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Comparing three differing approaches to identify a three-parameter gas-exchange model with noisy data

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ABSTRACT

Using mathematical models enables simulation of patient individual physiology. It can therefore be employed for predicting the outcome of various therapy settings. To be able to utilize a model at the bedside it has to be identifiable using the available data in a reasonable time. A previously presented identification approach that exploits hierarchical dependencies between models and that is independent of initial parameter estimates showed promising results. The presented work investigates how this approach behaves when the presented patient data is noisy. The method was evaluated employing data of twelve in-silico patients where noise of different amplitude was added. The results were compared to two alternative parameter identification approaches. One being the conventional method of identifying the model directly and the other being a method that iteratively reduces the dimension of the objective surface to optimize convergence (DRM – Dimensional Reduction Method). Both require a set of initial estimates which were taken arbitrarily from an increasing region around the true parameter values. Results show that the direct approach leads to a lower prediction error than both the hierarchical approach and the DRM when the initial estimates are close to the parameter values used to create the data, they become higher than the prediction error produced by the model identified with the hierarchical approach and the DRM when the initial estimates are drawn from a wider range around the true model parameters. Additionally, compared to the direct approach the DRM shows to be affected less by the initial estimates as shown by a more constant prediction error with respect to the region from which the initial estimates were drawn.

1. Introduction

Physiological models are increasingly used for decision support in care of critically ill patients (Carson & Cobelli, 2014). In particular, models are individualized by determining the physiological properties that capture the data from a patient. These individualized models can then be used to simulate and predict the outcomes of various therapeutic choices to determine optimal care. For patients that require mechanical ventilation, models of respiratory mechanics and gas exchange can be employed to predict the outcome of changes in ventilator settings. Thus, the inspired oxygen fraction (FiO_2), minute volume (MV), or PEEP (Positive end-expiratory pressure) can be optimized to the particular patient (Kretschmer et al., 2013; Rees et al., 2006; Schranz, Becher, Schadler, Weiler, & Moller, 2014; Tehrani & Abbasi, 2012). Furthermore, the identified model parameters may provide unique information about the underlying patient state or changes in patient state over treatment.

The potential benefit of the modeling strategy depends heavily on how well the model describes patient behavior and how well model variables can be identified via available data. In particular, models need to be structurally and practically identifiable. Structural identifiability of a model can be declared if a single, unique set of model variable values define the minimum error between the model and measured data (Pohjanpalo, 1978; Ritt, 1950). Structural identifiability can be assessed via a variety of mathematical tools including DAISY (Differential Algebra for Identifiability of Systems, University of Cagliari and University of Padova, Italy) (Bellu, Saccomani, Audoly, & D'Angio, 2007). In contrast, practical identifiability describes how repeatable identified model parameter values are under realistic conditions. In particular, if two or more variables in a model define similar behavior, noise in the measured data may lead to highly variable parameter values. While a unique minima set will exist in such cases, the variable values cannot be relied upon and are likely to

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lead to inaccurate simulation (Docherty, Chase, Lotz, & Desaive, 2011).

The variables in physiological models can be identified via a variety of means. Simple linear models can be identified with simple inversion or regression methods, and do not require initial estimates (Polak, 2011). However, more complex models generally require more sophisticated identification algorithms such as gradient descent or simplex-search based methods. Identification methods typically aim to minimize the sum of squared errors (SSE) between the model simulation and measured data.

Gradient descent and simplex-search methods can fail to converge to the global minima in some cases. While there can be a variety of causes for this failure, it is most often caused by convergence to a local minima or lack of ability to identify the direction that may further minimize the SSE value (Docherty, Schranz, Chase, Chiew, & Möller, 2014). These issues seem to be exacerbated in poorly conditioned models or in models with a large number of identified variables. It has been observed that when such premature convergence is encountered, the issue may be mitigated with improved initial value estimates, i.e. initial parameter value estimates that are close to the true values led to a higher chance of successful convergence than initial values that are distinct from the true parameters. Unfortunately, the true parameter values are unknown at the initiation of parameter estimation. Two parameter identification approaches have been mooted to overcome these issues — the hierarchical method (HM), and the dimensional reduction method (DRM).

