) on the gas composition of the arterial blood.
2. The "lung biomechanics" block, the equations of which permit the pressure and volume of the air in the lungs, ventilation rate and pressure in the pleural and abdominal cavities to be determined at each moment of time.

3. "Pulmonary blood flow" block, which permits calculation of the blood flow dynamics and transmembrane liquid exchange in the lung capillaries during the respiratory cycle, as well as estimation of the regional distribution of blood flow in the lungs, as a function of the magnitude and direction of the force of gravity.

4. The "alveolar gas exchange" block, in which the pattern of the oxygen, carbon dioxide and inert gas partial pressures in the alveolar air and the flows of these gases through the lung membrane are calculated during the respiratory cycle.

5. The "capillary blood composition" block, in which, for each instantaneous composition of the alveolar air, the basic characteristics of the capillary blood in equilibrium with it, the degree of dissociation of oxyhemoglobin, the hydrogen exponent,
the content of bound and dissolved \( \text{O}_2 \) and \( \text{CO}_2 \) per ml of blood and the ratio between the \( \text{CO}_2 \) concentrations in plasma and erythrocytes are calculated.

6. "Gas mixing in dead space" block, which describes the establishment of the compositions of the mixed exhaled air and air entering the gas exchange sections of the lungs during inhalation in the air pathways of the lungs.

7. "Arterial and venous blood composition" block, in which, from the composition of the blood entering from the pulmonary capillaries and the magnitude of the arterial venous shunt of the pulmonary blood circulation, the composition of the mixed arterial blood is determined and, from its composition and the metabolic rate of the body, the composition of the mixed venous blood.

Input and Outputs of the Model of the External Respiratory System

The basic inputs of the model are: a. external environment factors (external forces vector acting on the lungs, pressure and composition of the gaseous environment); b. parameters of other systems of the body, including the overall rate of metabolism, venous and arterial pressure in the pulmonary blood circulation, oxygen capacity of the blood and the excess of bases in it. The outputs of the model are the basic functional characteristics of the external respiratory system:

1. Depth and rate of respiration, dependence of the volume and ventilation of individual units of the lungs and the lungs as a whole on time;

2. Pattern of gas composition of alveolar air, arterial blood and exhaled air, both with stationary gas exchange and during transition processes caused by change in outside conditions or parameters of other physiological systems of the body;

3. Qualitative pattern of regional differences and patterns of local values of pulmonary blood flow, volumes of extracellular fluid and capillary blood in the lungs.

Functioning of Individual Blocks of the Model

At present, there are a number of mathematical models of the external respiratory system, which, by using the principle of chemical feedback, describe regulation of the minute volume of respiration. In these models, however, the rhythms of respiration are not taken into account, which significantly limits the possibilities of their use, for modeling transition processes in the external respiratory system [20, 21, 15, Proceedings of Symposium 1 IFAK, 1970, and others].
In the synthesis of the human external respiration model described here, the primary attention was devoted to establishment of the rhythmical activities of the respiratory center and of the respiratory movements of the lungs caused by it, as well as the pattern of pulmonary gas exchange during the respiratory cycle.

Respiratory Center Model

The proposed respiratory center model is based on the relationships between the respiratory volume and durations of inhalation and exhalation, observed experimentally in man and animals, as well as on the best known functional schemes of the respiratory center.

In the synthesis of the model, it was taken into consideration that 1. the respiratory center consists of several neuron pools, the presence of widespread connections inside each of which ensures their functioning as unified formations; 2. the excitation, which arises as a result of the "chemical drive" in the inspiratory neurons of the respiratory center, which increase during inhalation, and which become rhythmical, owing to the inhibiting effect of either single expiratory neurons, or else afferent pulses from the mechanoreceptors of the lungs, fed through the vagus nerve [11, 18].

The relationship between the depth and duration of inhalation observed during recurrent human respiration (usually called the Hering-Breuer "volumetric threshold curve") has two qualitatively different sections: vertical (section 1) and hyperbolic (section 2). They indicate the presence of two competing mechanisms of stopping inhalation [17]. In accordance with this fact, the proposed model has a variable structure: quiet respiration, i.e., section 1, corresponds to the scheme of the respiratory center shown in Fig. 2a; deep respiration (section 2), the scheme shown in Fig. 2b. Both of these schemes reflect the essence of the majority of hypotheses of the mechanism of the rhythmical activity of the respiratory center. Thus, the structure of the model for section 2 of the volumetric threshold curve (Fig. 2b) is based on a functional scheme of regulation of the duration of inhalation, in accordance with a signal of change in lung volume approaching by the vagus nerve [16, 3]. The structure of the model for the quiet respiration section (Fig. 2a) includes elements of a number of models, which describe the establishment of the respiratory rhythm, without information on lung volume [10, 8, 7].

