PREDICTION OF CARBON MONOXIDE TRANSPORT IN THE HUMAN RESPIRATORY SYSTEM

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Abstract. *The aim of this work is the development of a mass transfer mathematical model of the carbon monoxide transport in the human respiratory system. It considers the exchanges of carbon monoxide, oxygen and carbon dioxide in the lung, blood and tissues. The human body was divided in the following compartments: alveolar, pulmonary capillaries, arterial, venous, tissue capillary and tissues. The model enables the analysis of the carbon monoxide transient distribution in the human body, depending on the inspired air conditions. The equations were derived from principles of mass conservation. The gas transport in the blood and tissues is represented by empirical equations. The mutual influence of the gases on each other transport was also considered. The model was validated by comparing its results with experimental data of controlled CO exposition. The agreement was excellent.*

Keywords: *model of respiratory system, carbon monoxide, gas transport, compartment model*

1. INTRODUCTION

The carbon monoxide (CO) is a colorless, odorless and insipid gas. It has been the main cause of accidental deaths from poisoning. It is responsible for the biggest amount of pollutant launched in the atmosphere, produced by man and nature. The main source is the fossil fuels burning (coal, oil and natural gas), most produced by motorized vehicles. The human body produces CO at low levels.

The function of the human respiratory system is to provide oxygen (O_2) to the tissues and to eliminate the carbon dioxide (CO_2) produced by them. Most of the O_2 transported by the blood is through its reaction with hemoglobin molecules. The transport of CO happens in the same way, but its affinity with hemoglobin is about 250 times bigger than O_2. The presence of CO in the blood reduces its capacity to carry O_2. Therefore, large CO concentrations produce the lack of O_2 in the tissues. The linkage between CO and hemoglobin is called carboxyhemoglobin (COHb), represented by the amount (%) of hemoglobin reacted with CO. It is used to relate the effects of CO in the human body (Tab. 1). It is measured by analysis of blood or exhaled air. In the absence of measurement methods, the COHb can be estimated through mathematical models.

Table 1: Effects of COHb level in the blood of health subjects [adapted from WHO (1999)].

COHb [%]	Effect
> 2	Small decreases in work capacity
5	Decrease of oxygen uptake and exercise performance; decrements in neurobehavioral function
10	Shortness of breath on vigorous exertion; possible tightness across the forehead; dilation of cutaneous blood vessel
20	Shortness of breath on moderate exertion; occasional headache with throbbing in temples
30	Decided headache; irritable; easily fatigued; judgement disturbed; possible dizziness; dimness of vision
$40 - 50$	Headache; confusion; collapse; fainting on exertion
$60 - 70$	Unconsciousness; intermittent convulsion; respiratory failure; death if exposure is long continued
80	Rapidly fatal

Most of mathematical models are empirical (Forbes et al., 1945; Pace et al., 1946; Lilienthal and Pine, 1946; Goldsmith et al., 1963; Ott and Mage, 1978; Venkatram and Lough, 1979). The output of an empirical model has consistency only for the conditions in which the experiment was carried out. More elaborated empirical models were proposed by Peterson and Stewart (1970) and Stewart et al. (1973) for a large range of CO concentrations.

Recently, models describing the physiological processes related to CO transport in the human body have presented satisfactory results. Among them the CFK model (Coburn et al., 1965) has been extensively used. There are several applications and validations of that model (Marcus, 1980; Collier and Goldsmith, 1983).

The model of Sharan and Selvakumar (1999) divides the lung in compartments, one alveolar and several pulmonary capillaries. It considers, besides CO, the exchanges of the gases O_2, CO_2 and nitrogen (N_2). It was applied to the end-expired breath technique. The model of Bruce and Bruce (2003) also divides the human body in compartments, including the muscular and non-muscular tissues. The present model has characteristics of the lung's representation by Sharan and Selvakumar (1999) and the tissues's representation of Bruce and Bruce (2003).

The carbon monoxide transport model in the human respiratory system developed considers the exchanges of CO, O_2, and CO_2. The human body was divided in the following compartments: alveolar, pulmonary capillaries, arterial, venous, tissue capillary, and tissues (muscular and non-muscular). The transport of gases in the blood and tissues are represented by relations found in literature. The model enables the analysis of the gases transient distribution in the human body, depending on its condition and the gas concentration in the atmospheric air.