Schranz, Knöbel, Kretschmer, Zhao, and Möller (2011) previously presented the HM that uses parameter identification of low complexity models to provide good initial value estimates for higher complexity models. The models have to be in a hierarchical relation, i.e. the models all have a similar form but are of different complexity. Models of higher complexity are deduced from models of lower complexity by replacing linear elements by nonlinear elements or by extending the model by new elements. The method shows satisfactory improvements to the direct identification of the higher complexity model in isolation. The approach has been used successfully in respiratory models and models of gas exchange using synthetic patient data (Kretschmer, Docherty Paul, Riedlinger, & Möller, 2016; Schranz et al., 2011). However, in the latter case, an *in-silico* analysis was used, and clinically realistic noise was omitted from the data. Hence, the method was tested in structurally identifiable cases, but not in cases wherein practical identifiability would be an issue.

The DRM identifies the parameter values for a model of n variables with n distinct starting conditions. In poorly conditioned models, this leads to n distinct optimized points on an *n-1* manifold. A second round of parameter identification is undertaken on the *n-1* manifold to find an *n-2* manifold. This is continued until an optimized variable set is determined along a single non-orthogonal dimension. The approach has been tested in clinical glycemic data and *in-silico* respiratory data and shown to improve outcomes over the simple evaluation of the models (Davidson, Docherty, Kretschmer, & Murray, 2017).

This research aims at comparing how physiological parameters determined with three different parameter identification approaches (direct approach, hierarchical approach, dimensional reduction method) are affected by noise in the data. The model analyzed was chosen to be a three-parameter gas exchange model that has proved challenging to identify in the past. (Riedlinger, Kretschmer, & Möller, 2013)

2. Methods

2.1. Three parameter gas exchange model

The three variable gas exchange model presented by Karbing, Kjaergaard, Andreassen, Espersen, and Rees (2011) is used to assess the identification approaches. The alveolar gas exchange is modeled over two separate compartments that each receive a fraction of the inspired air. The fraction of inspired air in the first alveolar compartment is defined f_A. Gas is exchanged across each alveolar compartment and blood from the pulmonary artery. The fraction of blood accessible to the first compartments is defined by the variable f_Q. Furthermore, a certain proportion of blood is shunted past the alveolar compartments (f_S). The alveolar compartments provide difference levels of ventilation ($\dot{V}$) and perfusion (Q). Hence, the model can detect mismatches between ventilation and perfusion. Patient variability is captured by the variable set $\mathbf{x} = [\, f_S, f_A, f_Q \,]^T$

Arterial gas concentrations (Ca_x) can be defined:

$$Ca_x = Cc_{x,1} \cdot (1 - fs) \cdot (1 - fQ) + Cc_{x,2} \cdot (1 - fs) \cdot fQ + Cv_x \cdot fs \quad (1)$$

where, Cv_x is venous gas concentrations, Cc_x is the end-capillary gas concentrations. Venous concentrations $Cv_{x,1}$*and* $Cv_{x,2}$ are defined:

$$Cv_{x,1} = Cc_{x,1} - \frac{\dot{V}_{x,1}}{Q \cdot (1 - fs) \cdot (1 - fQ)} \quad (2)$$

$$Cv_{x,2} = Cc_{x,2} - \frac{\dot{V}_{x,2}}{Q \cdot (1 - fs) \cdot fQ} \quad (3)$$

where Q denotes blood flow while $\dot{V}_x$ describes oxygen consumption and carbon dioxide production. These rates can be defined across both alveolar gas exchange processes:

$$\dot{V}_{x,1} = (1 - f_A) \cdot \dot{V}_A \cdot \left(Fi_x - FA_{x,1}\right) \quad (4)$$

$$\dot{V}_{x,2} = f_A \cdot \dot{V}_A \cdot \left(Fi_x - FA_{x,2}\right) \quad (5)$$

where $\dot{V}_A$ is the alveolar ventilation and Fi_x are the inspired gas fraction of oxygen and CO_2. The alveolar gas fractions $FA_{x,1}$ can be defined:

