Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Bayesian Tracking of a Nonlinear Model of the Capnogram

Jorn Op Den Buijs, Lizette Warner, Nicolas W. Chbat, and Tuhin K. Roy

Abstract— **Capnography, the monitoring of expired carbon dioxide (CO_2) has been employed clinically as a non-invasive measure for the adequacy of ventilation of the alveoli of the lung. In combination with air flow measurements, the capnogram can be used to estimate the partial pressure of CO_2 in the alveolar sacs. In addition, physiologically relevant parameters, such as the extent of CO_2 rebreathing, the airway dead space, and the metabolic CO_2 production can be predicted. To calculate these parameters, mathematical models have been previously formulated and applied to experimental data using off-line optimization procedures. Unfortunately, this does not permit online identification of the capnogram to detect changes in the physiological model parameters.**

In the present study, a Bayesian method for breath-by-breath identification of the volumetric capnogram is presented. The method integrates a model of CO_2 exchange in the lungs, which is nonlinear due to the nature of human tidal breathing, with a particle filtering algorithm for estimation of the model parameters and changes therein. In addition, this allowed for a dynamic prediction of the unmeasured alveolar CO_2 tension. The method is demonstrated using simulations of the capnogram. The proposed method could aid the clinician in the interpretation of the capnogram.

I. INTRODUCTION

The capnogram is obtained by continuously recording carbon dioxide (CO_2) tension in the expired air. Capnography is a useful, non-invasive way to determine the adequacy of ventilation of the alveoli of the lung. As such, it can be used to assess respiratory distress in patients with airway obstruction [9]. In addition, capnography is capable of detecting events in the circulation and the metabolism. For example, severe pulmonary embolism and malignant hyperthermic CO_2 production can be observed in the capnogram [6]. Provided the data are carefully interpreted by the clinician, capnography can form an essential diagnostic tool.

Figure 1 presents a diagram of a normal capnogram during a single breath. The expiratory phase of the capnogram can be divided into three phases. Phase I represents expiration of CO_2-free gas from the airway dead space. During phase II, dead space gas mixed with CO_2-rich alveolar gas is measured. Phase III represents expiration of CO_2-rich gas from the alveoli and is often referred to as the alveolar plateau. When the capnogram is combined with measurements of air flow (volumetric capnography), additional information about the volumes of gas that delivered the CO_2 can be obtained. These combined measurements are useful to quantify certain physiological parameters such as airway dead space, alveolar volume, and metabolic CO_2 production [6].

J. Op Den Buijs, L. Warner and T. K. Roy are with the Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN 55905, USA {opdenbuijs.jorn; warner.lizette; roy.tuhin}@mayo.edu

N. W. Chbat is with Biomedical Informatics, Philips Research North America, Briarcliff Manor, NY 10510, USA chbat@philips.com

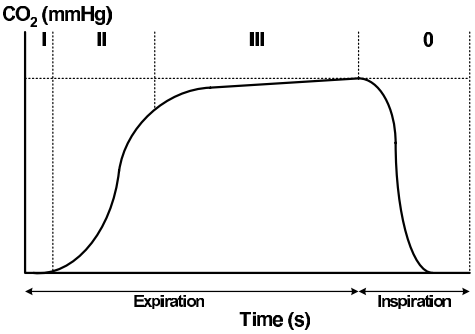

Fig. 1: Example of a normal time-based capnogram. Phase I indicates expiration of CO_2-free gas. Phase II is the mixing of dead space and alveolar gases. Phase III is the alveolar plateau resulting from expiration of CO_2 rich gas.