2. TRANSPORT

The respiration process starts with the air passing through the dead space, where it is totally humidified. The water vapor pressure (P_{H_2O}) at the body temperature of 37 °C is 47 mmHg (6.27 kPa). The pressure of the inhaled gases arriving in the alveoli is the barometric pressure less the water vapor pressure.

$$P_{g,in} = F_{g,in}\,(P_{bar} - P_{H_2O}) \tag{1}$$

where g = CO, O_2, CO_2; $P_{g,in}$ = partial pressure of g inspired [kPa]; $F_{g,in}$ = fraction of g in inspired air [0 to 1]; P_{bar} = barometric pressure [kPa]; P_{H_2O} = water vapor pressure [kPa].

The gas diffusion capacity through the respiratory membrane is known in physiology by D_L. It is the relationship between the flux of a certain gas through the respiratory membrane and its driving force, which is the difference between the alveolar partial pressure and the average of the pulmonary capillary partial pressures. It includes the diffusion through the membranes and the speed of the chemical reactions in the erythrocytes.

The CO, O_2 and CO_2 gases are transported by the blood dissolved and chemically reacted with hemoglobin. In the tissues, they are stored dissolved. In the muscular tissues, the CO and O_2 are also chemically reacted with myoglobin. The relationships of the O_2 and CO_2 transport are based on the work of Turri (2006).

The amount of dissolved gases is equal to their partial pressures multiplied by the gas solubility coefficient. These coefficients for the blood at body temperature (37 °C) are (1.7, 2.2 and 50.3) x 10^{-4} ml/(ml·kPa) for CO, O_2 and CO_2 respectively. For the tissues (assumed to be the same as water), these coefficients are (1.82, 2.36 and 56) x 10^{-4} ml/(ml·kPa) for CO, O_2 and CO_2 (Altman and Dittmer, 1971).

Most of O_2 is carried by the blood through its chemical reaction with hemoglobin, forming a compound called oxyhemoglobin (O_2Hb). The relationship between the amount of O_2Hb and the total amount of hemoglobin is the O_2 saturation (S_{O_2}), where 100 % corresponds to the maximum capacity of 1.34 ml/g of hemoglobin (Guyton and Hall, 2005). The hemoglobin concentration in the blood $[Hb]$ of a normal subject is 0.15 g/ml (Guyton and Hall, 2005). The relationship between the partial pressure of O_2 and its saturation is given by the dissociation curve. It varies in function of the CO_2 amount in the blood and temperature. The oxygen saturation is obtained as proposed by Kelman (1966), considering the temperature equal to 37 °C:

$$S_{O_2} = \frac{N^4 - 15\,N^3 + 2\,045\,N^2 + 2\,000\,N}{N^4 - 15\,N^3 + 2\,400\,N^2 - 31\,100\,N + 2.4 \times 10^6} \tag{2}$$

$$N = 7.5\,P_{O_2} \times 10^{[0.48\,(pH-7.4)-0.0013\,BE]} \tag{3}$$

where S_{O_2} = hemoglobin saturation of O_2 [0 to 1]; P_{O_2} = partial pressure of O_2 [kPa]; BE = base excess [mmol/L].

The blood carries CO in the same way that O_2, dissolved and chemically reacted with hemoglobin. The reversible reaction of CO with hemoglobin forms the carboxyhemoglobin (COHb), also known as the CO hemoglobin saturation (S_{CO}). The affinity of CO with the hemoglobin is about 250 times bigger than O_2. The following relationship represents the transport of CO and O_2 in the blood. The maximum blood capacity to carry reacted CO is the same of O_2.

$$x_g = \alpha_g\,P_g + 1.34\,[Hb]\,S_g \tag{4}$$

where x_g = content of g [ml/ml]; α_g = solubility coefficient of g [ml/(ml·kPa)]; P_g = partial pressure of g [kPa]; $[Hb]$ = hemoglobin concentration [g/ml]; S_g = hemoglobin saturation of g [0 to 1].

The classic work of Douglas et al. (1912) is the first theoretical study of the interdependence between the hemoglobin saturation of CO and O_2. They concluded that the presence of CO in the blood moves the dissociation curve of O_2 to the left, reduces its inclination and turns it more hyperbolic. That variation is known as the Haldane effect. Based on these observations some theoretical relationships were developed, known as the Haldane equation:

$$\frac{S_{CO}}{S_{O_2}} = M\,\frac{P_{CO}}{P_{O_2}} \tag{5}$$

where M = Haldane constant.