$$FA_{x,1} = \frac{Fet_x - fA \cdot FA_{x,2}}{(1 - fA)} \quad (6)$$

$FA_{x,2}$ is then calculated to ensure that $Cv_{x,1}$ and $Cv_{x,2}$ are equal. Finally, by assuming that end capillary gas concentrations are the same as alveolar gas concentrations, gas dissociation equations can be used to derive Cc_x as a function of FA_x (Kelman, 1966; Sharan & Selvakumar, 1998). Fig. 1 shows the three-parameter gas exchange model. Model inputs are inspired oxygen fraction (Fi_{O2}), air flow and end-tidal gas fractions (Fet_x).

2.2. Simple gas exchange model

A single alveolar compartment models divides blood flow into oxygenated and shunted blood and is a much simpler representation of the gas exchange dynamics (Kretschmer et al., 2013). Fig. 2 shows the simple gas exchange model. Assuming that CO_2 partial pressure in the alveolar compartment is the same as the partial pressure in the arterial blood can lead to simple evaluation of the partial pressure of oxygen (PA_{O2}) in the lung:

$$PA_{O2} = Fi_{O2} \cdot (P_{atm} - P_{H2O}) \frac{Pa_{CO2} \cdot \left[1 - Fi_{O2} \cdot \left(1 - R_Q\right)\right]}{R_Q} \quad (7)$$

where R_Q is the respiratory quotient, P_{atm} and P_{H2O} describe atmospheric and water vapor pressure, respectively, and Pa_{CO2} is the arterial partial pressure of CO_2.

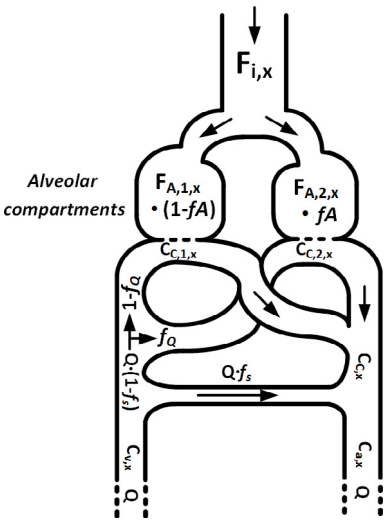

Fig. 1. Schematic representation of the three-parameter model of gas exchange.

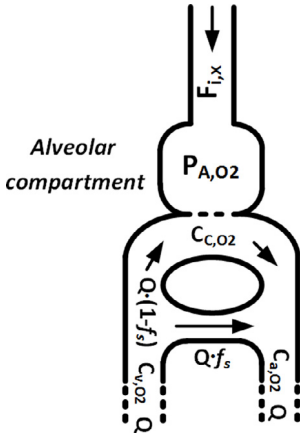

Fig. 2. Model structure of the simple one-parameter gas exchange model. A fraction of the venous blood gas is shunted away and mixed directly with the oxygenated blood that has passed the alveolar compartment.

Assuming that the partial pressure of the alveolar gas is equal to end-capillary partial pressure, oxygen dissociation equations can be used to define Cc_{O2} (Kelman, 1966). Assuming a constant arterial -venous oxygen difference (Δ_A^V), the venous oxygen concentration can be derived from Ca_{O2} (calculated from measured Pa_{O2} using the oxygen dissociation equation)(Lumb, 2000):

$$Cv_{O2} = Ca_{O2} - \Delta_A^V \tag{8}$$

(Benatar, Hewlett, & Nunn, 1973) shows that shunt can be calculated as:

$$f_S = \frac{(Cc_{O2} - Ca_{O2})}{(Cc_{O2} - Cv_{O2})} \tag{9}$$

Hence, via a series of moderately appropriate assumptions, the simple gas exchange model can define a value of f_S via a single blood gas measurement.

