Identification of Non-linear closed Loop Systems

by

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Identification of Non-Linear Closed Loop Systems

Analysis of the Human Respiratory System in Hyperoxia

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Abstract

A model of the human respiratory system is implemented and used for parameter estimation. The presented model includes the gas exchange dynamics (‘plant’) and respiratory controller, which are both based on models found in literature. One of the improvements to the plant-model is that for the oxygen dissociation curve, a lookup-table is used instead of a mathematical expression. This increases the accuracy of the implemented curve, under the assumptions made. One of the general problems in identifying the respiratory system is that it operates in closed loop under normal circumstances. To circumvent some of the problems associated with closed loop identification, rebreathing tests are used to acquire the ventilatory data for parameter estimation. Another difficulty in identification is that the presented model contains several non-linearities in both plant and controller, which have an effect on the uncertainty of the estimations. By using a novel Monte Carlo approach to approximate the joint confidence regions of the estimates, the effect of non-linearities is accounted for. In this study, the focus of the identification is the respiratory controller in hyperoxia. The choice for the parameters to be estimated is made by studying the parameter dependencies that exist in the used three-output (frequency, tidal volume and total ventilation) controller model. Two different approaches to estimation are taken. In the first approach the measured total ventilation is fit to the respective controller output, and the second approach separately fits breathing frequency and tidal volume. Because of the large intra-subject variation of breathing pattern, the second approach does not always result in a good fit of frequency and/or tidal volume. The first approach on the other hand, produces acceptable results in almost all cases. Generally speaking, fitting the total ventilation produces more reliable estimates and better fits than fitting both frequency and tidal volume. Thus, based on the responses for hyperoxic rebreathing, it seems more useful to base a general model of the respiratory controller on the total ventilation, than on frequency and tidal volume separately.

Introduction

Mathematical modelling of the respiratory system is a field of research that was pioneered in the mid-1950s by Grodins et al, eventually leading to one of the first models of the respiratory system [4]. Since then, all sorts of advances have been made in understanding the complicated workings of the human respiration. This led to many different respiratory models, some focussing on particular (isolated) aspects of the system [10], and some focussing on the system as a whole [2], [17].

One of the difficulties in modelling the human respiration is that under normal operating circumstances the respiratory system functions in closed loop. Furthermore, it contains several non-linearities, e.g. the dissociation curves of CO₂ and O₂, which relate partial pressure to content.

In this study, a model of the respiratory system is presented, including the gas exchange dynamics, respiratory controller and relatively simple, but effective descriptions of the dissociation curves. This model does not strive to explain and/or simulate clinical/pathological problems. Instead the emphasis will be on structured identification and estimation of the controller parameters.

Model Formulation

The respiratory model consists of two separate parts: the gas exchange dynamics (hereafter addressed as the ‘plant’), which describe the transport and use/production of the respiratory gases in the body, and the respiratory controller, which regulates the ventilation based on the concentrations of O₂ and CO₂ in the body. A functional block diagram of the respiratory system is shown in figure 1.

Gas Exchange in Lungs and Tissue

The model for the gas exchange used in this study is an adaptation from the model derived by Chiari et al [2]. This model comprises three compartments.
(lungs, tissue and brain), including transport delays and shunted blood. In figure 2, a schematic representation of the plant can be found, including the different compartments. The assumptions made for this model are stated in Appendix A. In Appendix B, the nominal values of the parameters, as well as the steady-state values can be found.

The lung is described by a single compartment, which is ventilated by a continuous unidirectional stream of gas. Explicitly including the pulmonary shunt, the mass balance for O2 and CO2 leads to the following equation for the alveolar partial pressure:

\[
V_A \frac{dP_A}{dt} = V_{dot} \cdot (P_I - P_A) + \lambda \cdot Q \cdot (1 - s) \cdot (C_e - C_v)
\]

Where \(V_A\) is the equivalent alveolar volume (l), \(V_{dot}\) is the alveolar ventilation (l/min), \(P_A\) and \(P_I\) are the alveolar and inspiratory partial pressures (mmHg), \(\lambda\) is the conversion-factor for Standard Temperature and Pressure Dry-units (STPD) to Body Temperature and Pressure Saturated-units (BTPS), \(Q\) is the cardiac output (l/min), \(s\) is the shunted fraction of blood, and \(C_v\) and \(C_e\) are the mixed venous and end-capillary concentrations (l/l). The alveolar and end-capillary pressures are assumed to be equal.

Because of the shunted blood (the blood that does not take part in gas exchange), the alveolar partial pressure \(P_A\) does not equal the arterial partial pressure \(P_a\). Instead, the arterial concentration is given by the following equation:

\[
V_A \frac{dC_a}{dt} = Q \cdot (C_e - C_a) + M_{o2}
\]

In this equation, subscript T indicates the tissue compartment, so that \(V_T\) is the equivalent tissue volume (l), \(C_T\) is the concentration of gas in the tissues (l/l), \(Q_T\) is the tissue blood flow (l/min), \(C_\text{vT}\) is the concentration in the blood leaving the tissue compartment (l/l) and \(M_T\) is the gas production rate in the tissue (l/min). This rate is positive for CO2 (since it is produced) and negative for O2 (since it is consumed). Different from the model described by Chiari et al, in the presented model the total oxygen consumption rate \(M\) (l/min) is defined as follows:

\[
M_{o2} = Q \cdot \theta
\]

Where \(\theta\) is the amount of used O2 (in litre) per litre blood. The rate of CO2 production can be computed from this value by using the respiratory quotient RQ:

\[
M_{cO2} = RQ \cdot M_{o2}
\]

Identical to the tissue compartment, the mass balance for the brain compartment is:

\[
V_B \frac{dC_B}{dt} = Q_B \cdot (C_e - C_B) + M_B
\]

With subscript B denoting the brain-compartment. The gas content of the mixed venous blood can be expressed in terms of \(C_\text{vT}\) and \(C_\text{vB}\) by use of the following equation:

\[
V_B \frac{dC_\text{vB}}{dt} = Q_B \cdot (C_e - C_\text{vB}) + M_B
\]

In which \(z\) is the fraction of \(Q\) entering the tissue compartment.