The value of the Haldane constant (M) is the relationship of the hemoglobin affinity between CO and O_2. Several researchers attempt to find a suitable value for this constant, being usually between 210 and 290. In the present work the value of 246, determined experimentally by Douglas et al. (1912), is used.

Due to the similarity between the reactions of the hemoglobin with CO and O_2, the dissociation curve of CO in the absence of O_2 has the same form of the dissociation curve of O_2 in the absence of CO. The total hemoglobin saturation for O_2 and CO can be obtained by the dissociation curve of O_2 in the absence of CO, considering the P_{O_2} as $P_{O_2} + M\,P_{CO}$.

CO_2 is transported dissolved in the blood, linked to the hemoglobin, and as bicarbonate ion. The CO_2 linked to the hemoglobin forms the carbamino (CO_2Hb). However, CO_2 does not occupy the same connections with the iron atom of CO or O_2. The amount of CO_2Hb depends on the saturation of the hemoglobin for CO and O_2. Most of CO_2 (approximately 70 %) is transported in the form of bicarbonate ion after reacting with water. To determine the total content of CO_2 in the blood, it is used the model proposed by Douglas et al. (1988):

$$x_{CO_2} = x_{CO_2,pl}\left(1 - \frac{0.0289\,[Hb]}{(3.352 - 0.456\,S_{O_2})\,(8.142 - pH)}\right) \tag{6}$$

$$x_{CO_2,pl} = \alpha_{CO_2}\,P_{CO_2}\left[1 + 10^{(pH-6,1)}\right] \tag{7}$$

where $x_{CO_2,pl}$ = content of CO_2 in the plasma [ml/ml].

In the tissues, the gases are stored dissolved and chemically reacted in the muscular tissues. The protein called myoglobin has a function similar to the hemoglobin in the blood. It is used for O_2 storage, forming the oxymyoglobin (O_2Mb). CO also competes with O_2 for the links with the myoglobin, with affinity about 25 times bigger, forming the carboxymyoglobin (COMb).

The maximum myoglobin capacity to store the gases is determined by the hemoglobin capacity multiplied by the relation of their molecular masses, $68\,000$ for Hb and $17\,600$ for Mb (Guyton and Hall, 2005), divided by four (hemoglobin carries four molecules and myoglobin one). That relationship was adapted from the model of Bruce and Bruce (2003). The myoglobin concentration in the muscles is 0.0053 g/ml (Coburn and Mayers, 1971). The myoglobin saturation is also represented by a dissociation curve. The Hill equation was used to represent this curve, according to Schenkman et al. (1997):

$$S_{O_2} = \frac{P_{O_2}}{P_{O_2} + P_{50}} \tag{8}$$

where $P_{50} = P_{O_2}$ necessary to saturate half of the myoglobins [kPa].

The P_{50} for mioglobin is equal to 2.33 mmHg (0.311 kPa) (Schenkman et al., 1997).

The energy in the human body is generated by the oxidation of some compounds with linkages between carbon and hydrogen. These compounds are the carbohydrates, fats and some carbon-hydrogen chains. CO_2 and water are generated as product of that oxidation. This process is known as metabolism. The relationship between the amount of CO_2 produced and the O_2 consumed is the respiratory quotient (RQ).

The human body produces CO in an endogenous way, mainly in the process of hemoglobin degradation (about 80 %). The organ responsible for producing most of CO is the liver. Coburn et al. (1963) experimentally determined the value of endogenous production of CO in rest as 0.007 ml/min.

The blood is distributed in the body by the cardiac output (Q_B). Through the lung, only a fraction of the cardiac output exchange gases with the alveoli. That fraction, known by σ, is equal to 0.98 for a normal person (Guyton and Hall, 2005).

The total blood volume in the human body of adults is approximately $5\,000$ ml (Guyton and Hall, 2005). That volume is divided in four parts. One represents the blood in the pulmonary capillary, with volume (V_{cp}) equal to 100 ml (Mountcastle, 1980). The others values, based on Guyton and Hall (2005), are the arterial blood (V_a), equal to $1\,000$ ml, the venous blood (V_v), equal to $3\,550$ ml, and the blood present in the tissues capillary (V_{ct}), equal to 350 ml.