2.3. Data

Twelve *in silico* patient models were simulated using the three-parameter model of Eqs. (1)–(6). Each patient had unique values for f_S, f_A and f_Q. The patient data sets led to simulations that would be considered healthy (Pa_{O2}/Fi_{O2} of 407 mmHg) to those that would be considered very unhealthy (Pa_{O2}/Fi_{O2} of 91 mmHg). Nine measurements of Pa_{O2} and Pa_{CO2} (at FiO_2 = 21%–100%) were sampled from simulations of each patient to evaluate the quality of the model identification, while four measurements of Pa_{O2} and Pa_{CO2} at Fi_{O2} levels of 21% 40%, 70% and 100% were used for each patient to identify the models. Multiplicative noise of ±2.5%, ±5% or ±7.5% was added to the data. *In silico* patient parameters are shown in Tables 1 and 2.

Table 1
Parameter combinations to create the synthetic patient data and their classification of impairment.

Patient	Model parameters			PaO_2/FiO_2	Classification
	f_s	f_A	f_Q		
1	0.03	0.6	0.8	407 mmHg	Healthy
2	0.03	0.4	0.6	403 mmHg	Healthy
3	0.1	0.4	0.6	304 mmHg	Mild
4	0.1	0.4	0.8	280 mmHg	Mild
5	0.03	0.3	0.8	226 mmHg	Mild
6	0.1	0.3	0.8	214 mmHg	Mild
7	0.2	0.4	0.6	169 mmHg	Moderate
8	0.2	0.6	0.8	169 mmHg	Moderate
9	0.2	0.3	0.8	153 mmHg	Moderate
10	0.3	0.4	0.6	98 mmHg	Severe
11	0.3	0.6	0.8	98 mmHg	Severe
12	0.3	0.3	0.8	91 mmHg	Severe

Table 2
Blood gas and other physiological parameters used to create the synthetic patient data.

Parameter	Value	Unit
Respiration rate	12	1/min
Cardiac output	5.5	L/min
Tidal volume	0.5	L
Dead space volume	150	mL
Hematocrit	42	%
Body temperature	37	°C
pH	7.4	–
BE	0	–
Hemoglobin concentration	140	g/L

2.4. Parameter identification

2.4.1. Hierarchical method (HM)

For the HM, the one compartment model described in Section 2.2 was used to calculate an estimate f_S using the Pa_{O2} that was measured at an Fi_{O2} of 100%. This value was then used in a two-compartment model of gas exchange that fixed the value of $f_Q \in \{0.1, 0.2, \ldots, 0.9\}$. The initial estimates for identification of that two-compartment model were thus $\mathbf{x}_{initial} = [f_S, f_A]^T = \left[f_{S,1comp}, 0.5\right]^T$, where $f_{s,1comp}$ is the value for fs estimated in the first step of the hierarchical approach, i.e. the shunt fraction calculated using the one compartment model. A simplex-search method (Lagarias, Reeds, Wright, & Wright, 1998) was used to determine optimized values of f_S and f_A for this intermediate model. The f_Q value that yielded the lowest SSE between measured and simulated Pa_{CO2} (see Eq. (10)) and the identified values for f_S, and f_A were used as initial values for a full three parameter model identification with $\mathbf{x}_{initial} = \left[f_S, f_A, f_Q\right]^T$. In this final stage, the objective function was defined to be the sum of SSE values across simulated and measured Pa_{O2} and Pa_{CO2} (see Eq. (11)). The implementation of the hierarchical method is shown graphically in Fig. 3.

$$W_{CO2} = \sum \sqrt{(PmCO_2 - PaCO_2)^2} \tag{10}$$

$$W_{O2,CO2} = \sum \sqrt{(PmO_2 - PaO_2)^2} + \sqrt{(PmCO_2 - PaCO_2)^2} \tag{11}$$

2.4.2. Dimensional reduction method (DRM)

The DRM optimizes convergence towards the global minimum by restricting iteration in dimensions where the error gradient is low. It does not modify the objective surface like e.g. the Tikhonov regularization does, but rather is a framework that can be placed around any parameter identification approach. Details of the DRM algorithm can be seen in (Davidson et al., 2017). The DRM requires a domain to initiate the identification. Initial conditions are defined randomly across the domain, but identification can converge outside of the bounds of the initial parameter range. In this analysis, a range of 0.01 – 0.99 was used for all parameter values. The same simplex-search method as in the HM and the direct approach was used inside the DRM to undertake identification on the manifolds of decreasing dimension. The DRM did not use the simple or intermediary models of the hierarchical method and identified the three-compartment model from Section 2.1 directly.

