Hierarchical Parameter Identification in Models of Respiratory Mechanics

C. Schranz*, C. Knöbel, J. Kretschmer, Z. Zhao, and K. Möller

***Abstract*—Potential harmful effects of ventilation therapy could be reduced by model-based predictions of the effects of ventilator settings to the patient. To obtain optimal predictions, the model has to be individualized based on patients' data. Given a nonlinear model, the result of parameter identification using iterative numerical methods depends on initial estimates. In this work, a feasible hierarchical identification process is proposed and compared to the commonly implemented direct approach with randomized initial values. The hierarchical approach is exemplarily illustrated by identifying the viscoelastic model (VEM) of respiratory mechanics, whose *a priori* identifiability was proven. To demonstrate its advantages over the direct approach, two different data sources were employed. First, correctness of the approach was shown with simulation data providing controllable conditions. Second, the clinical potential was evaluated under realistic conditions using clinical data from 13 acute respiratory distress syndrome (ARDS) patients. Simulation data revealed that the success rate of the direct approach exponentially decreases with increasing deviation of the initial estimates while the hierarchical approach always obtained the correct solution. The average computing time using clinical data for the direct approach equals 4.77 s (SD = 1.32) and 2.41 s (SD = 0.01) for the hierarchical approach. These investigations demonstrate that a hierarchical approach may be beneficial with respect to robustness and efficiency using simulated and clinical data.**

***Index Terms*—Hierarchical models, models of respiratory mechanics, parameter identification, robustness.**

I. Introduction

CURRENTLY mechanical ventilation therapy poses a dilemma to intensivists: On one side, it is the primary life saving therapy in many clinical situations in ICUs such as acute lung failure; on the other hand this therapy by itself carries the risk of deploying severe side effects, e.g., additional pulmonary trauma with the potential of life threatening inflammation reactions [1], [2].

To improve the situation for the patients, i.e., finding a lung protective compromise, model-based lung protective ventilation was proposed. It allows predictions of the effects of certain ventilator settings on the injured lung by simulating physiological models [3], [4]. These predictions can be used to optimize the ventilator settings, i.e., to reduce harmful effects of the ventilation therapy. The quality of the model predictions depends on the correspondence of the model parameters to the patient properties and on the complexity—the level of detail, of the model itself. To guarantee bedside application, the used models are supposed to be as simple as possible and as complex as necessary. Hence, the application itself puts a constraint on the used models as near real-time feedback is required to evaluate the optimal ventilator settings. To minimize the complexity, lumped parameter models are a common approach [5].

In the given investigation, models of respiratory mechanics are used to represent the mechanical properties of the patient's lung. In a bedside setting, the measurable information for analyzing respiratory mechanics is mostly restricted to airway pressure and air flow. With this limited information, the model has to be parameterized in order to reflect the patient's individual respiratory mechanics conditions.

In case of applying single compartment models, multiple linear regression methods are an established, fast, straightforward approach for parameter identification being independent on initial values [6]. The individualization of models of higher order is commonly performed by a numerical parameter identification process, tuning the model parameters to minimize the sum of squared errors (SSE) between measured data samples and simulated data. All gradient-based least-square-error (LSE) methods applied to nonlinear problems require initial guesses of the tunable parameters. The complexity of parameter identification increases with the number of tunable parameters as various parameter constellations (attractors) appear as additional possible solutions (local minima) [7]. The better this initial guess of parameters represents the patient's properties, the higher the chance of finding the correct attractor. Since the exact patient properties are unknown, arbitrary initial values may lead to wrong attractors.

One approach to find the global minimum (GM) is based on random search (RS), i.e., performing parameter identification repeatedly starting from randomly chosen initial values. The global minimum is finally selected according to the result with the lowest SSE (e.g., [8]). This procedure is time consuming and sometimes misleading, if the determined solution with the lowest SSE is physiologically interpretable but not correct.

Other existing methods for global optimization such as genetic algorithms or simulated annealing are time consuming as well and the quality of the solution is sensitive to the parameterization of the algorithm. In order to achieve breath-by-breath identification, these methods are not applicable.