The volume of muscular tissues (V_{tm}) is approximately $30\,000$ ml. The volume of the non-muscular tissues (V_{tn}) is approximately $7\,000$ ml. The alveolar volume (V_A) is approximately $2\,000$ ml in the end of expiration (Mountcastle, 1980).

It is considered in the present model the variations of the physiologic parameters that more significantly affect the respiratory process, related to the O_2 consumption ($\dot{V}_{O_2}$). These parameters are the alveolar ventilation ($\dot{V}_A$), cardiac output (Q_B), diffusion capacities (D_L), and respiratory quotient (RQ). Experimental data from several authors were used to interpolate linearly an equation for each parameter. The equations define the parameter equal to $a + b\,\dot{V}_{O_2}$. The values of the coefficients a and b are presented in Tab. 2.

The values of $\dot{V}_{O_2}$ for the activities of resting, sitting, standing and walking are 245, 346, 513 and $1\,020$ ml/min respectively (Mountcastle, 1980).

Table 2: Interpolated parameters (Parameter $= a + b\,\dot{V}_{O_2}$).

Parameter	a	b	Unit	Reference
$\dot{V}_A$	-99.7	17.55	ml/min	Guyton and Hall (2005)
Q_B	3 738	7.6	ml/min	Guyton and Hall (2005)
$D_{L_{O_2}}$	153	0.287	ml/(min·kPa)	Turrino et al. (1963)
$D_{L_{CO_2}}$	456	1.25	ml/(min·kPa)	Piiper et al. (1980)
$D_{L_{CO}}$	187	0.15	ml/(min·kPa)	Turrino et al. (1963)
RQ	0.826	0.0000985	–	Turrino et al. (1963)

3. MODEL

The method used to represent the respiratory system is the division of the several reservoirs of blood and gases of the human body in compartments. The model is formed by five compartments, besides some representing the pulmonary capillaries. It is represented in Fig. 1.

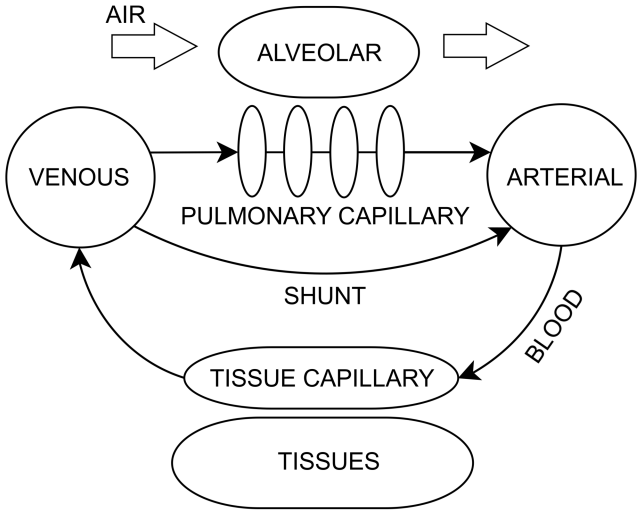

Figure 1: Model's representation.

In the model's equations development, principles of mass conservation were used. The gases and liquids inside the compartments are considered uniforms. The composition of the gases in each compartment is described by ordinary differential equations representing the time variation, one for each compartment and one for each gas. The sub-index g represents each one of the gases, being g equal to CO, O_2 or CO_2.

3.1 Alveolar compartment

The first compartment, that connects the human body to the external air, is the alveolar compartment. It represents the gas found in the lung's alveoli. The flow through that compartment is the alveolar ventilation. Inspired air get in after being humidified in the dead space. The expired air has the same composition of the air inside the alveoli. Another important process in the alveolar compartment is the transfer of gases by diffusion with the pulmonary capillaries compartments through the respiratory membrane. The following equation represents the overall process, with the diffusion coefficient correction from STPD (Standard Temperature and Pressure Dry) to BTPS (Body Temperature and Pressure Saturated) (Altman and Dittmer, 1971):

$$V_A \frac{dP_{g,A}}{dt} = \dot{V}_A \left(P_{g,in} - P_{g,A}\right) - \frac{310}{273} 101.325 \frac{D_{L,g}}{n} \sum_{i=1}^{n} (P_{g,A} - P_{g,cp(i)}) \tag{9}$$

where V_A = volume of the alveolar compartment [ml]; $P_{g,A}$ = partial pressure of g in the alveolar compartment [kPa]; $\dot{V}_A$ = alveolar ventilation [ml/min]; $D_{L,g}$ = diffusion coefficient of g through the respiratory membrane [ml/(min·kPa)]; i

= index of the pulmonary capillary compartment [1 to n]; n = number of pulmonary capillary compartments; $P_{g,cp(i)}$ = partial pressure of g in the pulmonary capillary compartment i [kPa].