The need for a separate brain compartment arises from the fact that the CO2-pressure in the brain (medulla) is an input of the used respiratory controller. The medullary CO2-pressure (\(P_m\)) can be derived from the partial CO2-pressure in the cerebrospinal fluid (\(P_{\text{csf}}\)). Assuming that CO2 diffuses from brain tissue to cerebrospinal fluid (csf) with a speed proportional to the pressure gradient, the \(P_{\text{csf}}\) can be described by:

\[
\frac{dP_{\text{csf}}}{dt} = \frac{1}{\tau_B} \cdot (P_B - P_{\text{csf}})
\]

With \(\tau_B\) the brain to csf diffusion time constant (min). Finally, the relationship between CO2-pressure in medulla and csf is:

\[
P_m = P_B + (P_{\text{csf}} - P_B) \cdot \exp(-k_B \sqrt{Q_B})
\]
Where \( k_c \) is a constant characterising the central chemoreceptors.

**Dissociation Curves**

To solve the equations described above, it is necessary to know the relationship between partial gas pressure in the blood and the corresponding concentration. For \( \text{CO}_2 \), this relationship is often assumed linear, which is correct in case of a normal working range. In the model, the linear approximation of the \( \text{CO}_2 \)-curve as described by Kelman [3] is used, which accounts for temperature, plasma pH and hematocrit. By assuming constant values for these variables, the elaborate equations of Kelman can be reduced to the following simplified form:

\[
C_{\text{CO}_2} = P_{\text{CO}_2} \cdot (a + b \cdot S_{\text{O}_2})
\]

Where the values for \( a \) and \( b \) are dependent on temperature, plasma pH and hematocrit. Temperature and hematocrit are assumed to be of nominal value. To account for the effect of pH, two different dissociation curves are used: one for the arterial blood (pH = 7.4) and one for the venous blood (pH = 7.36). The fact that the oxygen-saturation (\( S_{\text{O}_2} \)) has a (small) influence on the amount of carbon dioxide in the blood is known as the Haldane-effect.

The \( \text{O}_2 \) dissociation curve is S-shaped, with a possible shift to the left or right. Factors that cause this shift include the temperature, the blood pH, the concentration of 2,3-diphosphoglycerate (2,3-DPG) and the partial pressure of \( \text{CO}_2 \) [6]. It can be shown that under normal resting circumstances the influence of temperature, pH and 2,3-DPG is small. More important is the effect of \( \text{CO}_2 \) on the shift of the \( \text{O}_2 \)-curve (increase in \( \text{CO}_2 \)-concentration means a shift to right, decrease a shift to left), also known as the Bohr-effect. This effect plays an important part in the oxygen transport of the body, so it will be accounted for in the model.

The usual approach to describing the dissociation curve of \( \text{O}_2 \) is to derive a mathematical expression that approaches a certain reference-curve consisting of measured standard values (e.g. those reported by Severinghaus [13], [14]). Such an expression must meet several requirements: it must be invertible, since the inverted curve is also used in the model, and the expression and its inverse must give a sufficiently accurate description of the reference curve. However, the expressions found in literature (e.g. those by Kelman [8], Sharan et al [15]) fail to meet at least one of these requirements: the accurate equations are not invertible (e.g. [8], [16]), while the invertible ones are not accurate enough (e.g. [15]).

The approach taken in this study is to use a lookup-table containing the reference-data. This way both the requirements for accuracy and invertibility can be met. To account for the Bohr-effect, the partial \( \text{O}_2 \)-pressure is first converted to a ‘virtual \( \text{O}_2 \)-pressure’, by using the following relationship [2]:
After this conversion, the O$_2$-concentration corresponding to this virtual pressure is found in the table. It is assumed that all of the oxygen in the blood is bound to hemoglobin, i.e. the O$_2$ solved in the blood plasma is ignored. The implemented curve is pictured in figure 3.

**Respiratory Controller**

The controller used in the model is the one described by Duffin et al [3]. This controller has the form of the Oxford model, which means that the drive for ventilation is the sum of three components: central and peripheral chemoreflex drives and a basal drive (or wakefulness-drive [10]). The central drive is dependent on P$_{CO_2}$, the peripheral drive on both P$_{CO_2}$ and P$_{O_2}$, while the basal drive is independent of the partial pressures. The model features linear relations between ventilation and the partial pressure of carbon dioxide in the blood/brain (above a threshold). Further assumptions with regard to the controller and the nominal values of the controller parameters can be found in Appendices A and B respectively.

In the controller model, the central drive D$_c$ (l) and peripheral drive D$_p$ (l) are described by the following equations:

\[
D_c = SD_c \cdot (P_{CO_2} - T_c) \\
D_p = \frac{K}{P_{O_2} - AP_{O_2}} \cdot (P_{aCO_2} - T_c)
\]

Where SD$_c$ is the central chemoreflex slope (l/mmHg), T$_c$ is the chemoreceptor threshold (mmHg), K is the slope area constant (l/mmHg) and AP$_{O_2}$ is the P$_{O_2}$ asymptote (mmHg). These drives add to produce the total drive D (l):

\[
D = D_p + D_c
\]