2.4.3. Evaluation

The DRM and HM were compared to the direct approach (DA) of using an orthogonal identification directly on the three-compartment model of Section 2.1.

The Nelder–Mead Simplex-Search (Lagarias et al., 1998) that was used in the DA, the HM and the DRM was implemented via the *fminsearch.m* function in MATLAB (R2015a, The Mathworks, Natick, USA)

The DRM and the DA were evaluated using 100 initial estimates for each patient and noise level. Since noise on the measurements shifts the global minima from the parent parameter values, the precision of identification cannot be assessed. Hence, the approaches are assessed in their ability to achieve minimum deviation between measured and simulated Pa_{O2} and Pa_{CO2}. This was initially evaluated in the four identification data sets to assess parameter optimization across the approaches then across all nine measurements to assess predictive capability of the models. The influence of the initial estimates on the identification outcome was tested by extending the range from which the initial estimates were randomly drawn. The ranges were $\mathbf{x}_{true} \pm$n, where $\mathbf{x}_{true}$ was the true parameter values that were used to create the data and n was *{0.05, 0.1, 0.15, …,0.5}*. For each of those ranges, 100 identifications were done as described above. The HM does not require initial estimates, thus for each patient only one identification was done.

To ensure a fair comparison across the approaches, the maximum number of function evaluations (*MaxFunEvals*) was set to 10,000 for the DA. Each of the hierarchical steps (nine iterations with fixed *fQi* in the two-parameter model and one identification of the three-parameter model) was allowed to call the function 1000 times. The DRM was allowed a maximum number of function evaluations of 333 at each of the three stages. Hence, each approach was given the same ability to call the objective function. All other settings were the same across the three approaches.

3. Results

Fig. 4 shows the mean simulation error between the nine exact measurements in the *in-silico* patients and the PaO_2 and $PaCO_2$ predicted by the model when being identified using the three identification approaches and the noisy measurements. Crosses depict the simulation error (in %) if the model is identified using the direct approach, x-markers show the results for the model identified using the dimensional reduction method and the dash dotted line depicts the results when the model is identified using the hierarchical approach. The results are shown with respect to the range (n) from which the initial estimates ($\mathbf{x}_{initial} = \left[f_S, f_A, f_Q\right]^T$) were randomly drawn ($\mathbf{x}_{true} \pm n$). The graph shows an increase of simulation error in both the direct approach and the DRM when n is increased. Adding a noise of ±2.5% to the data, the model identified with the DA achieved a mean simulation error of 6.8% at $n = 0.05$ increasing to 10.6% at $n = 0.5$. In data with ±5% noise added the mean simulation error ranged from 13.7% ($n = 0.05$) to 18.5% ($n = 0.5$). Using data with ±7.5% noise to identify the model, the simulation error for the model identified with the DA was between 20.2% at $n = 0.05$ and 24.3% at $n = 0.5$. Identifying the model with the DRM lead to simulation errors of 8.2% – 9.5% at ±2.5% noise in the data, 16.2% – 17% at ±5% noise and 22.7% – 24.6% at ±7.5% noise The model identified using the HM resulted in a mean simulation error of 7.5% in data with ±2.5% noise, 13.4% using data with ±5% noise and of 20.3% in data with ±7.5% noise.