In recent literature, several mathematical models have been developed for simulation of volumetric capnograms during tidal breathing [2], [7]. To account for the alternation between inspiration and expiration, tidal-breathing models are described by two sets of distinct differential equations. To identify the parameters of these equations, the model output is matched with capnographic data using optimization algorithms. For example, a two-compartment model of a homogeneous lung has been used to provide an estimate of the arterial CO_2 pressure over a cycle of 50 breaths [3]. It should be noted that this approach requires the assumption that the model parameters are constant over the measurement period. Furthermore, the parameters are calculated during an off-line optimization procedure, which creates an unavoidable delay between data collection and results of the analysis. In a clinical setting, these limitations hamper the continuous monitoring of the parameter values and fluctuations therein, precluding immediate intervention.

In the present study, a Bayesian algorithm is presented for the breath-by-breath tracking of the parameters of a nonlinear model of the capnogram. This model accounted for tidal-breathing and incorporated a rebreathe compartment, an airway dead space compartment, and a compartment representing the alveoli. Using this model, a prediction for the unmeasured alveolar CO_2 tension could be made. Based on model simulations, it is shown that the adaptive algorithm is capable of rapidly tracking fluctuations in the parameters. The current method could aid the clinician in the interpretation of capnographic data, by providing an online determination of physiologically relevant parameters.

II. MODELING CO_2 EXCHANGE IN THE LUNG

In this section, a mathematical model of the CO_2 concentration in the different compartments of a tidally breathing human lung is described. The equations are similar to

previous compartmental models of tidal-breathing [2], [5], [7]. Figure 2 shows a schematic overview of the model. The fractional gas concentration of CO_2 is described in three compartments: a compartment for rebreathed CO_2, accounting for expired CO_2 to be left in the measurement valve; a compartment for airway dead space, where no gas exchange with the blood takes place; and a compartment representing the lung alveoli, where CO_2 enters from the pulmonary blood.

Each model compartment contains a gas volume V, of which a fraction F is occupied by CO_2. The compartments are denoted by indices r for rebreathed volume, d for airway dead space and A for alveoli. The airflow or ventilation $\dot{V}$ results in exchange of CO_2 between the different compartments. During inspiration ($\dot{V} > 0$), the direction of movement is from the inspired gas mixture (fractional concentration F_I) to the alveolar compartment (concentration F_A); during expiration ($\dot{V} < 0$), the direction is reversed. The measured fractional gas concentration at the mouth is assumed to be equal to the concentration F_r in the rebreathe compartment. F_I is the fraction of CO_2 in the inspired gas mixture, which is usually approximately zero ($F_I = 0$). The total CO_2 produced by the tissues as a result of metabolic rate M, is delivered to the alveolar compartment through the pulmonary circulation. A summary of the model parameters and their default values used in the simulations can be found in Table I.

The differential equations of the model describe the rate of change of the total volume of CO_2 in the p^{th} compartment (F_pV_p), where $p \in \{r, d, A\}$:

$$\frac{d(F_pV_p)}{dt} = (F_q - F_p)|\dot{V}| + J_p \tag{1}$$

The volume flow of CO_2 entering from compartment q is equal to $F_q|\dot{V}|$, whereas the outflow equals $F_p|\dot{V}|$. In addition, J_p represents exchange of CO_2 due to processes that are not directly caused by the airflow (e.g. delivery of CO_2 to the alveoli by the pulmonary blood flow).

For a constant compartmental volume V_p, Eq. 1 can be simplified by taking V_p outside of the derivative operator. In the model, it is assumed that the volumes of the rebreathe and dead space compartments are constant during a breath. However, the alveoli are compliant. They have an initial volume at the end of expiration ($V_A(0) = V_{A,0}$), and increase/decrease in volume during inspiration/expiration. The change in the alveolar volume is assumed to be equal to the airflow ($dV_A/dt = \dot{V}$). This concept is sometimes refered to as the 'balloon on a straw' model [7]. Applying the chain rule, the mass balance in the alveolar compartment can be written as:

$$\frac{d(F_AV_A)}{dt} = V_A\frac{dF_A}{dt} + F_A\dot{V} \tag{2}$$

The model can be described by a nonlinear state-space system with distinct matrices for the phases of inspiration (in) and expiration (ex). For each phase $j \in \{in, ex\}$, the state-space system is given by:

$$\begin{aligned} \dot{x} &= \mathbf{A}^j x + \mathbf{B}^j u \\ y &= \mathbf{C}^j x + \mathbf{D}^j u \end{aligned} \tag{3}$$

