Veronika Huttova*, Jakub Rafl, Knut Möller, Thomas E. Bachman, Petr Kudrna and Martin Rozanek

Sensitivity analysis of a computer model of neonatal oxygen transport

Abstract: Computer models of neonatal oxygenation could serve as a tool for a comprehensive comparison of closed-loop automated oxygen control systems. The behaviour of such models depends, besides the input data of the inspired fraction of oxygen and the premature infant's breath pattern, on internal parameters of the model. The aim of this study was to perform a sensitivity analysis of a computer model of neonatal oxygen transport to clarify the influence of its internal physiological parameters on the output signal of peripheral oxygen saturation (SpO_2). We performed a multi-parameter sensitivity analysis using Monte Carlo simulations for randomly generated values of eight internal parameters. The influence on the model output SpO_2 signal was evaluated using five characteristics of the output signal. The relations between the parameters and the output characteristics were displayed using scatter plots and analysed by linear correlation, standardized regression, and partial correlation. The main result of the study is that in our model the oxygen consumption in the tissue and the cardiac output have the greatest influence on the SpO_2 drop and minimal SpO_2 value during simulated desaturation. The rate of development of desaturation and its duration are most affected by the diffusion resistance of the alveolar-capillary membrane. The results of the sensitivity analysis will help to optimize the performance of the computer model of neonatal oxygen transport.

Keywords: Automated control, computer model, peripheral oxygen saturation, preterm infant, sensitivity analysis.

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1 Introduction

Closed-loop automated oxygen control systems for neonates have become commercially available. Recently published review articles confirmed that the automated control systems increase the success rate of maintaining peripheral oxygen saturation (SpO_2) within the target range, limit episodes of both hypoxaemia and hyperoxaemia, and reduce the workload of nurses in comparison with manual control [1, 2]. Despite this, the efficiency of automatic systems is still far from satisfactory with much room for improvement [2]. And, in contrast to the availability of comparison of the automatic and manual control, a complex mutual comparison of automatic control algorithms is missing [1].

A computer model of neonatal oxygen transport allows not only a comprehensive comparison of available automatic control algorithms, but it can also provide a verification platform to facilitate the development of the control algorithms [3]. Morozoff et al. [4] developed a model of neonatal oxygen transport consisting of the respiratory and circulatory system part that were linked by the oxygen dissociation curve (ODC) and scaled to a neonate weighing 1.5 kg. This model used the concept of shunts to simulate pathological conditions in a neonate. In different models, Sands et al. showed possibilities how to describe impaired gas transfer across the alveolar-capillary membrane by ventilation-perfusion mismatch [5] or elevated alveolar-capillary diffusion resistance [6]. In our project [7], Morozoff's model was enhanced in several ways; primarily a diffusion resistance (R_{diff}) has been introduced into the model and the range of some physiological parameters of the model was estimated from neonatal literature rather than scaling from adults. The search for optimal values of internal parameters of the model with respect to available neonatal clinical data raised a question of the relative influence of the parameters on the model output signal, SpO_2.

The aim of this study was to perform a sensitivity analysis of the computer model of neonatal oxygen transport to clarify the influence of individual internal physiological parameters of the model on its output SpO_2 signal.

2 Methods

We repeatedly run a 310s-long simulation that included a single desaturation episode due to apnoea. The desaturation episode was modelled based on the real clinical data of a premature male infant, 27 days old, weighing 1,019 grams that were used in our previous study [7] to preliminary validate the model.

The measured inspired fraction of oxygen (FiO_2) and expiratory tidal volume (VTe) were the inputs of the model and the signal of SpO_2 was the output of the model (Figure 1). Five selected characteristics of the SpO_2 signal were chosen for the sensitivity analysis: the lowest reached value of SpO_2 (Minimum SpO_2) during apnoea, the SpO_2 level before the onset of apnoea (Baseline SpO_2), the relative drop of SpO_2 during apnoea (Delta SpO_2), the rate of development of desaturation (Descent Time) evaluated as the time needed for SpO_2 to drop from 90% to 10% of Delta SpO_2, and the duration of desaturation (Desaturation Time) evaluated as the time where SpO_2 was below 50% of Delta SpO_2.