Furthermore, there are two thresholds: the chemoreflex drive threshold T$_D$ (l) and the patterning threshold T$_P$ (l), with T$_P > T_D$. When the total drive is smaller than T$_D$, there is only basal ventilation. For T$_D < D < T_P$ the ventilation Vdot (l BTPS/min), tidal volume V$_T$ (l BTPS) and breathing frequency f (breaths/min) equal:

\[
Vdot = SWVdot \cdot (D - T_D) + Vdot_s \\
V_T = SW \cdot (D - T_D) + V_s \\
f = S1F \cdot (D - T_D) + f_s
\]

With S1Vdot, S1V and S1F the slopes of ventilation, tidal volume and frequency respectively. When the total drive rises above the patterning threshold, the pattern of breathing changes, corresponding to the changes observed in the respiration of the majority of people. Below T$_P$, a rise in total ventilation is mainly caused by an increase in tidal volume while above T$_P$, the rise in ventilation follows largely from an increase in breathing frequency. In other words, the slope of the equations for tidal volume and frequency change, leading to:

\[
Vdot = SWVdot \cdot (T_P - T_D) + Vdot_s + Vdot_s \\
V_T = SW \cdot (T_P - T_D) + S2V \cdot (D - T_P) + V_s \\
f = S1F \cdot (T_P - T_D) + S2F \cdot (D - T_P) + f_s
\]

With this model structure, two different approaches to the parameter estimation can be taken. The first is to simply take the Vdot output, and fit it to measured ventilation data by tuning the respective parameters. This will be called “approach A”. When using this approach, the dead space is accounted for by subtracting the dead space ventilation Vdot$_D$ (in l BTPS/min) from the total ventilation to get the alveolar ventilation:

\[
Vdot_a = Vdot - Vdot_D
\]

The second proposed approach, called “approach B”, is to fit both frequency and tidal volume to the respective model outputs. When using the V$_T$ and f outputs, the alveolar ventilation is computed by multiplying tidal volume V$_T$ minus dead space volume V$_D$ (l BTPS) with the frequency f. The resulting alveolar ventilation functions as the input of the plant. Thus:

\[
\dot{V}_a = f(V_T - V_D)
\]

It is expected that the second approach allows for the estimation of more parameters, since more data is available.

**Parameter Estimation**

After implementing the described respiratory model in Simulink, the focus is on estimating the controller parameters from measurements. In both approaches described above, it will be assumed that the central drive is the only drive to breathe. This is true in a situation of abundant O$_2$ (‘hyperoxia’). The reason for this assumption is that by evaluating only the central chemoreflex response, the amount of parameters is reduced, which significantly simplifies the parameter estimation procedure. For both approaches, the estimation procedure uses the measured end-tidal P$_{CO_2}$ (which is assumed to equal the capillary P$_{CO_2}$) as the input, and then tries to fit the resulting model output – Vdot for approach A, V$_T$ and f for
approach B – to the measured data by tuning the parameters.

Fitting the data is done by means of an optimisation algorithm, which tries to find the minimum of a certain cost function. It is important that a good cost function is used. Also important is the choice of the input signal, since this is one of the factors that can influence the outcome of the estimation procedure.

As can be seen in the previous description of the controller, there are many different parameters. Of course, not all of these variables can be estimated. A choice of the parameters to be estimated can be made by studying the controller equations.

**Input Signals**

Due to the physiological nature of the respiratory system, the possible input signals are severely limited. Commonly used are pseudo random binary signals (PRBS) on the inspired CO₂ [5] and rebreathing tests [3], tests in which the subject inhales its own exhaled gases by breathing in and out of a bag.

One of the difficulties in identification of the human respiratory system is that normally the system functions in closed loop. General problems with closed loop identification are the effect of feedback noise, as well as the fact that closed loop data typically contains less information about the open loop system. After all, an important purpose of feedback is to make the closed loop system less sensitive to changes. In the case of the respiratory system, one of the functions of the controller is keeping the partial CO₂-pressure in arterial blood at a nominal level. When this pressure is viewed as the input of the controller, it is easy to see that the amount of information in this input decreases because of the controller.

An advantage of using rebreathing is that it ‘opens the feedback loop’ [9]. During rebreathing, the PCO₂ in the blood linearly rises because of metabolic production and the fact that the subject inhales its own exhaled gases. This of course produces a rise in ventilation, since the body wants to washout the excess of CO₂. Because of rebreathing however, the increased ventilation does not reverse the rise in PCO₂, as is the case in the closed loop situation. So, in rebreathing experiments, one essentially observes the system as if functioning in open loop.

Another advantage of rebreathing is that one requires only a simple setup for the experiments. Effectively, only a suitable bag is needed (of course in addition to suitable sensors and a measuring setup). For the creation of a PRB input on the other hand, an elaborate setup is needed, involving such things as computer controlled valves.

**Dependencies**

By looking at the controller equations, it becomes clear that certain dependencies between parameters exist. Assuming that the total drive is larger than the chemoreflex drive threshold T_D, but smaller than the patterning threshold T_P, the for approach B relevant equations for tidal volume and frequency are:

\[
V = SW(D - T_D) + V_s = SW(SD(P_{CO2} - T_c) - T_D) + V_s
\]

\[
f = SIF(D - T_D) + f_s = SIF(SD(P_{CO2} - T_c) - T_D) + f_s
\]

Taking P_{CO2} as the input, these equations can be rewritten as:

\[
V = a_1 \cdot P_{CO2} + b_1
\]

\[
f = a_2 \cdot P_{CO2} + b_2
\]

Assume that values of the four unknown parameters in these equations (a_1, b_1, a_2, b_2) follow from the aforementioned estimation method. By definition, these four are combinations of the seven controller parameters:

\[
a_1 = SW \cdot SD_c
\]

\[
b_1 = -SW(SD_c \cdot T_c + T_D) + V_s
\]

\[
a_2 = SIF \cdot SD_c
\]

\[
b_2 = -SIF(SD_c \cdot T_c + T_D) + f_s
\]

From the seven controller parameters, only V_s and f_s are directly measurable, the rest are unknown. It can easily be seen that when knowing a_1, b_1, a_2 and b_2, not all of the five unknown parameters can be uniquely derived. In fact, it can be shown that for this model structure a maximum of three parameters can be uniquely estimated. Since we want a_1 and a_2 to be independent (no fixed relation between the slopes for tidal volume and frequency), it is assumed that SD_c is known so that S1V and S1F can be estimated. From b_1 and b_2, either T_c or T_D can be estimated. The choice is more or less arbitrary, but we choose T_D.

