Estimation of Rodent Airway Parameters Using a Two Chamber Plethysmograph

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Abstract. **A system was developed to estimate airway parameters of rodents using a two chamber plethysmograph. Rodent respiration in a two chamber flow-flow plethysmograph was modeled as a second order system in the continuous time domain. The model was converted to the equivalent digital filter, and the animal respiratory signals fitted to the filter using a least squares technique. The filter coefficients were then used to calculate the rodent airway parameters. These parameters included the product of airway resistance and thoracic gas compliance, which is a measure of airway constriction. Another calculated parameter was the thermal time constant associated with the heating and cooling of inspired and expired room temperature air.**

Keywords: Airway Constriction, Least Squares, Compliance, Thermal Time Constant

1. Introduction

Airway constriction is a parameter commonly used to evaluate the results of animal inhalation studies. This constriction, which resists gas flow, is sometimes calculated from lumped parameter models of the respiratory mechanics and the measurement system. Typically, these models are developed as the electric circuit analogue of the actual physical system, where resistance to flow is modeled as a resistor, gas compliance is modeled as a capacitor, and gas inertance is modeled as an inductor.

Many examples of these circuit analogues applied to respiratory mechanics in animals and humans can be found in the literature. Some of these respiratory circuits are based on measurements made during spontaneous breathing or mechanical ventilation [1-6], while others are developed to measure pulmonary parameters using forced oscillations or forced random noise as input to the respiratory system [7-12]. As might be expected, all of these models contain at least one parameter which is a measure of airway resistance.

Another modeling issue is the temperature effect of respiration of room temperature air. Although conditioning the air to body temperature and humidity is an option, this is a somewhat more technically demanding approach. Another method is to compensate for thermal effects in the respiratory model [13-15].

The purpose of this project was to develop a noninvasive method of estimating airway constriction without having to build a system capable of conditioning the air. This was done using a two chamber plethysmograph and a second order model of animal respiration. The method was evaluated with two sets of data. The first set of data was simulated using the mathematical model. The second set of data was measured animal data. This data was from four Sprague-Dawley rats measured in a two chamber plethysmograph both before and after inhalation exposure to methacholine.

2. Methods

The plethysmograph consisted of two chambers: one housed the animal's body and the other housed the animal's head. A latex seal separated the two chambers. Flow into and out of each chamber was measured by a Setra model 239E pressure transducer across each of two Fleisch #000 pneumotachographs. The pressure transducers were interfaced to an analog-to-digital converter connected to a computer. The animal flows from the plethysmograph were sampled at 512 Hz.

The first part of the model was the electric circuit analogue of animal respiration. This consisted of a current source driving a capacitor in parallel with a resistor. The current source represented the flow produced by an animal's thorax (U_t), the resistor represented airway resistance (R), and the capacitor represented compliance of thoracic gas (C). If the inverse of the circuit time constant (RC) is defined as the variable τ, the equation describing airway flow, I_a, can be written:

$$\tau U_t = \frac{dI_a}{dt} + \tau I_a \qquad (1)$$

The second part of the model was the description of the thermal flow (I_{th}) produced by the heating and cooling of room temperature air as it entered and exited the rodent's nares. The thermal flow was modeled as a first order process [13,14] with time constant $1/\theta$ and final value given by $G \cdot I_a$, where I_a is airway flow at BTPS conditions as given above. The constant G was given by:

$$G = 1 - \frac{T_i}{T_a}\left[\frac{P_B - P_{H_2O_a}}{P_B - P_{H_2O_i}}\right] \qquad (2)$$

where the subscripts *i* and *a* denote conditions of inspired and alveolar gas, respectively. The value of G used in the model

was 0.1, which was close to that given by Hankinson and Viola [16]. The equation describing the thermal flow can be written:

$$G\theta I_a = \frac{dI_{th}}{dt} + \theta I_{th} \tag{3}$$

We know that on inspiration, room temperature air is drawn through the pneumotachograph and is then warmed as it enters the nares. If we assume on expiration that the air cools before passing out through the pneumotachograph, then the measured flow (y) into and out of the head chamber is the airway flow minus thermal flow, I_a-I_{th}. Coupling (1) and (3), and taking the Laplace transform, the system transfer function from input, U_t, to output, y, can be written as:

$$H(s) = \frac{Y(s)}{U_t(s)} = \frac{\tau(s+\theta-G\theta)}{(s+\tau)(s+\theta)} \tag{4}$$

Equation (4) represents a continuous time transfer function. Given that the flow from the thorax, U_t, as well as the head chamber flow, y, are sampled signals, the next logical step was to convert H(s) into a discrete domain counterpart, H(z). The sampled signals can be used to estimate the model parameters. This was a typical system identification approach which was similar to the one used in [5].