TABLE I: Model parameters

Parameter	Description	Value	Unit
F_I	Inspired CO_2	0	-
V_r	Rebreathe volume	20	ml
V_d	Airway dead space volume	100	ml
$V_{A,0}$	End-expiratory alveolar volume	2500	ml
M	Metabolic CO_2 production	300	ml min^{-1}
V_T	Tidal volume	600	ml
f_r	Respiratory frequency	12	breaths min^{-1}

with state variables $x = [F_r\ F_d\ F_A]^T$, inputs $u = [F_I\ 1]^T$ and output $y = F_r$. $\mathbf{C}^j = [1\ 0\ 0]$ and $\mathbf{D}^j = 0$ during both respiratory phases. During inspiration ($j = in$), matrices $\mathbf{A}^{in}$ and $\mathbf{B}^{in}$ are given by:

$$\mathbf{A}^{in} = \begin{bmatrix} -1/V_r & 0 & 0 \\ 1/V_d & -1/V_d & 0 \\ 0 & 1/V_A(t) & -1/V_A(t) \end{bmatrix} |\dot{V}(t)| \tag{4a}$$

$$\mathbf{B}^{in} = \begin{bmatrix} |\dot{V}(t)|/V_r & 0 \\ 0 & 0 \\ 0 & M/V_A(t) \end{bmatrix} \tag{4b}$$

During expiration ($j = ex$), the direction of the air flow is reversed, and $\mathbf{A}^{ex}$ and $\mathbf{B}^{ex}$ are given by:

$$\mathbf{A}^{ex} = \begin{bmatrix} -1/V_r & 1/V_r & 0 \\ 0 & -1/V_d & 1/V_d \\ 0 & 0 & 0 \end{bmatrix} |\dot{V}(t)| \tag{5a}$$

$$\mathbf{B}^{ex} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ 0 & M/V_A(t) \end{bmatrix} \tag{5b}$$

Note that nonlinearities in the state-space system above are introduced by the time-variant air flow $\dot{V}$ and alveolar volume V_A. To simulate the model, a sinusoidal forcing function for $\dot{V}$ was used [3]:

$$\dot{V} = V_T\pi f_r \sin(2\pi f_r t)\ , \tag{6}$$

where V_T is the tidal volume and f_r is the respiratory frequency.

Discrete-time domain implementation

The experimental data (F_r and $\dot{V}$) are recorded at a sample frequency f_s. Therefore, the model was implemented in the discrete-time domain, using an Euler integration scheme. The discrete samples are taken at the time instances $t = kf_s^{-1}$, and the state-space system with discrete system matrices $\mathbf{A}^j(k)$, $\mathbf{B}^j(k)$, $\mathbf{C}^j(k)$ and $\mathbf{D}^j(k)$ can now be written as:

$$x(k+1) = x(k) + f_s^{-1}\left(\mathbf{A}^j(k)x(k) + \mathbf{B}^j(k)u(k)\right) \tag{7a}$$

$$y(k) = \mathbf{C}^j(k)x(k) + \mathbf{D}^j(k)u(k) \tag{7b}$$

The system matrices $\mathbf{A}^j(k)$, $\mathbf{B}^j(k)$, $\mathbf{C}^j(k)$ and $\mathbf{D}^j(k)$ are essentially the same as the time-continuous version of the model, with the notion that the time-variant air flow $\dot{V}(t)$ and alveolar volume $V_A(t)$ are replaced by their discrete versions $\dot{V}(k)$ and $V_A(k)$.