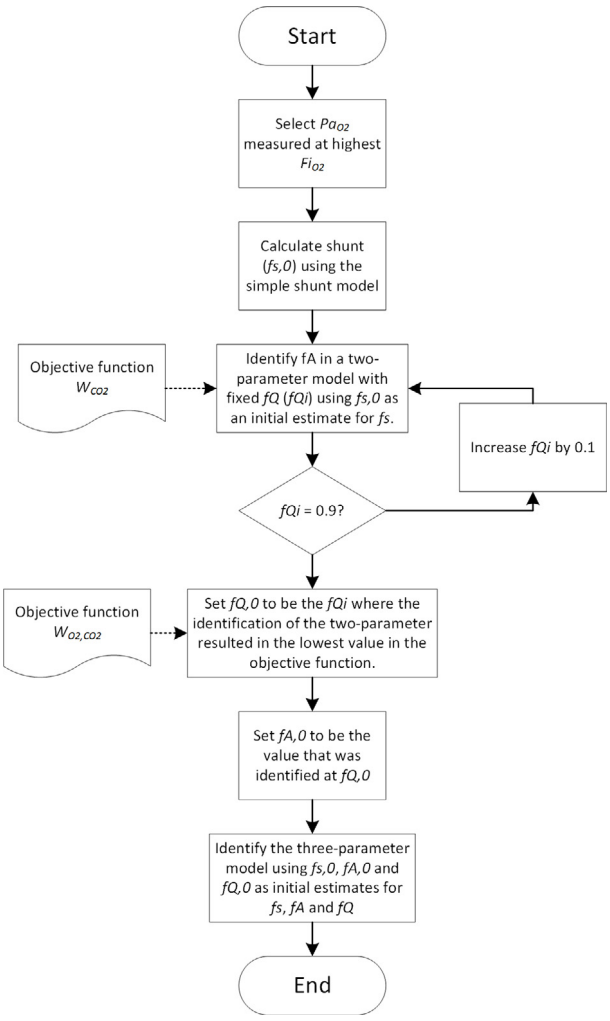

Fig. 3. Flowchart describing the hierarchical identification of the three-parameter model. The one-parameter model is used to calculate a valid initial guess $f_{s,0}$ that is then used in identifying the two-compartment model. There, f_Q is fixed at various levels and f_s and f_A are identified. The resulting values of f_A and f_Q are used as $f_{A,0}$ and $f_{Q,0}$ along with $f_{s,0}$ from the one-parameter model in the identification of the three-parameter model.

Computing time was measured on an i7-4770 CPU with 12GB RAM and showed an average computing time of 59.4 s for direct approach, 353.9 s for the hierarchical approach and 92.9 s for the dimensional reduction method.

4. Discussion

The use of mathematical models can help to attain a more detailed understanding of patient physiology. By adapting a model to the individual physiology of a patient, it is possible to reproduce the physiological reactions that occur when the therapeutic regime is modified. Thus, such a model may be used to predict those reactions. Decision support system can utilize those predictions to optimize therapeutic outcomes or to achieve goals defined by a clinician. To be able to use such a system in a real clinical setting, the implemented models need to be identifiable from data that is available at the bedside. Additionally, the identified model parameters need to be trustworthy, i.e. the parameter values that are found through parameter identification need to be repeatable and they need to reflect the true patient physiology correctly. Poorly optimized parameters will not accurately represent patient physiology and therefore bear the risk of incorrect predictions. Additionally, they would lead to a false indication of the current state of patient health or response to treatment and therefore my lead to false therapeutic strategies.

The three identification approaches were evaluated using different multiplicative noise in the patient data and running 100 identification attempts for each range from which the initial estimates were drawn. To draw the initial estimates, the function 'rand()' was used in MATLAB, which calculates uniformly distributed random numbers. Considering the distribution of initial estimates along the largest possible range (0.01–0.99), i.e. considering the largest n-Range to be 0.5 and in the case that the true value of a parameter is at 0.5, then the initial estimate could be between 0.01 and 0.99. Classifying those initial estimates into ranges of 0.01–0.1, 0.1–0.2, 0.2–0.3, …,0.9–0.99, then there would be ten distinct classes. Hence, the enforced variance in initial parameter values ensures that the analysis tested the effects of initial parameter estimation robustly.