The sensitivity analysis evaluated the influence of eight internal physiological parameters of the model, summarized in Table 1, on the output SpO_2 signal shortly before and during the simulated desaturation. The analysis was based on Monte Carlo simulations: 100 samples of parameter vectors were generated as combinations of random values of the investigated internal parameters. All the parameters were described by the uniform distribution. The upper and lower boundaries of the generated parameter values were set according to typical values and variability of the relevant physiological parameters described in neonatal literature [8–10], with respect to the age and weight of a simulated neonate. The simulations were prepared, performed and analysed using Sensitivity Analysis Tool of Matlab–Simulink programming and simulating environment (MathWorks, Natick, USA).

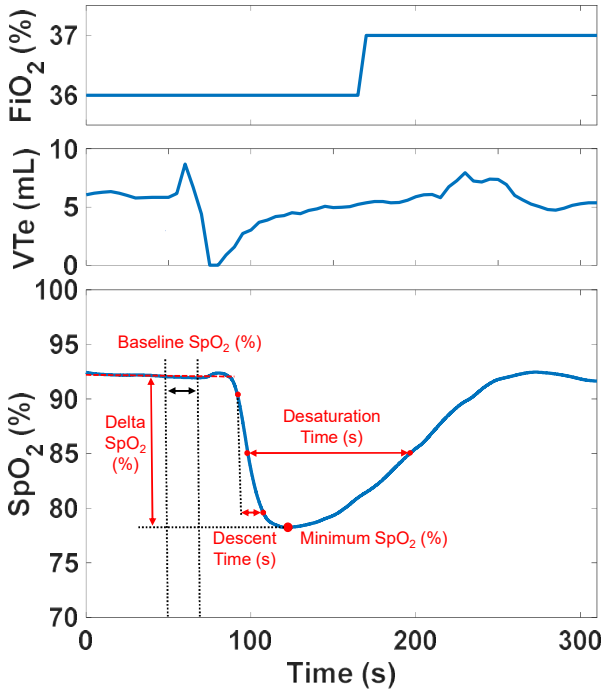

Figure 1: An episode of desaturation utilized for sensitivity analysis. Model inputs (top and middle panel) were extracted from available clinical data. The influence of internal parameters of the computer model on the model output (bottom panel) was evaluated using the selected signal characteristics (red).

Table 1: Limits of the internal physiological parameters of the model used for sensitivity analysis.

Parameter	Symbol	Lower Limit	Upper Limit
O_2 Capacity (mL O_2/mL)	MAXX	0.097	0.149
2,3-DPG (mmol/L of RBCs)	cDPG	1.933	10.257
HbF (% of Total Hb)	xHbF	80.6	99.0
Cardiac Output (mL/s)	FB	2.5	6.3
O_2 Consumption (mL O_2/s)	K	0.1	0.2
Pulmonary Shunt (%)	S3	5	30
Diffusion Resistance (mmHg□s/mL O_2)	R_{diff}	58	873
SpO_2 Meas. Delay (s)	DelaySpO_2	0	30

3 Results

The results of the multi-parameter sensitivity analysis using Monte Carlo simulations are presented in Figure 2 and Figure 3. Scatter plots in Figure 2 show relations between values of individual examined internal parameters of the model and values of selected characteristics of the model output SpO_2 signal. A pattern in scatter plots suggests a systematic dependence between an internal parameter and the model output. Histograms show the distributions of selected characteristics of the model output when tested with uniformly distributed internal parameters. Tornado plots in Figure 3