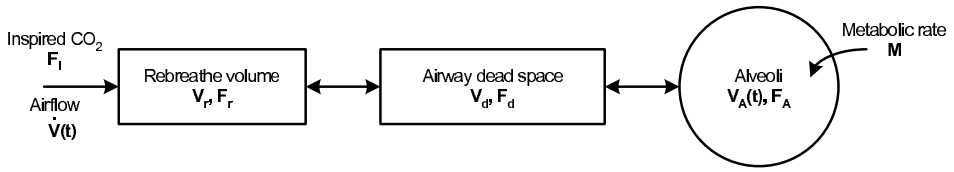

Fig. 2: Schematic overview of the compartmental gas exchange model.

Particle filtering

Particle filtering is a technique for recursive Bayesian filtering by Monte Carlo simulations [1], [8]. A particle filtering approach was implemented for the tidal-breathing model as follows. Each particle represents a parameter set $[V_r\ V_d\ V_{A,0}\ M]$ and is used to simulate the tidal-breathing model. Initially, N_p particles are generated using a uniform distribution of the different parameters within a realistic physiological range. The set of particles is then used to generate N_p model simulations of a complete breath n, consisting of N_m measurements. The measured fractional CO_2 concentrations at the mouth during this breath, $F_{r,n}$ are compared with the simulated trajectories $\hat{F}^i_{r,n}$ of all the N_p particles. Based on this comparison, a likelihood p^i_n is computed for each particle, asumming the measurement noise is Gaussian distributed with standard deviation σ:

$$p^i_n = \frac{1}{\sigma\sqrt{2\pi}} e^{-V^i_n/\sigma^2}, \tag{8}$$

where V^i_n is the sum of squared errors between data and prediction:

$$V^i_n = \frac{1}{N_m} \sum \left(\hat{F}^i_{r,n} - F_{r,n} \right)^2 \tag{9}$$

The particles are assigned weights w^i_n by normalizing the likelihood function:

$$w^i_n = \frac{p^i_n}{\sum_{i=1}^{N_p} p^i_n} \tag{10}$$

Using this approach, particles that can explain the measurement obtain a high weight. Finally, the particle distribution is resampled, so that the weights are approximately reset to $w^i_n = 1/N_p$. This has the consequence that the density of particles that result in small prediction error increases. To improve the ability to track changes in the parameters, Gaussian zero-mean white noise with low power compared to the desired accuracy in the parameters is added to the particles before predicting the next breath.

III. RESULTS

Figure 3 show a simulation of the capnogram using the set of default parameters, using a sampling rate of $f_s = 20$ Hz. The particle filtering algorithm was initialized using N_p = 1000 particles with uniform distributions of the parameters in the following ranges: $5 \leq\ V_r\ \leq 45$ ml, $20 \leq\ V_d\ \leq 320$ ml, $500 \leq\ V_{A,0}\ \leq 5500$ ml, and $50 \leq\ M\ \leq 450$ ml/min. Each breath, the particles are given weights and resampled according to the likelihood function. It can been seen in Figure 4 that after eight breaths, the particle distribution has a high density around the true parameters.

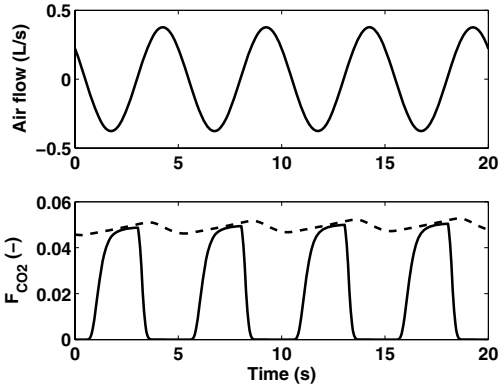

Fig. 3: Simulation of a capnogram, using default model parameters. *Top panel:* Airflow signal. Lower panel: Fractional CO_2 concentrations in the rebreathe volume (solid line) and alveoli (dashed line).