The problem of dependency of course also arises for approach A. Here, we have only one equation, which contains five parameters:

\[
V_{dot} = SD_{dot} \cdot (D - T_D) + V_{dot_s}
\]

\[
= SD_{dot} \cdot (SD_c(P_{CO2} - T_c) - T_D) + V_{dot_s}
\]

Just as with approach B, these equations can be rewritten:

\[
V_{dot} = a_1 \cdot P_{CO2} + b_1
\]
The parameters \( a_3 \) and \( b_3 \) are combinations of the five parameters:

\[
a_3 = SW \cdot ddotV \cdot SD_c \\
b_3 = -SW \cdot ddotV (SD_c \cdot T_v + T_c) + ddotV 
\]

Again, only the basal value \( V \cdot ddot_b \) is measurable, so that four parameters remain for estimation. Theoretically, when knowing only \( a_3 \) and \( b_3 \), two parameters can be estimated. The choice for either \( S1V \cdot ddot \) or \( SD_c \) is arbitrary, since the equation only contains the multiplication of \( S1V \cdot ddot \) and \( SD_c \). We choose \( S1V \), which means that \( SD_c \) is assumed nominal. For the second parameter we choose \( T_D \), just like in approach B. Thus, for approach A we define \( S1V \cdot ddot \) and \( T_D \) as the parameters to be estimated.

Next, the cost functions for the two approaches have to be chosen. For approach A, the cost function is simply taken as the sum of the squared errors between measured data and model output:

\[
J = \sum (V \cdot ddot_d - V \cdot ddot_m)^2
\]

In this function the subscript \( d \) denotes the measured data and \( m \) the model output.

Since in approach B we want to fit two model outputs simultaneously, the choice of a cost function is less trivial than in the case of just one output. Minimization of the following cost function puts an equal weight on both frequency and volume and gives a good fit of both:

\[
J = \sum [(V_a (f_a - f_m))^2 + (f_a (V_a - V_m))^2]
\]

Again, subscript \( d \) denotes the measured data and \( m \) the model output.

Providing that a good enough fit is possible, it is expected that the second approach produces estimates with the least uncertainty, since more data – and thus more information – is available.

**Parameter Reliability**

If performed correctly on a sufficiently rich dataset, the estimation procedure leads to numerical values for the parameters \( S1V, S1F \) and \( T_D \). An important question is: how accurate are these values? The reliability of the estimated parameters is investigated by using the Monte Carlo Parameter Sets approach, as described by Lutchen et al [11]. This approach gives an approximation of the 100(1-\( \alpha \))% joint confidence region of the parameters from a single dataset/measurement, by evaluating how much the parameters can vary from their optimised values such that the resulting increase in the cost function is statistically indistinguishable from the minimized cost function. In other words, we want to find the values of the parameter vector \( \theta \) for which the following holds:

\[
\Delta J = J(\theta) - J(\theta^*) < \varepsilon
\]

Where \( \theta^* \) is the optimised parameter vector and \( \varepsilon \) is the error bound [12]:

\[
\varepsilon = p \cdot \sigma^2 \cdot F_{1-p}(p, n - p)
\]

In this equation \( p \) is the number of parameters, \( n \) is the number of samples, \( \sigma^2 \) is the noise variance and \( F(a,b) \) is the F-distribution for (\( a \),\( b \)) degrees of freedom. Under the assumption that the model structure is correct and contains no unmodeled dynamics, the noise variance can be approximated as [11]:

\[
\sigma^2 = \frac{J(\theta^*)}{n - p}
\]

With this method, one can approximate the joint confidence region of each dataset. In the linear case, these have the shape of a p-dimensional ellipsoid, but non-linearities may change the shape of the region (as can be seen in figure 4). How must this confidence region be interpreted? Well, assume that we have computed the 95% confidence region for an estimated parameter combination
from a certain dataset. This can also be done for other datasets, which will produce somewhat different estimations and regions. The ‘95%’ means that for 100 computed intervals, the true value of the parameters is contained in 95 of these intervals [1].

**Measurements**

Data for the estimation procedure is acquired by performing several rebreathing experiments on different test subjects.

**Measuring Protocol**

The data presented in this study is based on the respiratory response of two test subjects, both healthy, non-smoking men around the age of 25.

The experimental setup used in the measurements consists of a 12 litre rebreathing bag, which is connected to a mouthpiece. Since we want to measure in the situation of hyperoxia, it is necessary that the bag is filled with oxygen at the start of rebreathing. For the filling of the bag with 100% O₂ (medical gas, provided by Hoek en Loos), the bag can be easily disconnected from the mouthpiece. Connected to the mouthpiece are a capnograph (Weinmann Capnosleep), with a resolution of ±2 mmHg between 3 and 38 mmHg and ±5% between 39 and 75 mmHg, and a spirometer (Cosmed Microquark) with an accuracy of ±2%. By means of a built in temperature sensor, the spirometer automatically converts the measured Ambient Temperature Pressure Saturated (ATPS) units to Body Temperature Pressure Saturated (BTPS) units for use in the model. The capnogram is measured continuously and sampled with a period of 0.05 seconds, while the volume flow can only be measured for five periods of 50 seconds, separated by a short variable time (several seconds). The sample time of the spirometer data is 0.01 seconds.