Performing partial fraction expansion on (4) yields an expression of the form:

$$H(s) = \frac{A}{s+\tau} + \frac{B}{s+\theta} \tag{5}$$

Converting (5) from the s-domain to the z-domain gave:

$$H(z) = \frac{Az}{z-e^{-\tau T}} + \frac{Bz}{z-e^{-\theta T}} \tag{6}$$

Combining and collecting terms in (6) yields a digital filter of the form given below, whose poles are shown above as $e^{-\tau T}$ and $e^{-\theta T}$:

$$H(z) = \frac{b_0 + b_1 z^{-1}}{1 + a_1 z^{-1} + a_2 z^{-2}} \tag{7}$$

This filter represents the following difference equation:

$$y(k) = b_0 U_t(k) + b_1 U_t(k-1) - a_1 y(k-1) - a_2 y(k-2) \tag{8}$$

This equation can be written in vector form as:

$$y(k) = h^T(k)\phi \tag{9}$$

where,

$$h^T(k) = [U_t(k)\ U_t(k-1)\ -y(k-1)\ -y(k-1)] \tag{10}$$

and

$$\phi = [b_0\ b_1\ a_1\ a_2] \tag{11}$$

This equation is now in the proper form for common batch least squares estimation. Let the estimates of the digital filter coefficients be given by:

$$\hat{\phi} = [\hat{b}_0\ \hat{b}_1\ \hat{a}_1\ \hat{a}_2] \tag{12}$$

This gives estimates of y(k) as:

$$\hat{y}(k) = h^T(k)\hat{\phi} \tag{13}$$

The estimation error can then be written as:

$$v(k) = y(k) - \hat{y}(k) \tag{14}$$

For a given set of N data, it desirable to estimate a set of filter coefficients that minimizes the following function:

$$J(\theta) = \sum_{k=1}^{N} v(k)^2 = v(1)^2 + v(2)^2 \cdots v(N)^2 \tag{15}$$

Equation (15) can be rewritten in matrix form as:

$$J(\theta) = (Y_N - H_N\hat{\theta})^T(Y_N - H_N\hat{\theta}) \tag{16}$$

where

$$Y_N = [y(1)\ y(2)\cdots y(N)]^T \tag{17}$$

and

$$H_N = [h^T(1)\ h^T(2)\cdots h^T(N)]^T \tag{18}$$

Taking the derivative of (16), setting the result equal to zero, and solving for θ yields the least squares estimate. The estimate can be shown to be:

$$\hat{\theta} = (H_N{}^T H_N)^{-1} H_N{}^T Y_N \tag{19}$$

This technique was used to estimate the digital filter coefficients shown in (7). The roots, r_1 and r_2, of the denominator polynomial were then found from these

coefficients. The model parameters τ and θ can then be calculated as:

$$\tau \text{ (or } \theta) = -\frac{1}{T}\ln(r_1)$$
$$\theta \text{ (or } \tau) = -\frac{1}{T}\ln(r_2) \qquad (20)$$

Next, based on results found in the literature, it was assumed the smaller root represented θ, and the larger root represented τ. Typical values of τ in rats found from airway resistance and compliance reported by Jackson [17] were approximately 100 rad/sec. From Peslin's work [13,14], θ was found to be in the range of 10-15 rad/sec. Given that Peslin's system was a body plethysmograph for humans and ours was a flow plethysmograph for rats, it was certainly possible that the thermal time constant in our system was not in this same range. This was not a critical issue, however, as the proper choice of roots can be easily verified by substituting them back into the model and evaluating the squared error.

The use of the method outlined above was tested with two data sets. The first data set was simulated data. The selected input (U_t) for simulation was a filtered square wave with an amplitude of 20 mL/sec and a frequency of 2 Hz. The filter was a first order lowpass Butterworth with a cutoff frequency of 10 Hz.. The model was simulated for thermal time constants of 100, 50, 25, and 10 milliseconds, corresponding to θ = 10, 20, 40, and 100 rad/seconds, respectively. For each value of θ, the value of RC was varied as RC = 2, 3, 4, and 4 milliseconds, corresponding to τ = 500, 333, 250, and 200 rad/seconds, respectively.

The second set of data was actual two chamber plethysmograph data from four Sprague-Dawley rats. These rats were exposed to an aerosolized solution (15 mg/m^3) of methacholine (300 mg/mL) for approximately six minutes. Six seconds of data was recorded for each animal three times before exposure, and three times after exposure. Fig. 1 shows the thorax flow for one of the rats before and after exposure. Methacholine, which is a known bronchoconstrictor, was delivered to elicit an increase in airway resistance, which could then be seen in the estimates of RC.