The resulting model satisfactorily describes the relationships between ventilation of the lungs and the durations of inhalation and exhalation of man, as well as the activity rhythms of the basic groups of respiratory neurons and changes in this activity with change in gas composition of the arterial blood. Structure 1 of the model (Fig. 2a), which provides a constant respiration rate with changes in respiratory volume, covers practically the
entire range of change in the human external respiration characteristics, as a result of space flight factors. At the same time, structure 2 of the model (Fig. 2b), which predicts an increase in respiration rate with increase in ventilation, describes well the data obtained on animals (cats, in particular), over almost the entire range of their respiratory volumes. Thus, two volumetric threshold curves, calculated by means of model data and experimental data obtained on cats [Euler, 1972], are shown in Fig. 3a. Neurograms of the inspiratory neurons, calculated by means of the same model and observed experimentally on cats, are presented in Fig. 3b. They enable the conclusion to be drawn that this model more adequately takes account of the effect of a chemical stimulus on the respiratory center, than the best of the existing models, the von Euler model [16].

External respiratory system receptors

Feedback action in the external respiratory system has been described in this model by means of the respiratory relationships generally accepted in physiology. In description of the volumetric feedback, the action of the slowly adapting lung stretch receptors, the only groups of lung mechanoreceptors which play a significant role in establishment of rhythmical respiration, has been considered [2].

The signals of these receptors, fed into the respiratory center by the vagus nerve, are proportional to the magnitude and rate of change in lung volume [5, 19].

Within the framework of only one external respiration model, i.e., without consideration of exchange processes in the organs and tissues of the body, only the rapid phase of the respiratory reactions, the duration of which does not greatly exceed the time of passage of blood through the circulation system, can be considered. Only the arterial chemoreceptors of the aortic and carotid bodies, which have a delay time of not over 5-10 seconds, can participate in this rapid phase of the reactions. The signals of the central (medullary) chemoreceptors, the delay times of which are much greater than those of the arterial, can be considered constant in consideration of such processes [1].

Participation of the chemoreceptor signals in the working of the respiratory center is expressed in this model by the amount of "chemical drive," the input which activates the inspiratory neurons. The minute volume of respiration calculation relationships, the composition of the arterial blood and other external respiration characteristics vs. the amount of "chemical drive," received by open feedback, are presented in Fig. 4. In themselves, these relationships permit estimation of the effect of irregularity in regional distribution of ventilation and blood flow in the lungs on their functioning.
Fig. 2. Functional diagrams of respiratory center.
Fig. 3. Calculated and experimental curves: a. volumetric threshold curves; b. inspiratory neuron neurograms.

Key:  
- c. Pulse rate (pulse/sec)  e. Discharge frequency (pulse/sec)  
- d. Standard  
- f. Time
The relationships presented in Fig. 4 were compiled with experimental data on the linear dependence of minute volume of respiration on CO2 tension in the arterial blood and of the hyperbolic relationship of minute volume of respiration to arterial O2 tension [1, 21, 12]. As a result, the connection of the chemical "drive" to the gas composition of the arterial blood was obtained in explicit form, which permitted closing the chemical feedback in this model, between the controlled link and the respiratory center. The delay time in this feedback circuit was chosen somewhat less than actually observed in man. During each respiratory
cycle, the chemical drive was a function of the average gas composition of the blood passing through the lungs in the preceding cycle.

Biomechanics of the Lungs and Alveolar Gas Exchange

A complicated mechanical system, including the lungs themselves, the diaphragm, the abdominal cavity, the abdominal wall and the thoracic cage, participate in the respiratory movements of the lungs (Fig. 5a). Its elements possess nonlinear viscous and elastic properties. Besides, the lung pressure and volume depend on alveolar gas exchange, the magnitude and direction of the gravity vector and other external forces.

In modelling the respiratory act, it was considered that, in the range of respiratory volumes under study, the thoracic cage remains motionless, i.e., stretching of the lungs during inhalation is carried out only by the diaphragm muscles, and exhalation is passive.