3.2 Pulmonary capillary compartment

The pulmonary capillaries are represented by a series of compartments. The unshunted blood flows through these compartments where the transfer of gases occurs. Venous blood enters in the first compartment. Then the blood flows to the next capillary pulmonary compartment exchanging gases with the alveolar compartment through the respiratory membrane. The diffusion coefficient is considered constant in all compartments.

The reason of using several compartments is the need of an adquate value of the local driving force since the gases change its concentration as they flow in the capillaries. Considering the computational effort and the need of a smooth curve, 10 compartments were considered enough. The following equation represents the gas content variation of each pulmonary capillary compartment:

$$\frac{V_{cp}}{n}\,\frac{dx_{g,cp(i)}}{dt} = Q_B\,\sigma\,(x_{g,cp(i-1)} - x_{g,cp(i)}) + \frac{D_{L,g}}{n}\,(P_{g,A} - P_{g,cp(i)}) \tag{10}$$

where V_{cp} = volume of one pulmonary capillary compartment [ml]; $x_{g,cp(i)}$ = content of g in the pulmonary capillary compartment i [ml/ml]; Q_B = cardiac output [ml/min]; σ = fraction of unshunted blood.

3.3 Arterial compartment

The unshunted blood that leaves the pulmonary capillaries mixes with the shunted blood and goes to the arterial compartment. It works as a system time delay. The following equation represents the arterial content variation:

$$V_a\,\frac{dx_{g,a}}{dt} = Q_B\,[\sigma\,x_{g,cp(n)} + (1-\sigma)\,x_{g,v} - x_{g,a}] \tag{11}$$

where V_a = volume of the arterial compartment [ml]; $x_{g,a}$ = content of g in the arterial compartment [ml/ml]; $x_{g,v}$ = content of g in the venous compartment [ml/ml].

3.4 Tissue and tissue capillary compartments

The next compartment in which the blood flows is the tissue capillary compartment. There the blood exchange gases with the tissue compartment, where the metabolism takes place. The mechanism of tissue diffusion is complex. Because of that, it was simplified in the present model considering the gases partial pressure in the tissue capillary being the same of the tissues.

The tissue compartment is divided in two volumes, one representing the non-muscular tissues and another representing the muscular tissues, where the gases CO and O_2 are linked to the myoglobin. In the tissues, the O_2 is consumed ($\dot{V}_{O_2}$) and the gases CO and CO_2 are produced with rates $\dot{V}_{CO}$ and $\dot{V}_{CO_2}$, respectively. The partial pressure variation of both compartments is represented by the following equation:

$$\left(V_{ct}\,\frac{dx_{g,ct}}{dP_{g,t}} + V_{tm}\,\frac{dx_{g,tm}}{dP_{g,t}} + V_{tn}\,\frac{dx_{g,tn}}{dP_{g,t}}\right)\,\frac{dP_{g,t}}{dt} = Q_B\,(x_{g,a} - x_{g,ct}) - \dot{V}_g \tag{12}$$

where V_{ct} = volume of the tissue capillary compartment [ml]; $x_{g,ct}$ = content of g in the tissue capillary compartment [ml/ml]; $P_{g,t}$ = partial pressure of g in the tissue and tissue capillary compartment [kPa]; V_{tm} = volume of the muscular tissues [ml]; $x_{g,tm}$ = content of g in the muscular tissues [ml/ml]; V_{tn} = volume of the non-muscular tissue [ml]; $x_{g,tn}$ = content of g in the non-muscular tissues [ml/ml]; $\dot{V}_g$ = metabolic rate in the tissues [ml/min].

3.5 Venous compartment

After the tissue capillary compartment, the blood goes to the venous compartment. Leaving it, the blood returns to the lung. The venous compartment also works as a system time delay. The following equation represents the venous content variation:

$$V_v\,\frac{dx_{g,v}}{dt} = Q_B\,(x_{g,ct} - x_{g,v}) \tag{13}$$

where V_v = volume of the venous compartment [ml].