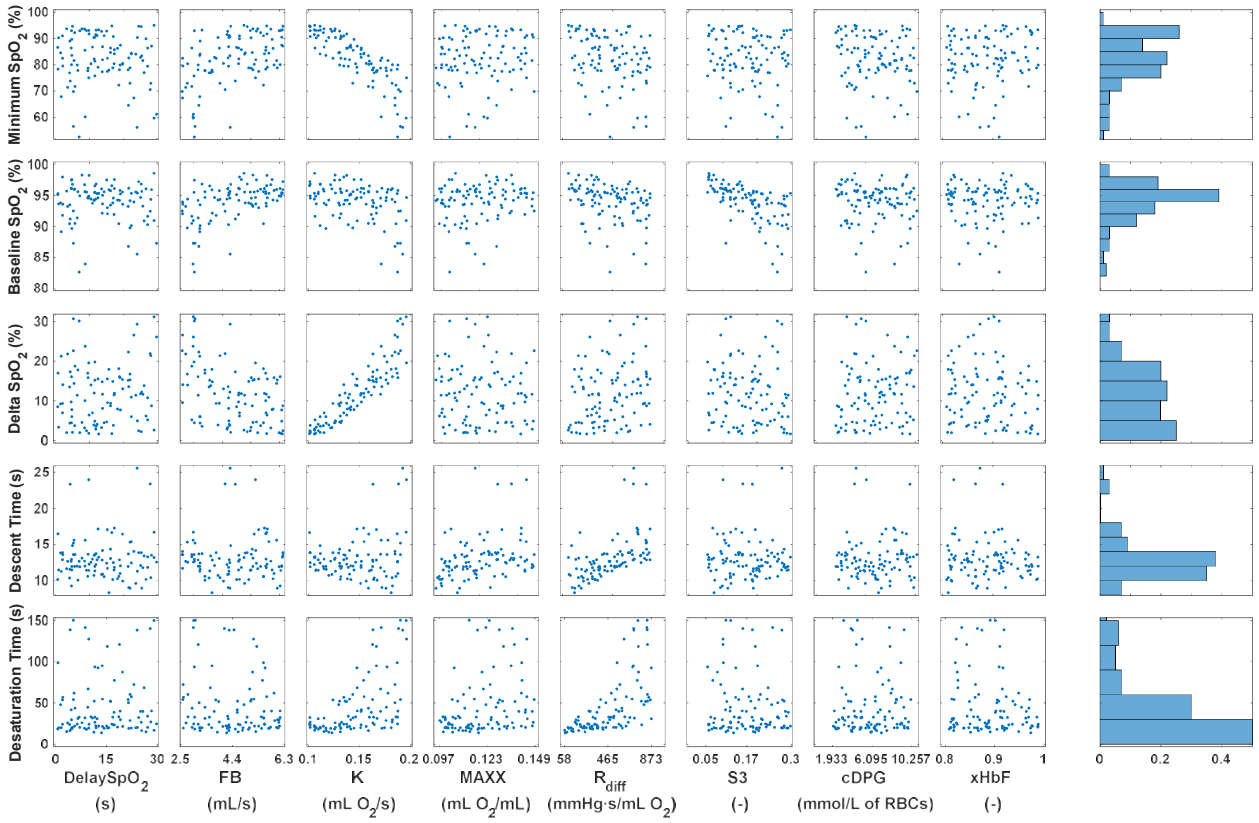

Figure 2: The scatter plots show relations and possible systematic dependence between individual examined internal parameters of the model (x-axis) and selected characteristics of the model output SpO_2 signal (y-axis). The histograms show distributions of values of the selected signal characteristics.

summarize and compare the systematic influence of each internal parameter on selected characteristics of the model output using linear correlation, standardized regression, and partial correlation.

The most influential internal parameter is the oxygen consumption in the tissue (K) which affects systematically both the absolute SpO_2 minimum and SpO_2 drop during apnoea. The high value of the oxygen consumption parameter in the model means stronger desaturation manifested both by a lower absolute minimum of the SpO_2 signal and a more significant SpO_2 drop. Both the output signal characteristics are also affected by cardiac output (FB), which also systematically affects the baseline of the SpO_2 signal. Among other internal examined parameters, pulmonary shunt (S3) affects indirectly the baseline of SpO_2 signal and the diffusion resistance (R_{diff}) affects directly the rate of development and duration of desaturation (Descent Time and Desaturation Time, respectively). On the other hand, the simulations did not demonstrate a substantial influence of the examined parameters of ODC, the relative concentration of HbF, and 2,3-DPG, on any characteristics of the output SpO_2 signal.