The pattern of the gas partial pressures in the alveolar space of the lungs is determined by the balance between the air flow through the boundary of the dead space caused by the respiratory movements of the lungs and the diffusion flows of gases through the pulmonary capillary membranes. On the assumption that complete mixing takes place in the entire alveolar space and that the gases of the blood leaving the pulmonary capillaries are in equilibrium with the alveolar air, the following alveolar gas exchange equation can be obtained [13]

\[
(V-V_D) \frac{dP_{AJ}}{dt} = F \cdot P_{DJ} - V \cdot P_{AJ} - Q \cdot AVD_{J} \cdot (P_A - 47), \quad J=1,2,3 \tag{1}
\]

where \( J \) is the number of the gas (O\(_2\), CO\(_2\), inert gas); \( V \) and \( V_D \) are the volumes of the lungs and the pulmonary air passages (dead space); \( F \) is the bulk airflow rate through the boundary of the alveolar space with the dead space; \( P_{DJ} \) are the partial pressures of the gases in this flow; \( Q \) is the bulk blood flow rate; \( AVD_{J} \) is the arteriovenous difference in content of the \( J \)-th gas per ml of whole blood (in ml BTFS/ml); \( P_{AJ} \) is the gas partial pressures.

In calculation of \( AVD_{O2} \) and \( AVD_{CO2} \) in (1), which are complex nonlinear functions \( P_{AO2} \) and \( P_{ACO2} \), known models of the oxyhemoglobin dissociation curve and the acid base balance of the blood were used [22-24].

Equation (1) permits calculation of the changes in alveolar pressure \( P_A \), equal to the sum of all \( P_{AJ} \) and the water vapor pressure. Then, by means of the equations of motion of the air in the air passages of the lungs, \( F \) is determined [Shik, 1973]:

\[
K_1F + K_2FF_1 = P_{AT} - P_A, \tag{2}
\]
where \( P_{AT} \) is the external pressure and \( K_1' \) and \( K_2' \) are coefficients of loss.

Fig. 5a. Diagram of mechanical apparatus of external respiration;

Key: 
- c. Lungs
- d. Thoracic cage
- e. Pleural fissure
- f. Diaphragm
- g. Abdominal wall
- h. Abdominal cavity

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Fig. 5b. Curves of change of functional residual capacity of lungs.

Key: 1. Residual functional capacity with longitudinal g-forces (+Gz)
   j. Residual functional capacity with deviations of longitudinal body axis by angle $\alpha_z$ from vertical
   k. Residual functional capacity (R)
   l. $\alpha$ (degrees)
Analysis of the diagram in Fig. 5a shows that the equation of motion of the lungs, diaphragm and the abdominal cavity and wall can be presented in the form:

\[ K_{11} \dot{V} = PA - PAT + D \cdot E(t)(V_{\text{max}} - V) - \frac{V - V_0(g, \alpha)}{EL(g, \alpha)}. \] (3)

where \( E(t) \) is the electrical activity of the phrenic nerve; \( K_{11}, D, V_{\text{max}} \) are coefficients; \( V_0(g, \alpha) \) and \( EL(g, \alpha) \) are the functional residual capacity of the lungs and the effective elasticity of the system under consideration as a whole, dependent on angle \( \alpha \) between the longitudinal axis of the body and the direction of the gravity (or other force) vector; \( g \) is the magnitude of this vector.

The calculation relationships of \( V_0(g, \alpha) \) are presented in Fig. 5b. Equation (3) permits calculation of the magnitude and rate of change in lung volume. Thus, equations (1), (2) and (3) form a closed system, which has an asymptotically stable solution. In combination with the respiratory center model, this system permits calculation of the variations of \( V, PA \), and \( PA \) during the respiratory cycle.

The calculation results with the most typical parameters of the external respiratory system are shown in Fig. 6.

Gas Composition of Exhaled Air

As is evident from Fig. 6, each respiratory cycle can be divided into three phases by gas exchange conditions: 1. start of inhalation, during which residual air in the air passageways at the end of expiration return to the gas exchange sections of the lungs; 2. true inhalation; 3. exhalation. Thus, for calculation of the pattern of alveolar gas exchange and composition of the exhaled air, the distribution of the gas partial pressures in the dead space of the lungs must be known. In this model, this distribution is calculated on the basis of the morphometric data of Veybel' [4]. In accordance with his classification of the respiratory passages, the dead space of the lungs is divided into "conducting" and "transition" zones. In each zone, movement of the gases takes place only along the axes of the air passages, and there is complete mixing in each cross section. In the "transition" zone, partial mixing of the gases along the longitudinal axis occurs, while, in the conducting zone, longitudinal mixing is completely absent.