3.6 Numerical solution

A computational program based on C++ language was developed in order to solve the equations in the steady state and transient conditions. The steady state solution is necessary to define the subject's conditions in the beginning of the simulation. The conservation equations were solved using the successive approximation method for the steady state solution and the explicit Euler integration method for the transient solution.

4. VALIDATION

4.1 Dissociation curve

The modeling of the gases transport by the blood was validated comparing its dissociation curve with experimental data obtained by Routhgon and Darling (1944), for different values of O_2 saturation (S_{O_2}) and pH. It is represented in Fig. 2a, for approximately the same S_{CO} and different values of pH, and in Fig. 2b, for the same pH and different values of S_{CO}. The agreement between the theoretical curve (–) and the experimental data (○ and •) was good.

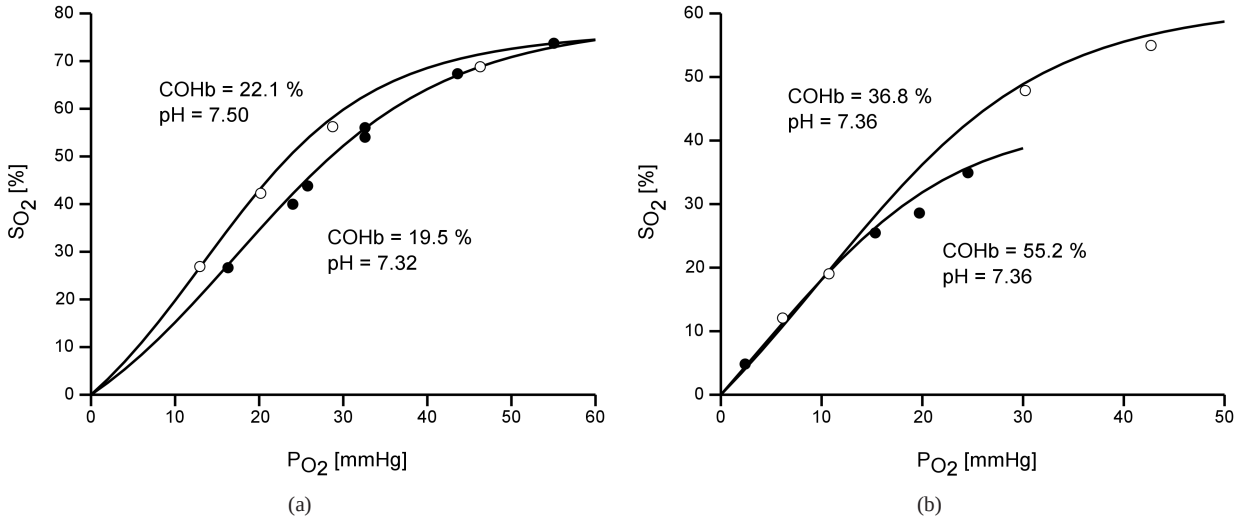

Figure 2: Comparation of the model's O_2 dissociation curve (–) and the experimental data (○ and •) from Routhgon and Darling (1944) for (a) approximately 20 % of S_{CO} and different values of pH, and for (b) different values of S_{CO} and the same pH.

4.2 Model

Stewart et al. (1970) conducted experiments exposing several subjects to CO concentrations of 50, 100, 200, 500 and 1000 ppm for periods from half hour to twenty-four hours. The COHb was obtained by the analysis of venous blood samples along the experiment. It was also measured the post-exposition, breathing pure air. These data were used to validate the model in a transient state. Figure 3a, 3b and 3c present the experimental data (○) and the numerical simulation (–) for constant CO concentrations of 50, 100 and 200 ppm respectively. Figure 3d presents the validation for a constant exposition of 500 ppm and an exposition with the CO concentration being incremented from 0 to 1000 ppm.

It was considered a typical subject, male, with 70 kg weight, 1.74 m height, and 30 years old at sea level. Light levels of physical activity were also considered, depending on the exposition time. For the 50 and 100 ppm expositions the sitting activity was considered. For the 200, 500 and 1000 ppm exposition the activity was considered to be an average between sitting and standing. The initial condition was adjusted according to the data for each experiment.

The numerical results agree very well with the experimental data. For the post-exposition period, the agreement is also good.

5. CONCLUSIONS

In the present work, a CO transport model for the human respiratory system was developed, considering the exchanges of CO, O_2 and CO_2. The human body was divided in compartments, representing the places where these gases are present (alveolar, several pulmonary capillaries, arterial, venous, tissue capillary and tissues). The mathematical modeling generated a set of equations describing the gases transient concentration in each compartment, in function of physiological parameters. The model's validation was done by comparing its results with experimental data. The agreement between

the results was excellent.