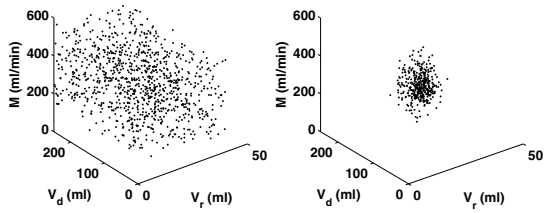

Fig. 4: Distribution of the particles as a function of the rebreahte volume (V_r), the airway dead space volume (V_d), and the metabolic rate M. *Left panel:* after initialization; *right panel:* after eight breaths.

To examine the ability of the algorithm to track parameter changes, the metabolic rate M was decreased in steps of 100 ml/min after 10, 12, and 14 breaths, while the other parameters were kept unchanged. The mean values of the particles were compared with the true parameter values (see Figure 5). It can be seen that the particle filtering method is able to rapidly track the changes in M, while it leaves the other parameters unchanged.

It was assumed that the most likely trajectory of the alveolar fractional CO_2 concentration was generated by the particle with the highest likelihood during a particular breath. In Figure 6, the predicted alveolar CO_2 is compared with the true trajectory.

IV. DISCUSSION & CONCLUSION

In this paper, a model of the capnogram, which is inherently nonlinear, is combined with a particle filter to be able to track changes in the physiologically meaningful model parameters. These parameters are the extent of rebreathing,

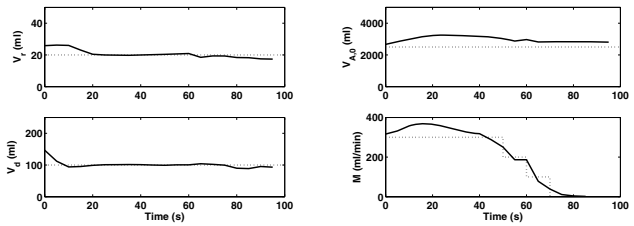

Fig. 5: Tracking of the model parameters after changes in the metabolic rate M. Solid lines: estimated parameters; dashed lines: true parameters.

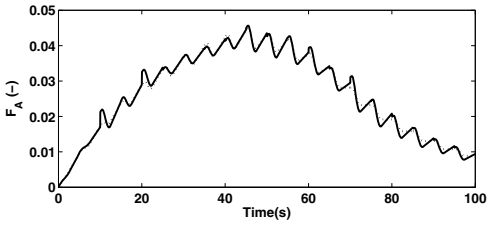

Fig. 6: Tracking of the alveolar CO_2 level (F_A) upon changes in the metabolic rate M. Solid line: prediction; dashed line: true F_A.

the airway dead space volume, the end-expiratory alveolar volume, and the metabolic CO_2 production. The model equations are based on a previously published model of human tidal breathing, that has been extensively validated against experimental data [2], [3], [4]. A simulation example is presented to demonstrate the fast adaptation of the method to changes in the metabolic rate. When applied to volumetric capnography data in a clinical setting, the algorithm could provide early alerts about the respiratory condition of the patient.

The model structure presented in this paper is based on physiological knowledge, where the model parameters have clear physical meanings. This has the advantage that the model can be used to aid in the interpretation of the capnogram. Unfortunately, accurate physical models often contain nonlinearities, such as the time-variant airflow and alveolar volume, as well as the alternation between inspiration and expiration in the tidal-breathing model. Because of these nonlinearities, identification of the model parameters requires some type of optimization algorithm. Nonlinear least squares methods, e.g. the Levenberg-Marquardt algorithm, have been succesfully applied to gas exchange data in the past [4], but are offline and require the assumption that the model parameters are constant over the analyzed period. Possible approaches to this problem are the linearization of the model equations, or the assumption of steady-state. Although simple ventilation models have been extensively used in respiratory physiology, these models often fail to accurately represent the tidal nature of human breathing [7]. With the improvement of computational tools for Bayesian statistics, such as particle filtering and Markov chain Monte Carlo (MCMC) technologies [8], it has become feasible to process nonlinear biomedical data on-line as it arrives. A particle filtering approach for the tidal-breathing model is presented in this paper, enabling the breath-by-breath identification of the nonlinear model, without the need for a physiological steady-state to occur.

