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Evaluation of a two-compartment CO_2 gas exchange model for neonates in preterm lamb data

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Abstract: Gas exchange models have the potential to individualize therapy for patients requiring mechanical ventilation and aid in its automation. This is especially true in neonates, who face an increased risk for respiratory complications and ventilator-induced lung injury. Low-order, low-complexity models are commonly used for controller design due to their computational efficiency. Controller performance is affected by the model's prediction accuracy, necessitating thorough evaluation. This work evaluates the prediction accuracy of a two-compartment CO_2 gas exchange model with animal trial data. Individual parameter sets have been estimated within physiological bounds.

I. Introduction

Neonates often require mechanical ventilation due to respiratory complications that may result in hyper- or hypocapnia. Clinicians need to monitor each patient and manually adjust their ventilator settings to keep the partial pressure of arterial CO_2 (P_aCO_2) within normocapnic bounds. P_aCO_2 is an indicator for the respiratory CO_2-elimination. Closed-loop controllers for mechanical ventilation are employed with the goal of automatically determining the ventilator settings using measurements that reflect respiratory sufficiency, like P_aCO_2. Controller design can greatly benefit from mathematical gas exchange models. Low-order, low-complexity models are preferred in this case, as the main dynamics of the system are captured while computational effort is reduced. This paper evaluates the P_aCO_2 prediction accuracy of a two-compartment CO_2 gas exchange model with neonatal parameter sets. Ventilation data collected during an animal trial was used as reference.

II. Material and methods

II.I Preterm lamb ventilation data

This is a secondary study using data collected for in-vivo evaluation of a P_aCO_2 controller for neonates [1,2]. In the primary study preterm lambs were mechanically ventilated on the first day of life and ventilation settings were either adjusted by a neonatologist or the P_aCO_2 controller under test. Measurements of Minute Ventilation and the end-tidal CO_2 partial pressure ($P_{et}CO_2$) were received through a connection with the ventilator and automatically logged as described in [3]. Blood samples were taken every 30 minutes to obtain P_aCO_2 by Arterial Blood Gas Analysis (ABG). P_aCO_2 was estimated for continuous feedback by adjusting $P_{et}CO_2$ with a constant offset, determined by the difference between P_aCO_2 measured through an ABG and $P_{et}CO_2$. This estimate is defined as $\widehat{P}_aCO_2$. Out of the 58 individuals available in the data base, the data of 9 individuals with large variations in P_aCO_2 were manually selected prior to performing parameter identification.

II.II. Gas exchange model

A two-compartment CO_2 gas exchange model proposed by Kim et al. was used for this work [4]. Equations (1) and (2) represent the continuous CO_2 transport between the lungs and the body tissue via blood. For abbreviation, $\frac{dx}{dt} = \dot{x}$.

$$V_L \dot{P}_A CO_2(t) = MV_A(t)[P_I CO_2 - P_A CO_2(t)] + \alpha\lambda Q[P_v CO_2(t-\tau_1) - P_A CO_2(t)], \quad (1)$$

$$V_B \dot{P}_v CO_2(t) = Q[P_A CO_2(t-\tau_2) - P_v CO_2(t)] + \frac{MR_{CO_2}}{\alpha}. \quad (2)$$

V_L and V_B are the respective gas holding volumes of the compartments. P_ACO_2 and P_vCO_2 describe the alveolar and venous partial pressures of CO_2. P_ICO_2 is the CO_2 partial pressure in the inspired air. MV_A denotes the alveolar minute ventilation, describing only the volume of supplied gas that effectively participates in gas exchange. α and λ are natural constants for the conversion between concentrations and partial pressures. The effective cardiac output is represented by Q. Transport delays for venous and arterial blood are considered through τ_1 and τ_2. MR_{CO_2} denotes the metabolic production rate of CO_2. P_ACO_2 and

P_vCO_2 are the system states. Furthermore, $P_ACO_2 = P_aCO_2$ is assumed due to fast diffusion of CO_2. MV_A is the input to the model. It is calculated by considering the total volume of gas supplied to the animal during one minute and subtracting an estimate for the dead space ventilation.