During a rebreathing test the following steps are performed:

1. At the start of the test, the subject breathes room air through the mouthpiece until ventilation is stable. The measurements are continued for several minutes, in order to acquire data for determination of the basal values.
2. During this time, the detached rebreathing bag is emptied, and then filled with 100% O₂. It is not essential that the bag contains exactly 100% oxygen; a small amount of mixture with room air is allowed.
3. Next, the rebreathing bag is connected to the mouthpiece, and the subject starts rebreathing. A nose clip is worn by the subject to prevent loss of volume.
4. Rebreathing is continued until P_{ETCO2} equals 60mmHg (measured by the capnograph). The experiment is also stopped when the test subject feels uncomfortable. During each 50s period, the subject is asked to hold his breath for several seconds. This allows for synchronisation between data from spirometer and capnograph (as will be discussed later).
5. Resting periods of at least 45 minutes separate repeated tests on the same subject, and no more than three rebreathing tests per day are performed on each subject.

**Results**

As stated before, the chosen controller parameters are estimated by fitting the model output to the measured data. The processing of the data is done on a PC with Mathworks’ Matlab. First, the volume and capnograph data are synchronised by using the short periods of breath holding as described in step 4 of the experiment. Synchronisation is possible since breath holding is visible in both volume and capnograph data as a prolonged constant period. After synchronisation, the relevant values (i.e. maxima and minima of the volumedata and end-expiratory and end-inspiratory values for the capnograph-data) are selected from the data. From this selection the frequency, tidal volume and total ventilation can be computed. Since the end-tidal partial CO₂-pressure, the pressure at the end of expiration, equals the pressure in the alveoli at the end of the previous inspiration, the timestamps of the end-inspiratory values are synchronised with the respective timestamps of the end-tidal CO₂-pressures. This is illustrated in figure 5.

After the data processing, Matlab is used for the
estimation procedure. For the minimisation, the Matlab-function ‘fminsearch’ is used (with all tolerances on the default setting), which tries to find a minimum in a user-specified cost function by changing certain parameters (also user-specified). In this case, the function to be minimized is the cost function \( J \), whose value depends on the output of the Simulink-model for the evaluated parameter values.

The estimation procedure produces optimal values for the parameters, i.e. the values for which the cost function \( J \) is minimal, which are the values that produce the best fit of model output to measured data. Next, an approximation of the 95% confidence interval of the estimations is determined by using the Monte Carlo Parameter Sets approach described earlier.

Previously, we have postulated two different approaches, in which certain controller parameters are estimated by fitting either the measured total ventilation (approach A) or the measured tidal volume and frequency to the controller output (approach B), using the measured end-tidal \( P_{CO2} \) as the input of the model. The basal values of total ventilation, frequency and tidal volume, which differ between subjects, are determined from the resting data (step 1 in the experimental protocol).

Using the two approaches with the experimental data produces the results as shown in Table 1 and 2. To get an idea of the allowed deviation of the cost function \( J \) in the MCPS-approximation of the confidence regions, the ratio between \( \varepsilon \) and the optimal value for \( J \) is also shown.

### Discussion

The goal of this investigation was to implement a model of the human respiratory system and use this model for parameter estimation, by fitting measured data to the model output.

The gas-exchange part (‘plant’) of the implemented model is an adaptation of the description by Chiari et al [2]. This model includes the blood shunt, which has a nominal value of 2.4%. One could argue that modelling the shunt is unnecessary, since its value is very small. For partial pressures in the normal working range, this argument is correct. For larger pressures however, the shunt cannot be neglected. Assume for example that the partial oxygen pressure in the alveoli equals 175 mmHg, which corresponds to a saturation of 99% or a concentration of 195 ml O\(_2\) per litre blood (following from the reference dissociation curve). The \( O_2 \) concentration in the veins is assumed to be 145 ml/l. Neglecting the shunt, upon passing the lungs the blood will be replenished with oxygen up until a saturation of 99% (195 ml/l). However, with a shunt of 2.4% (nominal value), the amount of arterial oxygen equals:

\[
C = (1 - s) \cdot C_e + s \cdot C_v
\]

\[
= 0.976 \cdot 195 + 0.024 \cdot 145 = 193.8 \text{ml/l}
\]

This seems a small difference compared to the 195 ml/l in the case of no shunt, but a conversion of