Any model is based on assumptions, and the analysis of the model must be considered within these limitations. The division into single compartments for airway dead space and alveolar volume seems to be quite crude, as the human airways consist of numerous bronchi and millions of alveoli, which all may have different properties in terms of gas exchange. However, noninvasive measurements of flow and CO_2 fractional concentration at the mouth enable estimation of a limited number of parameters only, and therefore an optimum between model complexity and identifiability has to be found. Furthermore, the metabolic rate is a lumped parameter, which reflects changes in e.g. pulmonary blood flow, CO_2 production in the tissues and possible mismatches between ventilation and blood perfusion in the alveoli. Hence, the model cannot distinguish between these events. Finally, to guarantee convergence of the parameters, certain (unknown) conditions on the input/output data should be met for persistence of excitation. In a clinical setting, it is often not possible to meet these conditions, e.g. because of restrictions on varying the airflow and inspired CO_2 level.

Proof-of-concept is demonstrated in this paper using a single noise-free simulation, where the metabolic CO_2 production is stepwise decreased. In order to warrant future use in a clinical setting, extensive testing on both simulated and experimental data is required to further characterize the limitations of the method. In addition, the particle filtering algorithm may be fine tuned by using several available Bayesian computational tools.

V. ACKNOWLEDGMENTS

The authors thank Aleksandar Lj. Juloski for helpful discussion on particle filters.

REFERENCES

[1] M.S. Arulampalam, S. Maskell, N. Gordon and T. Clapp, A Tutorial on Particle Filters for Online Nonlinear/Non-Gaussian Bayesian Tracking. *IEEE Trans. Signal Proc.*, vol. 50, 2002, pp 174-188.

[2] H. Benallal and T. Busso, Analysis of End-tidal and Arterial PCO_2 Gradients Using a Breathing Model. *Eur. J. Appl. Physiol.*, vol. 83, 2000, pp 402-408

[3] H. Benallal, C. Denis, F. Prieur and T. Busso, Assessment of Arterial Gas Pressures and Cardiac Output Using a Breathing Lung Model. *Med. Sci. Sports Exerc.*, vol. 34, 2002, pp 1750-1756.

[4] H. Benallal, K.C. Beck, B.D. Johnson, T. Busso, Evaluation of Cardiac Output from a Tidally Ventilated Homogeneous Lung Model. *Eur. J. Appl. Physiol.*, vol. 95, 2005, pp 153-162.

[5] M.E. Cabrera, G.M. Saidel and M.H. Cohen, Noninvasive Estimation of Cardiac Output with Nonprescribed Breathing. *Ann. Biomed. Eng.*, vol. 19, 1991, pp 723-742.

[6] J.S. Gravenstein, M.B. Jaffe and D.A. Paulus, *Capnography: Clinical Aspects*, Cambridge University Press, NY; 2004.

[7] C.E.W. Hahn and A.D. Farmery, Gas exchange modelling: no more gills, please. *British. J. Anest.*, vol 91, 2003, pp 2-15.

[8] C.P. Robert, "Bayesian Computational Tools: a Brief Tutorial", *in 14^{th} IFAC Symposium on System Identification*, Newcastle, Australia, 2006, pp 33-45.

[9] N.O.T. Strömberg and P.M. Gustafsson, Ventilation Inhomogeneity Assessed by Nitrogen Washout and Ventilation-perfusion Mismatch by Capnography in Stable and Induced Airway Obstruction. *Pediatr. Pulm.*, vol. 29, 2000, pp 94-102.