Such a model of the dead space permits calculation of the exhaled air capnograms shown in Fig. 6, in the case of uniform lungs. In analysis of the regional irregularity in functioning of the lungs, with consideration of the conducting zone common to all lung units and by varying the dimensions of the transition zones adjacent to them (its own for each lung unit), the corresponding changes in slope of the plateau of the exhaled air composition curves can be obtained, and the asynchronism of filling and evacuation of different sections of the lungs can be described [9].
Fig. 6. Pattern of variations in lung volume and gas partial pressure in alveolar and exhaled air during respiratory cycle.
Result of Modelling of Respiratory Reactions

1. Orthostatic test. The results of modelling of transition processes in the external respiratory system, during sudden rising of a man from a horizontal position to the vertical (orthostatic test), are presented in Fig. 7. The moment of rising is adopted as $t=0$. It was considered in the calculation that, as a result of the orthostatic test, because of the increase in hydrostatic pressure in the right atrium and in the abdominal cavity, a gradual increase in pulmonary blood flow and the functional residual capacity of the lungs and a decrease in elasticity of the external respiratory apparatus, the calculated values of which are shown in the table of Fig. 7, occurs. In the graphs of the left half of Fig. 7, the results of modelling the orthostatic test, with a constant chemical "drive," which corresponds to the assumption of the absence of an afferent signal of the arterial chemoreceptors, for example, with their denervation, are shown. The reactions of the respiratory system to the orthostatic test, with active arterial chemoreceptors, are shown on the right. The modelling results graphically demonstrate the important role which this group of chemoreceptors plays in stabilization of arterial blood composition, during sudden changes in the parameters of the external respiratory system.

2. Breathing pure oxygen. The result of modelling of the rapid phase of the ventilation reactions to inhalation of pure oxygen, called the "oxygen test," are presented in Fig. 8 [1]. As is evident from Fig. 8, after one or two inhalations of pure $O_2$, a small decrease in ventilation occurs, due to "physiological denervation" of the chemoreceptors by the hypercapnic blood reaching the receptors of the carotid body. In this case, an increase in arterial $CO_2$ tension begins, which subsequently should cause an increase in activity of the respiratory center, acted on by the central chemoreceptors.

It should be noted that, for an adequate description of alveolar gas exchange in breathing pure oxygen, the differences between $V$ and $F$ in (1) must be taken into account, i.e., accounting for the differences between the actual changes in lung volume and air volume entering the lungs or leaving them. In the case shown in Fig. 8, this difference increases from ~0.25 ml/cycle in breathing air to 9.5 ml/cycle in breathing oxygen. With a metabolic respiratory coefficient of man appreciably different from one, the role of this factor may prove to be highly significant.

3. Breathing of hypoxic and hypercapnic mixtures. The results of modelling the transition of man to breathing an oxygen poor mixture (14% $O_2$), with (right hand graph) and without (left hand graph) addition of 3% $CO_2$ of this mixture, are presented in Figs. 9 and 10. Fig. 9 illustrates the phenomenon of hypoxic stimulation of respiration, an increase in ventilation of the lungs and, as a consequence, negligible hypocapnia. A more noticeable increase in ventilation...
Fig. 7. Orthostatic test modelling.

Key:
a. Moment of rising
b. Position
c. $Q(\ell/min)$
d. $I/C_b$ (mm Hg/\ell)
e. Functional residual capacity ($\ell$)
f. Prone
g. Standing
h. Model without chemoreceptors
i. Effect of arterial chemoreceptors
j. $n$(cycles)
k. $t$(sec)
Fig. 8. Hyperoxia modelling.
Key: a. n(cycles) b. t(sec)

Fig. 9. Modelling of ventilation reactions in hypoxia.
Fig. 10. Modelling of changes in alveolar $O_2$ in hypoxia.

and an increase in arterial $CO_2$ tension is seen in the second graph, in breathing a hypoxic-hypercapnic mixture. As is seen in Fig. 10, in breathing a hypoxic mixture with 3% $CO_2$, the arterial oxygen tension is approximately 5 mm Hg higher than in breathing a mixture without $CO_2$. This positive effect of the addition of carbon dioxide, caused by the action of only some arterial chemoreceptors in this case, is considerably less marked than is actually observed [6]. Thus, the modelling results indicate the leading role of the central chemoreceptors in this effect.
References