<table>
<thead>
<tr>
<th>Subject A, approach A</th>
<th>Data (n)</th>
<th>S1Vdot (10(^{-5}))</th>
<th>TD (10(^3))</th>
<th>Vdotb</th>
<th>( \varepsilon / J(0^1) ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (22)</td>
<td>1.24 ± 0.104 (8%)</td>
<td>2.11 ± 0.055 (3%)</td>
<td>9.5</td>
<td>35.3</td>
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<td>2 (22)</td>
<td>0.63 ± 0.142 (22%)</td>
<td>1.75 ± 0.146 (8%)</td>
<td>10.1</td>
<td>34.6</td>
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<tr>
<td>3 (26)</td>
<td>1.17 ± 0.111 (10%)</td>
<td>1.70 ± 0.067 (4%)</td>
<td>10.6</td>
<td>28.2</td>
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</tr>
<tr>
<td>4 (23)</td>
<td>1.47 ± 0.095 (7%)</td>
<td>1.70 ± 0.045 (3%)</td>
<td>11.4</td>
<td>32.6</td>
<td></td>
</tr>
<tr>
<td>5 (30)</td>
<td>2.07 ± 0.141 (7%)</td>
<td>1.91 ± 0.044 (2%)</td>
<td>10.6</td>
<td>23.6</td>
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</tr>
<tr>
<td>6 (26)</td>
<td>1.78 ± 0.086 (5%)</td>
<td>1.78 ± 0.033 (2%)</td>
<td>11.8</td>
<td>28.2</td>
<td></td>
</tr>
<tr>
<td>All (( \theta = 6 ))</td>
<td>1.39 ± 0.504 (36%)</td>
<td>1.82 ± 0.160 (9%)</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Subject A, approach B</th>
<th>Data (n)</th>
<th>S1V</th>
<th>S1F (10(^{-3}))</th>
<th>TD (10(^3))</th>
<th>fb</th>
<th>Vb</th>
<th>( \varepsilon / J(0^1) ) (%)</th>
</tr>
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<tbody>
<tr>
<td>1 (44)</td>
<td>0.74 ± 0.091 (12%)</td>
<td>2.89 ± 0.41 (14%)</td>
<td>2.00 ± 0.092 (5%)</td>
<td>8.4</td>
<td>1.1</td>
<td>21.8</td>
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<td>2 (44)</td>
<td>0.67 ± 0.074 (11%)</td>
<td>0.60 ± 0.35 (58%)</td>
<td>1.59 ± 0.100 (6%)</td>
<td>8.5</td>
<td>1.0</td>
<td>21.9</td>
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<tr>
<td>3 (52)</td>
<td>1.09 ± 0.098 (9%)</td>
<td>0.24 ± 0.33 (138%)</td>
<td>1.57 ± 0.076 (5%)</td>
<td>9.5</td>
<td>1.0</td>
<td>18.4</td>
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</tr>
<tr>
<td>4 (46)</td>
<td>0.96 ± 0.041 (4%)</td>
<td>1.24 ± 0.24 (19%)</td>
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<td>0.8</td>
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<tr>
<td>5 (60)</td>
<td>1.16 ± 0.066 (6%)</td>
<td>3.60 ± 0.26 (7%)</td>
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<td>1.0</td>
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<tr>
<td>6 (52)</td>
<td>1.17 ± 0.049 (4%)</td>
<td>2.42 ± 0.16 (6%)</td>
<td>1.74 ± 0.031 (2%)</td>
<td>9.9</td>
<td>1.2</td>
<td>17.1</td>
<td></td>
</tr>
<tr>
<td>All (( \theta = 6 ))</td>
<td>0.97 ± 0.216 (22%)</td>
<td>1.83 ± 1.34 (73%)</td>
<td>1.65 ± 0.275 (17%)</td>
<td></td>
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</table>

Table 1. Results of the parameter estimation procedure for subject A for the two described approaches. In approach A, the total ventilation is fit to the model output, while in approach B, frequency and tidal volume are fit simultaneously. The values are reported as mean ± standard deviation (and percentage of mean), the bottom row in each table gives the mean and standard deviation of the n datasets.
193.8 ml/l to partial pressure leads to a value of 130 mmHg. This differs significantly from the aforementioned 175 mmHg, which of course is a direct effect of the flatness of the O₂ dissociation curve for high partial pressures. The effect of the shunt decreases as the partial oxygen pressure gets smaller, because the dissociation curve is far less flat there.

For the implementation of the oxygen dissociation curve a lookup-table containing reference data is chosen, instead of the usual approach of deriving a mathematical formula that fits the reference data. This guarantees accuracy, under the assumptions made (e.g. no influence of temperature and 2,3-DPG). It must be noted that the contribution of the O₂ solved in the blood plasma with regard to the total amount of oxygen in the blood is neglected. When the partial oxygen pressure is at nominal level this does not introduce large errors, since then the amount of solved O₂ is very small. However, for large P O₂s, as in the described hypoxic rebreathing experiments, larger quantities of oxygen are dissolved. A possible improvement of the model is accounting for the solving of oxygen in the plasma, which is not a trivial adaptation.

For the CO₂ dissociation curve, a linear approximation of the 'real' curve is used. Since no numerical reference values for the CO₂-curve were found in literature, the exact error introduced by the linearisation could not be studied. An advantage of the availability of a numerical reference curve is the possibility of using a lookup-table in the model instead of a mathematical description, as is done for the O₂-curve. It can be expected that this will improve the accuracy of the CO₂ curve. Using a lookup-table or an accurate, non-linear mathematical expression will also solve the problem that during the performed rebreathing experiments, the partial CO₂ pressure increases beyond the normal working range, where the accuracy of the linear approximation decreases.

The controller used in the model is the one described by Duffin et al [3]. This relatively simple controller is more or less a variable gain (with some non-linearities, such as saturations), dependent of the partial CO₂ and O₂ pressures in blood and brain. The controller contains no dynamics, which is one of the main reasons why in this case a PRB-testsígnal, which has rich frequency content, is not expected to result in far better data for controller estimation. Fitting the data, as will be described further on, proves that this model produces a fairly accurate description of the responses measured in hyperoxic rebreathing experiments, under the condition that the Vdot output of the controller is used. It can however not be concluded that this combination of plant and controller is equally suitable for different kinds of experiments. For example, phenomena like hypoxic ventilatory depression [19], periodic breathing or sleep apnea [7] most likely cannot be explained or simulated by using this model. Another, more elaborate (dynamical) model of the chemoreceptor response may be needed for this. Also, in this study only the situation of hyperoxia is evaluated, there is no verification that the model is correct for other situations, e.g. hypoxia.

Since the presented model, like all models, is merely a simplified description of the real respiratory system, it is inevitable that several
assumptions will have to be made, with regard to both the plant and controller. These are mentioned in Appendix A. Some of the assumptions mentioned are clearly not true when performing the experiments. For example, during rebreathing the respiration increases significantly, which can be compared to light exercise. As such, the assumption that the subject is in rest does not hold.