Manuscript received May 6, 2011; revised July 12, 2011 and August 11, 2011; accepted August 21, 2011. Date of publication August 30, 2011; date of current version October 19, 2011. This work was supported by the Deutsche Forschungsgemeinschaft DFG under Grant MO 579/1-2 PAR. *Asterisk indicates corresponding author.*

*C. Schranz is with the Institute of Technical Medicine, Furtwangen University, 78054 Villingen-Schwenningen, Germany.

C. Knöbel, J. Kretschmer, Z. Zhao, and K. Möller are with the Institute of Technical Medicine, Furtwangen University, 78054 Villingen-Schwenningen, Germany (e-mail: scc@hs-furtwangen.de).

Digital Object Identifier 10.1109/TBME.2011.2166398

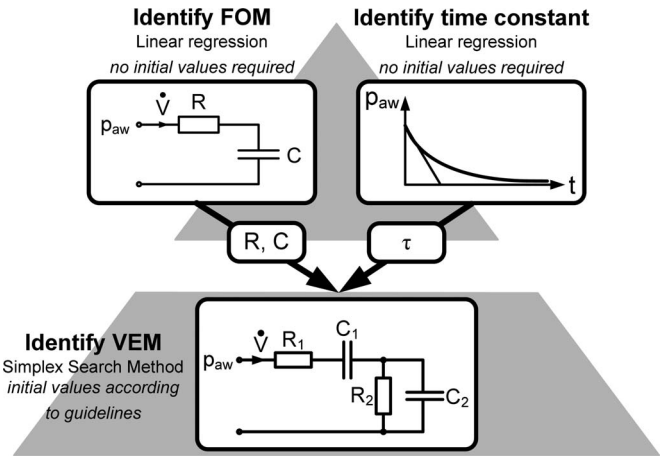

Fig. 1. Structure of the *Hierarchical Approach*: Identifying the parameters of the 1st order model and the time constant of the relaxation phase during zero-flow situation using linear regression. Incorporate the fitting results to set the initial estimates according to defined guidelines to identify the viscoelastic model using the Simplex-Search method.

To offer a fast robust approach, a new concept based on a divide-and-conquer strategy using a hierarchical model structure was developed. Its advantages over a direct fitting process using randomized initial values are demonstrated. The potential of parameter identification in respiratory mechanics using hierarchical model structures was preliminarily demonstrated [9]. Thereby a measurement set was reproduced using models of increasing complexity achieving a stepwise minimization of the SSE.

This project aims to establish an online tool that estimates the patient's conditions at the bedside for clinical use. A fast and robust parameter estimation strategy is pursued. The new concept is rigorously tested with simulation data and finally clinical data are used to demonstrate the applicability to real settings.

II. Material and Methods

A. Models

First Order Model (FOM): The FOM (Fig. 1) consists of a serial arrangement of a resistance R and compliance C. R is representing the total airway resistance and resistive tissue contributions, while C is a measure for the elasticity of the respiratory system (lung and chest wall) [10]. The FOM and the VEM were applied according to volume-controlled ventilation, with the flow rate ($\dot{V} = dV/dt$) being the input and the airway pressure (p_{aw}) the output of the model. p_C is the elastic pressure component generated by the volume stored in the compliance C:

$$\dot{p}_C = \frac{1}{C}\dot{V}$$
$$p_{\mathrm{aw}} = p_C + R\dot{V}, p_C(0) = 0. \tag{1}$$

A fundamental prerequisite for parameter identification to be a well-posed problem is *a priori* global identifiability of the parametric model [11]. This necessary but nonsufficient criterion states, that under ideal conditions of noise-free observations and error-free model structure, the unknown parameters of the postulated model can be uniquely recovered from the knowledge of the input-output variables of the designed input-output experiment. In fact, the property of global identifiability applies only to the uniqueness of the global minimum. It does not prevent numerical methods to be caught in local minima, due to inappropriate initial values.

The FOM is a simple identifiable linear model consisting of two parameters. At least two measured samples of noise-free input and output signals would be sufficient to set up a system of linear equations to uniquely determine the parameters R and C.