4 Discussion and Conclusion

Our sensitivity analysis of the computer model of neonatal oxygen transport confirmed the dominant role of two parameters—the oxygen consumption in tissues and cardiac output—both on the absolute value of the model output SpO_2 signal and on the magnitude of desaturation. The findings are consistent with the study of Sands et al. [10]. The same authors found in [6] that increased lung diffusion resistance prolongs hypoxemia as it slows down reoxygenation. Our results correspond to that as the rate of development and duration of desaturation in our simulations were influenced the most by the diffusion resistance.

The sensitivity analysis evaluated the influence of selected internal physiological parameters on the output of the computer model of neonatal oxygenation and identified the parameters that are the most closely related to the model output. The results of the sensitivity analysis will help to decide on the clinical data that are the most important to collect

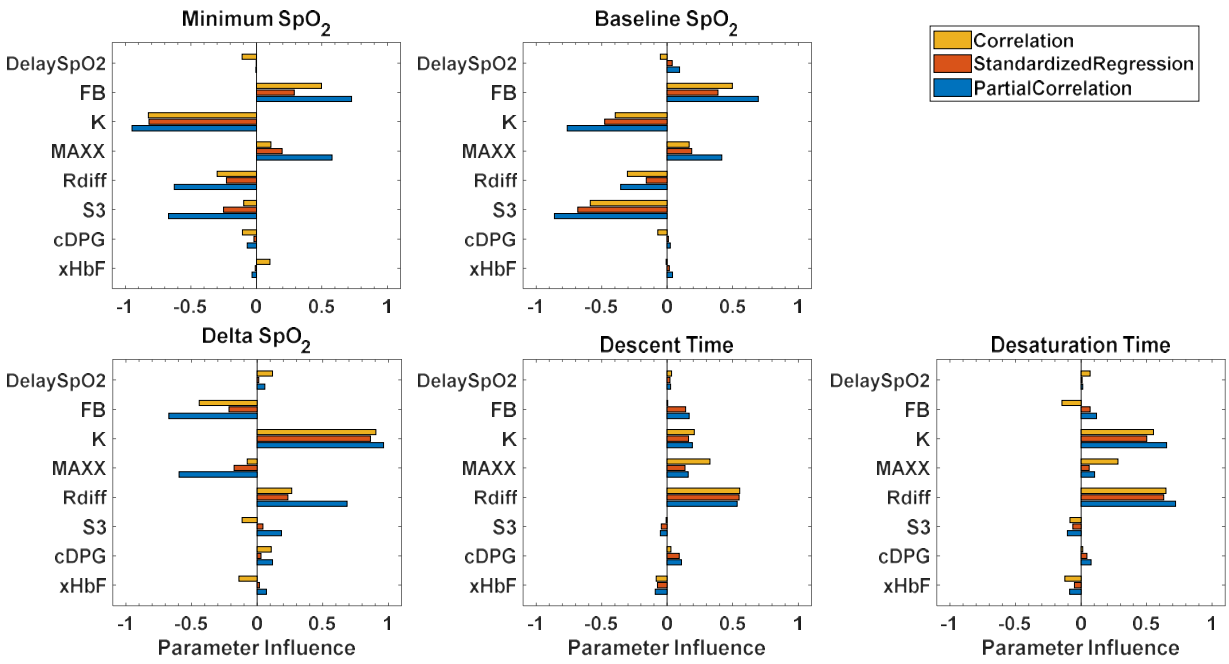

Figure 3: Comparison of the strength of systematic relation between eight internal parameters of the model and five selected characteristics of the model output signal.

with high accuracy for model validation and will help to focus the final optimization of the model performance.

Author Statement

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