After implementation of the model in Simulink, the model is used for the estimation of controller parameters. It is assumed that the peripheral chemoreflex is suppressed (which is true in a situation of hyperoxia), because this lowers the amount of parameters to be estimated. Identifying the controller while both peripheral and central reflexes are active is much more difficult. The parameters to be estimated were chosen by looking at the structure of the controller, and by studying the existing dependencies of the controller equations.

In order to acquire data for estimation of the central parameters, two subjects took part in a set of hyperoxic rebreathing experiments, during which they inhaled (part of) their own exhaled gases from a 12 litre bag, starting with a bag filled with 100% oxygen (to create hyperoxia). The main problem with these experiments, which is the problem in all kinds of respiratory experiments with awake, alert subjects, is that it is difficult to recreate natural, spontaneous breathing in a laboratory setting. For example, in our case the subject has to breathe through a mouthpiece while wearing a nose clip, which hardly represents a natural situation. It is easy to see that this will have an influence on the (pattern of) respiration. Furthermore, during the experiment, it is possible for the subject to (un)willingly influence the pattern of breathing, for example when focusing too much on the breathing. One measure that can help to prevent this, is to divert the attention of the subject. In the described experiments this is done by playing music. However, it is necessary for the subject to be alert because of the requests for breath holding. This is one of the reasons why it cannot be guaranteed that the influence of the subjects own will is entirely absent.

During the experiments, the in- and exhaled CO₂ is measured and recorded, as well as the volume flow through the mouthpiece (from which tidal volume and frequency can be derived). The inspired partial O₂-pressure is used in the model, but is not measured during the experiments. As such, certain assumptions must be made for the oxygen pressures. In this case we assume that during the course of each experiment, the inspired partial pressure is large enough to suppress the peripheral chemoreceptor. A small calculation shows the validity of this assumption. At the start of the experiment, the rebreathing bag contains roughly 12 litres of oxygen. Assuming an average oxygen consumption of 0.2 litres per minute and an experiment duration of five minutes, 1 litre O₂ is consumed during the experiment. This leaves 11 litres of oxygen in the bag, which is more than enough to create a situation of hyperoxia.

For the sampling of the volume- and CO₂-data, sample frequencies of 100Hz and 20Hz are used respectively. Because of the low frequency nature of the human respiration (nominally around 0.25Hz) and the fact that in this study only a small portion of the acquired data is used, these sample frequencies are much too high. Assuming a hypothetical upper limit on the breathing frequency of 100 breaths per minute, the highest frequency in the signal equals 100/60 ≈ 1.7Hz. Theoretically (Nyquist), a sample frequency of 2*1.7Hz = 3.4Hz would be enough. However, sampling with a higher frequency does not introduce large disadvantages, other than the fact that it produces larger data-files, and thus requires more storage capacity.

The experimental setup used in this study has some limitations. The main restriction is that the spirometer can only measure a maximum of five periods of 50s, separated by short pauses of several seconds. The variable length of these pauses introduces the need for some sort of synchronisation between capnograph and spirometer data. As stated in the experiment description, this synchronisation is performed by using the short periods of breath holding, which take place once in each 50s segment. It can be shown that a few seconds of breath holding only has an effect on respiration for one breath cycle. This means that by removing the breath holding from the data together with the following cycle, the resulting data can be treated as if no breath holding took place.

After processing, the measured data is used for the estimation of certain controller parameters. This is realised by taking the measured end-tidal P_{CO₂}, which is assumed to be equal to the capillary pressure, and fit the model output to the measured ventilatory data by tuning the parameters. By using the end-tidal P_{CO₂} as an input for estimation, it is implied the brain compartment (where the conversion of arterial CO₂-pressure to medullar pressure takes place) is correctly described. Of course, it would be preferred to also estimate the brain compartment, but this is impossible due to experimental limitations.

To investigate the reliability of the estimations, the Monte Carlo Parameter Sets (MPCS) approach as
described by Lutchen et al [12] is used. This gives a good indication of the uncertainty of the estimations when the parameters under investigation are allowed to change simultaneously. One of the main advantages of this approach is that it takes non-linearities into account. But there are also limitations to the method. The main limitation is that this method assumes that the model is correct, which implies that there are no unmodeled dynamics. Of course, this is never the case: there will always be a difference between model fits and data (i.e. a non-random distribution of residuals). This increases $\sigma^2$, which leads to an overestimation of the parameter uncertainty bounds. Furthermore, when the discrepancy between model output and data is too large (i.e. a ‘bad fit’), as is sometimes the case in approach B (e.g. subject A, set 3), the expressed confidence regions lose most of their relevance. Thus, the resulting variances in the parameter estimations as presented in this paper can only be treated as rough approximations.

In examining the results of the estimation procedure and the MCPS confidence region approximation, one of the conclusions is that parameter $T_D$ (chemoreflex threshold) can be estimated with low uncertainty and relatively small variation in the estimates. Another remarkable observation is that the breathing patterns of the subjects seem to vary per experiment (figure 6). In some tests, both frequency and tidal volume show the expected linear rise, while in some tests only tidal volume shows a clear rise and the frequency more or less fluctuates around a constant value (and vice versa), and several other forms were also observed. In some cases this leads to a bad fit of frequency and/or tidal volume, since approach B assumes that both tidal volume and frequency show a linear course. In the estimation results, the uncertainty of the estimated parameters gives an indication of the allowed deviation and thus of the quality of fit. For example, it can be seen that for parameter $S1F$, which is the slope for the breathing frequency, fairly large uncertainties in the estimations exist, sometimes indicating an almost erratic course of frequency (figure 7). The cause for the variation in breathing pattern is not clear (although it has been shown that each human has a unique pattern, this pattern is reproducible under identical circumstances [18]), but it is not unlikely...
that the varying pattern is (at least partly) caused by the laboratory setting and the awareness of the subject, as discussed before. Nevertheless, even though a variation in frequency and tidal volume response exist, fitting the total the total ventilation (approach A) gives estimations with relatively low uncertainty in most cases. This is logical: the total ventilation has to rise because of the increasing CO₂ in the body, regardless of the way in which this is accomplished. In other words, the product of tidal volume and frequency has to rise in a specific way (in this case linear) to satisfy the desire of the body to washout more CO₂. Taking this into account, approach A is the preferred approach. This also means that when designing a general model for the respiratory controller (one that is applicable for the 'average person'), as is done by Duffin et al [3], it makes more sense to base this on the total ventilation, than to separately model the frequency and tidal volume.