Viscoelastic Model (VEM): The VEM (Fig. 1), an extension of the FOM, assumes that the tissues comprising the walls of the alveolar compartment are viscoelastic rather than simply elastic. R_1 is mainly hypothesized to represent airway resistances. C_1 is the static compliance of the respiratory system. R_2 and C_2 are related to the viscoelastic properties of the tissue [10], [12]. The model is given as state space representation using the pressure in the compliances C_1 and C_2 as state variables p_{C1}, p_{C2} in (2). In this underlying study the VEM is used as target model for parameter identification. The four parameters correspond to the unknown patient-specific parameters and are defined as $X := \{R_1, C_1, R_2, C_2\}$. The initial values of p_{C1} and p_{C2} were assumed to be zero.

$$\begin{pmatrix} \dot{p}_{C1} \\ \dot{p}_{C2} \end{pmatrix} = \begin{pmatrix} 0 & 0 \\ 0 & -1/(R_2C_2) \end{pmatrix} \begin{pmatrix} p_{C1} \\ p_{C2} \end{pmatrix} + \begin{pmatrix} 1/C_1 \\ 1/C_2 \end{pmatrix} \dot{V}$$
$$p_{\mathrm{aw}} = \begin{pmatrix} 1 & 1 \end{pmatrix} \begin{pmatrix} p_{C1} \\ p_{C2} \end{pmatrix} + R_1\dot{V}, p_{C1}(0) = p_{C2}(0) = 0. \tag{2}$$

In the more complex case of the VEM, *a priori* identifiability is checked by a computer program called DAISY (Differential Algebra for Identifiability of Systems, University of Cagliari and University of Padova, Italy) [11]. This tool provides an automatic check for identifiability of linear and nonlinear dynamic systems described by polynomial or rational functions. Given the model in state space representation DAISY computes the characteristic set. The characteristic set is a family of differential polynomials belonging to the differential ring

$$R(p)[\dot{V}, p_{\mathrm{aw}}, p_{C1}, p_{C2}]$$

which allows to eliminate the state variables and to find the input-output relation polynomials (A_i) of the dynamic system.

In this particular situation handling a model linear in its state space, the calculations of the characteristic set can be avoided and the input-output relation polynomial (4) is derived by applying the inverse Laplace transform to the transfer function of the model (3).

$$H(s) = \frac{p_{\mathrm{aw}}}{\dot{V}} = \frac{s^2R_1R_2C_1C_2 + s(R_1C_1 + R_2(C_1 + C_2)) + 1}{s^2R_2C_1C_2 + sC_1} \tag{3}$$

$$A = -\ddot{p}_{\mathrm{aw}}R_2C_1C_2 - \dot{p}_{\mathrm{aw}}C_1 + \dddot{V}R_1R_2C_1C_2 + \ddot{V}(R_1C_1 + R_2(C_1 + C_2)) + \dot{V}. \tag{4}$$

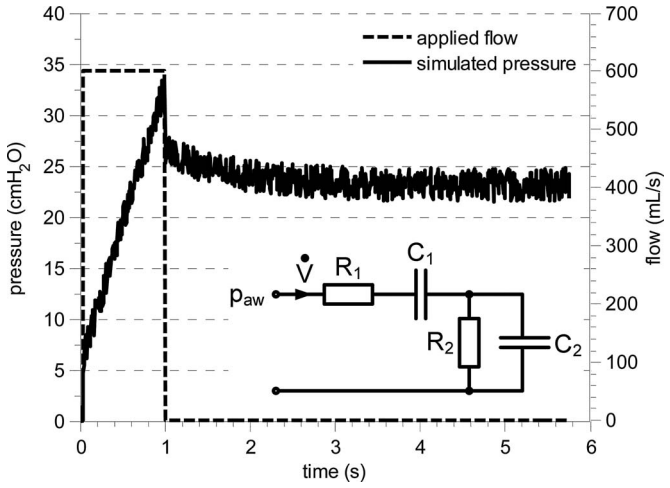

Fig. 2. Setup to generate simulation datasets: A defined flow profile is applied to a parameterized VEM and the pressure response is calculated and additionally disturbed by white noise.