Due to the added noise, the true global optima PaO_2 and $PaCO_2$ values were unknown. With increasing noise, the simulation error of all three approaches increased. With a higher level of noise naturally comes a greater difference between model output and measured values, i.e. as the model is unable to reproduce the noise, the identification algorithm tries to find the best curve fit. That fit can never be exact because the data that is used as a goal is noisy (Burnham & Anderson, 2002). Thus, data with more noise will ultimately lead to optimal solutions with higher residual levels. Still, the results show a dependence of the direct approach and the dimensional reduction method on the initial estimates. More specifically, the model identified with the direct approach showed a lower deviation if the initial estimates were close to the values that were used to create the data ($n \approx 0.05$). In contrast, the simulation error increased when the initial estimates were drawn from a broader initial condition distribution ($n \approx 0.5$). The DRM showed an analogous behavior, however with a less distinctive influence of the range from which the initial estimates were drawn from. However, the DRM results in a higher simulation error than the DA when the initial estimates are close to the true values. Those results hint to the conclusion that the DA is highly susceptible to reaching local minima in the objective surface when the initial estimates are further away from the true parameter values while the DRM is less prone to terminate in local minima. That advantage is however paid for by a higher residual when the optimization is terminated.

The hierarchical method is independent from initial estimates because appropriate estimates are calculated through models related to the three-parameter model but of less complexity. The model identified with the hierarchical method showed a slightly higher simulation error than the model identified with the DA when the initial estimates are very close to the values used to create the data. But it showed a significantly lower simulation error if the initial estimates for the DA are drawn from a wider range around the true values. The increased simulation error from the hierarchical method at low n values is likely due to a lower number of iterations available for convergence of the three-parameter model. In contrast, at higher n values, the direct approach was more likely to converge to local minima while the DRM has a higher simulation error overall.

While the direct approach performs better than the hierarchical approach or the DRM when low noise is present and the initial estimates are close to the global minimum, such conditions are difficult to achieve with clinical data. In particular, the true values of the model parameters are unknown and thus, initial estimates are random and unlikely to be accurate. This ambiguity of the suitability of the direct approach implies that it should not be incorporated into protocols that are intended to guide therapy.

Employing alternative parameter identification approaches such as genetic algorithms or a grid search using a small enough grid might lead to lower simulation errors than achieved by the hierarchical method, but those algorithms require much higher computing costs and are thus not applicable at the bedside. While the hierarchical method requires a computing time about six times the computing costs required by the direct approach and about four times the costs of the DRM the required time is still acceptable for a clinical application.

The study that is presented here however has some limitations. First, the noise model in this analysis has some limitations. In particular, measurement noise was added to measured PaO_2 and $PaCO_2$ but was not added to the other variables such as pH, Hemoglobin concentration or body temperature. A more realistic study should add noise to all patient parameters and should distribute that noise differently with respect to the usual uncertainty of the measurement technology. Moreover, the multiplicative noise levels of $\pm 2.5\%$, $\pm 5\%$ and $\pm 7.5\%$ are not necessarily clinically related. Secondly, the simple model of gas exchange that was used to calculate a valid estimate of $f_{s,0}$ uses several assumptions, e.g. the respiratory quotient is assumed to be constant at 0.8 and the arterio-venous oxygen difference is assumed to be constant at 0.05. Those assumptions might not lead to a clinically precise calculation of shunt, but that estimation, used as $f_{s,0}$ in the following identification of the more complex gas exchange model, was shown to still be close enough to the correct shunt to aid in the identification of the three-parameter model.

Using synthetic patient data to test algorithms is valid during their development and initial evaluations. However, since those *in-silico* data sets only approximate clinical conditions and patient dysfunctions, the algorithm performance still has to be evaluated with real clinical data. Therefore, tests with data from real patients are planned for the future.

Additionally, the presented work has shown that both the HM and the DRM are valid tools for identification as they are independent or less susceptible to the quality of the initial estimates. A combination of both approaches might further increase fit quality.