Conclusions

The human respiration is a system that normally operates in closed loop and contains several non-linearities. In this study a model of the respiratory system is presented, based on models found in literature, and an attempt was made to identify the respiratory controller in hyperoxia. As a part of the modelling of the gas exchange in lungs and tissue a fairly novel approach is taken in implementing the oxygen dissociation curve, namely the use of a lookup-table with reference values instead of a mathematical approximation. The resulting model, implemented in Simulink, can be used to simulate the respiratory response to situations like hypoxia, hypocapnia, hyperoxia or asphyxia. In this study, the focus is on the response to hyperoxic rebreathing. One of the goals of this study was to estimate the parameters of the controller model, by fitting model output(s) to measured data. However, due to several dependencies between parameters for the implemented controller, the amount of parameters that can be uniquely estimated is limited. Data for the estimation is acquired by performing rebreathing experiments, which circumvents some of the problems associated with closed loop identification (such as decrease of information because of feedback). Two subjects took part in several rebreathing tests, all performed in hyperoxia, which suppresses the peripheral chemoreflex. In order to study the reliability of the estimations, the joint confidence region of the estimation is acquired by using a Monte Carlo approach. The big advantage to this (little used) method is that is specifically takes non-linearities into account. It is important to note that this method only produces an approximation of the confidence regions. Nevertheless, as follows from the estimation results, this approximation gives a good indication of the uncertainty of the estimation and the quality of fit. Of the two approaches to parameter estimation that are described, the first one, which takes the total ventilation output of the controller and fits this to the measured ventilation, produces estimates of the parameters S₁Vdot and T₀ with only moderate uncertainty. The second approach, whereby both the frequency and tidal volume outputs are fit to measured data by tuning the slopes S₁F and S₁V, as well as T₀, produces larger uncertainties for the slopes. Furthermore, for the performed rebreathing tests significant variations between the tidal volume and breathing frequency responses were observed within both subjects, indicating a strong variation in breathing pattern per experiment. It is not unlikely that this intra-subject variation in pattern is – at least partly – caused by the awareness of the subject, the laboratory-setting (which may lead to mild forms of anxiety in the subject) and the unnatural means of breathing (e.g. while wearing a noseclip, and breathing through a tube). Because of the variations, it is sometimes impossible to get a good linear fit of frequency or tidal volume. In almost all of these cases however, a fit of total ventilation (the first approach) does give proper results with little uncertainty. This suggests that it is more useful to base a general respiratory controller on total ventilation than on tidal volume and frequency.

Appendix A. Model Assumptions

For the model of the plant, the following assumptions are made:

- The model is based on healthy persons during a state of rest. This means that the metabolism M, heart rate Q and oxygen uptake θ are assumed constant.
- The O₂ consumption is constant and the respiratory quotient RQ (the fraction CO₂/O₂) equals 0.8 for the tissue compartment and 1.0 for the brain compartment.

- The brain blood flow is a constant fraction of the total blood flow.

- The end-tidal partial gas pressure is equal to the partial pressure in the alveoli, which equals the end-capillary pressure.

- Continuous, unidirectional gas flow.

- In the O₂ dissociation curve, the effects of pH, temperature and concentration of 2,3-DPG are neglected.

- In the CO₂ dissociation curve, the effect of temperature is neglected.

The assumptions for the respiratory controller are as follows:

- The respiratory controller has only influence on the circulation, which means that the cardiac output is constant.

- Respiration is determined by three drives: peripheral, central and basal drives.

- The peripheral drive is linearly related to the arterial CO₂-pressure PₐCO₂ with a slope that varies hyperbolically with PₐO₂. A rise of PₐO₂ results in a decrease in slope.

- A slope constant and a P O₂ asymptote describe the hyperbolic relation between PO₂ and PCO₂.

- The central drive is linearly related to the CO₂ pressure in the medulla (PₘCO₂) with a slope that is independent of PₐO₂.

- The basal drive is independent of both P O₂ and PCO₂.

- The central and peripheral drives share a common chemoreceptor threshold (Tc) and add to produce the total drive.

- The total drive does not affect breathing until a chemoreflex drive threshold (TD) is exceeded.

- The total drive produces changes in tidal volume, breathing frequency and ventilation that are scaled versions of the drive.

- The pattern of breathing changes when the drive exceeds the patterning threshold (TP). Below TP, the rise in ventilation is mainly caused by an increase in tidal volume while above TP, the rise in ventilation is caused by an increase in breathing frequency.

- In hyperoxia, the peripheral chemoreflex is completely suppressed.

Appendix B. Nominal Parameter Values [2], [3] and Steady State Values of the Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
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<tbody>
<tr>
<td>VA</td>
<td>3.28</td>
<td>(BTPS)</td>
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<tr>
<td>VB</td>
<td>0.90</td>
<td>(BTPS)</td>
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<tr>
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<td>l (BTPS)</td>
</tr>
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<td>VD</td>
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<td>l (BTPS)</td>
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<tr>
<td>λ</td>
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<td>mmHg</td>
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<tr>
<td>Q</td>
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<td>s</td>
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<td>z</td>
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References