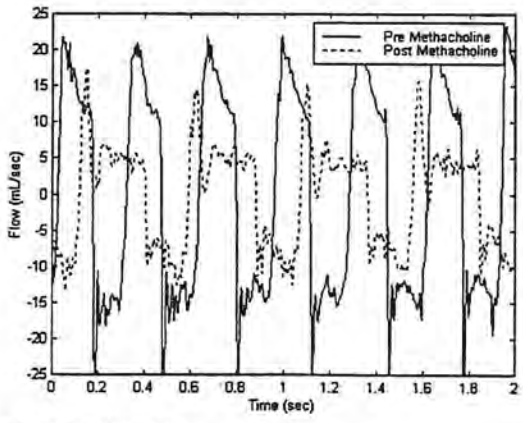

Figure 1. Rat thorax flow.

3. Results

The results of the model simulation are shown in Table 1. The table shows that the error in RC tends to get larger as RC gets larger. It is largest when the thermal time constant is smallest. However, even the larger error in RC is still very small. The error in thermal time constant is somewhat larger, having a maximum of 5.36%. In general, the estimation error is small, and the least squares technique calculates the model parameters well.

The plethysmograph data for each animal was compiled as the average of three runs. It is listed as average (± standard error). The values of RC for each of the four rats before methacholine challenge were 5.11 (±.89), 3.70 (±.38), 6.43 (±1.10), and 6.22 (±1.35) milliseconds. The values for thermal time constant were 53.3 (±27.4), 23.0 (±1.17), 31.2 (±7.41), and 14.3 (±1.70).

The calculated results for the data collected after methacholine challenge were all found to be complex conjugate pairs, except for the results of one trial. This trial returned a value of 8.47 milliseconds for τ and a value of 15.8 milliseconds for θ. Possible explanations of these results are given in Discussion.

4. Discussion

First of all, it should be noted that the parameter of interest is R rather than RC. Given this particular setup, the noninvasive nature of this method, and the corresponding model, there is no apparent way to separate the R and the C. The parameter RC, however, is a good measure of airway constriction. In fact, "specific airway resistance" [18], has

Table 1. Model simulation results. All values in msec.

Actual		Estimated		% Error	
RC	1/θ	RC	1/θ	RC	1/θ
2.00	100.00	2.00	102.84	0.02	2.84
3.00	100.00	3.00	102.69	0.04	2.69
4.00	100.00	4.00	102.46	0.06	2.46
5.00	100.00	5.00	102.18	0.09	2.18
2.00	50.00	2.00	51.25	0.01	2.50
3.00	50.00	3.00	51.20	0.02	2.40
4.00	50.00	4.00	51.13	0.05	2.25
5.00	50.00	5.00	51.03	0.07	2.06
2.00	25.00	2.00	25.70	0.02	2.81
3.00	25.00	3.00	25.70	0.02	2.81
4.00	25.00	4.00	25.69	0.01	2.75
5.00	25.00	5.00	25.66	0.00	2.66
2.00	10.00	2.00	10.33	0.11	3.29
3.00	10.00	3.00	10.39	0.19	3.89
4.00	10.00	3.99	10.45	0.29	4.55
5.00	10.00	4.98	10.54	0.46	5.36

been defined as RC divided by P_B-P_{H2O}, and is a parameter often measured in animal inhalation studies.

The results of the model simulations show very good agreement between the parameters and their estimates. This technique obviously works well for this linear model and is a good first step. However, the actual noise found during animal measurements should be characterized, and a rigorous noise analysis on the model should be performed.

The results of the animal data before methacholine challenge gave values that were in the expected range. There appeared to be an outlier (thermal time constant of 107 milliseconds) in one of the three trials for the first reported thermal time constant. Other than this one trial, there appeared to be good agreement between results, with values in the range that would lead one to believe the model is an appropriate representation of the physical system.

Perhaps the most interesting results are found from the animal data collected after methacholine challenge. For purposes of estimating RC, the results are not useful. However, it does show that methacholine elicited some response. In that manner, the technique could still have some use.

There are several possible explanations for why the estimates are calculated as complex conjugate pairs. One is that the animal may have shifted during the measurement, producing an added flow component not accounted for in the model. Another explanation is that a leak developed in the latex seal during the measurement, again producing an unmodeled effect. However, a more likely explanation is that the model simply failed to adequately describe the physical events taking place in the airways. It is possible that before methacholine challenge the acceleration of the air in the respiratory system was negligible, while after methacholine, this effect became important. This possibility will be investigated in the near future.

This technique for estimation of rodent airway parameters has been shown to be effective for simulated data, as well as some animal data. Although the model appears to break down in some situations, the technique still shows promise. With some modifications to both the model and the estimation method, it is believed that this technique could prove to be a valuable tool in the evaluation of animal inhalation studies.

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