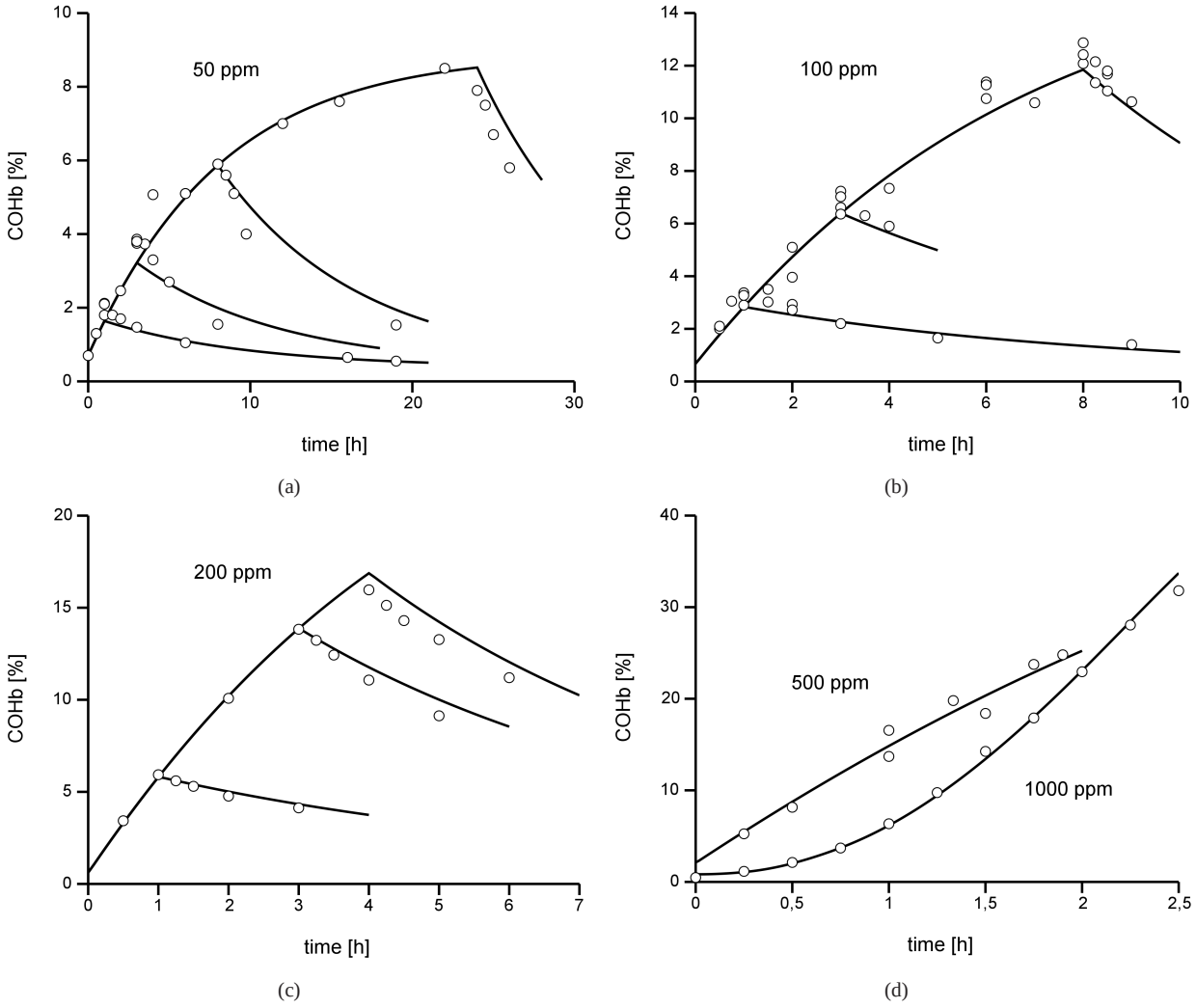

Figure 3: Comparation of COHb levels from the present model (–) and the experimental data (○) from Stewart et al. (1970) for CO concentrations of (a) 50 ppm, (b) 100 ppm, (c) 200 ppm, (d) 500 and 1000 ppm.

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