5. Conclusions

Model based medical decision support strongly depends on the correct identification of the implemented physiological model. In models of higher order where linear regression methods are not applicable to identify the model parameters, the use of gradient or simplex-search based methods is necessary. This analysis shows that the efficacy of three examples of such gradient or simplex-search methods are dependent on the quality of the initial estimates. Real-time data typically available in an ICU setting is noisy and the model parameters and thus the global minimum of the objective function in parameter identification are

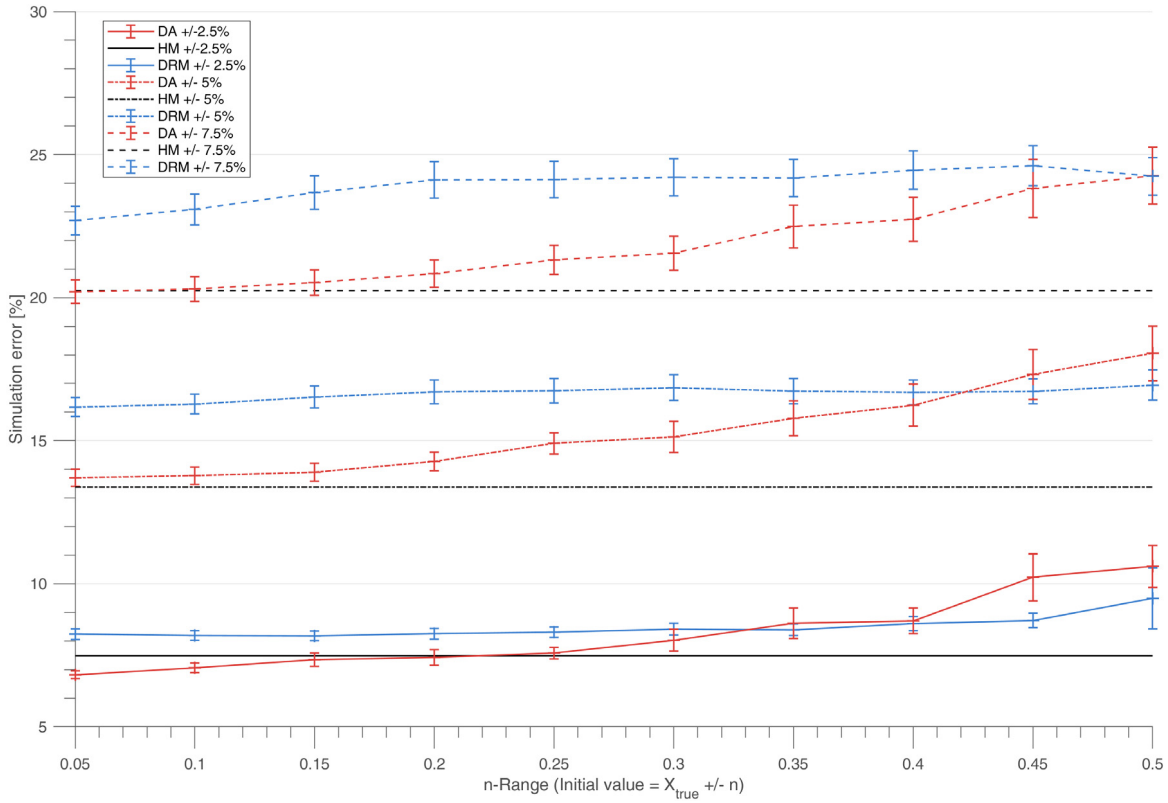

Fig. 4. Mean deviation between measured and predicted PaO_2 and $PaCO_2$ for identification of the model with direct approach (DA), hierarchical method (HM) and dimensional reduction method (DRM). Results are shown with respect to noise added to the identification data and with respect to the range from which the initial estimates for the DA and the DRM were drawn *(n-Range)*. The greater the n-Range, the further away the initial estimates might be set from the global minimum. Error bars depict 95% confidence bounds.

is unknown. Thus, the initial estimates can only be estimated a-priori. In general, the further away the initial estimates are from the global minimum, the higher the risk of terminating in local minima. Two methods (hierarchical method and dimensional reduction method) proved to be affected less or not affected by initial estimates compared to a direct identification approach. The hierarchical method that exploits models of lower order to find good initial estimates for models of higher order showed the best overall identification outcome as it is generally robust to poor initial estimates. The dimensional reduction method showed to be less affected by the selected initial estimates than the direct approach but as the method includes a payoff between convergence and residual, the overall fit quality is less than the hierarchical approach.

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