II.III. Model parameters

Kim et al. derived individual parameter sets for pediatric patients by fitting the model equations to data collected during surgery [4]. For this work, two neonatal parameter sets were derived. Both were based on parameter ranges specifically for neonates, which were obtained from literature. 'Nominal parameter set' refers to the mean values of the obtained physiological parameter ranges. 'Estimated parameter set' describes parameter values that were estimated for each animal individually by fitting the model output to $\hat{P}_aCO_2$-trajectories. Neonatal development was considered through weight-specific parameter values. If not available from the literature, values were normalized to a standard weight of 3.3 kg. If no ranges were reported in the literature, values of ±10 % around the given value were assumed. The resulting parameter ranges were obtained as $39 - 47$ ml/kg for V_L [6], 263-322 ml/kg for V_B [5], 126-220 ml/min/kg for Q [7], and 6-18 ml/min/kg for MR_{CO_2} [8]. The range for the physiological dead space was 2-4 ml/breath/kg [9]. A sum of squared error (SSE)-minimization approach was used to estimate individual parameter sets within the physiological ranges. Fitting intervals contained a dynamic phase and a succeeding steady state if available. Periods of steady ventilation settings and $\hat{P}_aCO_2$ were chosen otherwise. Data with obvious outliers or faults in the ventilator setup were excluded. The interval lengths were approximately 20 minutes for fitting and 40 minutes to 2.5 hours for validation. The prediction error was calculated as the difference between minimal model P_aCO_2 and $\hat{P}_aCO_2$. SSE on the fitting intervals was minimized via a script in Matlab (The MathWorks, Natick, MA, USA). The Model prediction accuracy was evaluated by computing the root mean squared error (RMSE) on the validation intervals.

III. Results and discussion

The RMSE for each animal is depicted in Fig. 1. Mean (SD) RMSE among all simulated animals is 5.95 (6.70) mmHg for the estimated parameter sets and 16.31 (12.98) mmHg for the nominal parameter sets.

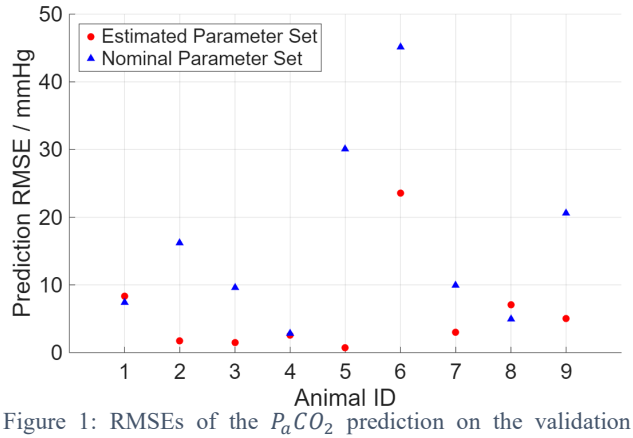

Figure 1: RMSEs of the P_aCO_2 prediction on the validation intervals for each evaluated animal.

In comparison to the nominal parameter sets, the estimated parameter sets improve the prediction accuracy of the model noticeably, with the exceptions of the first and eighth animal. Differences between pre- and post-fitting RMSEs in these two cases are small however. An RMSE of over 10 mmHg after fitting occurred only in animal 6. Potential changes in the animal metabolism or the ventilation effectivity cannot be considered with constant model parameters. As the parameters successfully minimized the SSE on the fitting interval, we assume unmodeled time-variability in the physiology on the validation interval to cause this large RMSE. Most RMSE values were below 5 mmHg with the estimated parameter sets. The values for the estimated dead space and MR_{CO_2} had the biggest impact on model prediction accuracy. Validating parameter sets for human neonates on animal trial data poses a significant limitation. Even though an established animal model was used, validation with human neonatal data is needed in the future.

IV. Conclusions

The prediction accuracy of a two-compartment CO_2 gas exchange model has been evaluated against animal trial data. While predictions with the nominal parameter set generally were not accurate, the estimated parameter set yielded good prediction accuracy in most animals. Model accuracy could be increased further by applying continuous online-estimation methods. The considered model, assuming individualized parameters, is well suited to be used in controller design. CO_2 and O_2 gas exchange models could be combined for holistic ventilation control.

Author's Statement

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