To construct the exhaustive summary of the model, the coefficients of the above input-output polynomial are extracted. The range set is calculated by evaluating the coefficients at symbolic parameter values $p = [\alpha, \beta, \gamma, \delta]$ leading to the following set of equations:

$$\begin{aligned} &-R_2C_1C_2 + \gamma\beta\delta = 0, -C_1 + \beta = 0 \\ &R_1R_2C_1C_2 - \alpha\gamma\beta\delta = 0 \\ &R_1C_1 + R_2(C_1 + C_2) - \alpha\beta - \gamma(\beta + \delta) = 0. \end{aligned} \tag{5}$$

Solving this system of equations provides the Gröbner basis of this model:

$$R_1 = \alpha, C_1 = \beta, R_2 = \gamma, C_2 = \delta \tag{6}$$

showing that the model parameters have a unique solution [11], [13].

With the given information of measured air flow and airway pressure, the FOM and the VEM are thus *a priori* globally identifiable.

B. Data

To obtain controllable conditions and an error-free model structure, first evaluation datasets were generated by simulating parameterized models with predefined flow profiles. To show the potential for clinical applications the processes were also tested under realistic conditions using clinical data.

Simulation Data: A VEM is provided during inspiration with a constant flow rate of 600 mL/s over a period of 1 s, followed by a zero-flow phase simulating an occlusion of the expiratory valve before a passive expiration is initiated. To implement a controllable degree of complexity the simulated pressure response is disturbed by additional white noise (noise amplitude equals -26 dB of the maximal pressure signal). The predefined flow profile and the simulated pressure response are shown in Fig. 2. The pressure response during inspiration seems to be linear, but is in fact curved due to second order effects. To improve statistical significance four different parameter constellations in physiological plausible ranges were defined to generate the data (Table I). To avoid the influence of transient states, simulation runs were all started in equilibrium at 0 cmH_2O.

TABLE I
PARAMETER SETS FOR VEM SIMULATIONS

Param.	VEM_1	VEM_2	VEM_3	VEM_4
R_1	0.0114	0.0114	0.0202	0.0051
C_1	24.89	97.89	97.89	105.78
R_2	0.0081	0.0081	0.0162	0.0041
C_2	90.44	90.44	120.44	180.87

Four different parameter constellations are used to generate data sets. Units for resistances are $cmH_2O{\cdot}s/mL$ and for compliances mL/cmH_2O.

Clinical Data: Thirteen mechanically ventilated patients were selected from a previous ARDS—Study [14], [15] with appropriate SCASS-Maneuver (Static Compliance Automated Single Step) cycles [15], [16].

The SCASS-Maneuver consists of airway occlusions within the inspiration phase of a breathing cycle resulting in a quasistatic pressure-volume relation. After reaching a randomized inspiration volume, the occlusion starts and lasts for 5 s.

Gas flow was measured using a calibrated, nonheated pneumotachograph (Fleisch No.2, F+G GmbH, Hechingen, Germany). Airway opening pressure was measured by a piezoresistive pressure transducer (1790, Si-instruments, Nördlingen, Germany). Flow and pressure data were recorded at a sampling rate of 125 Hz. (Please refer to [15] for a detailed description of the experimental setup.)

C. Parameter Identification

The identification process is based on a least-squares-estimation (LSE) method calculating the best fit between the time series of modeled data and observed data. For this purpose, the Nelder-Mead Simplex-Search method, an unconstrained nonlinear optimization algorithm, was used which finds a local minimum of a scalar function of the unknown variables *X*, starting at an initial estimate *X0* [17].

Direct Approach: In the following *Direct Approach* refers to parameter identification with the Simplex-Search algorithm.

To evaluate the robustness, i.e., the influence of the initial estimates to the *Direct Approach*, simulation data are used. A trial was rated as successful if it converges to the known global minimum within a tolerance of 1% for each parameter. Therefore, $N = 100$ constellations of initial estimates were randomly generated within a defined range. The number of successful evaluations within 100 attempts is called Hit Rate (Fig. 3). These evaluations were repeated for several extending ranges of initial estimates around the original values.

To find the global minimum (GM) within a breathing cycle of clinical data, an RS process was applied consisting of $N = 16$ runs of *Direct Approaches* (DA) using randomized initial values within physiological ranges. The solution with the lowest SSE is assumed to be the global minimum of the random search process:

$$\mathrm{GM_{RS}} = \min_n \mathrm{SSE_{DA},}_n \quad 1 \le n \le N. \tag{7}$$

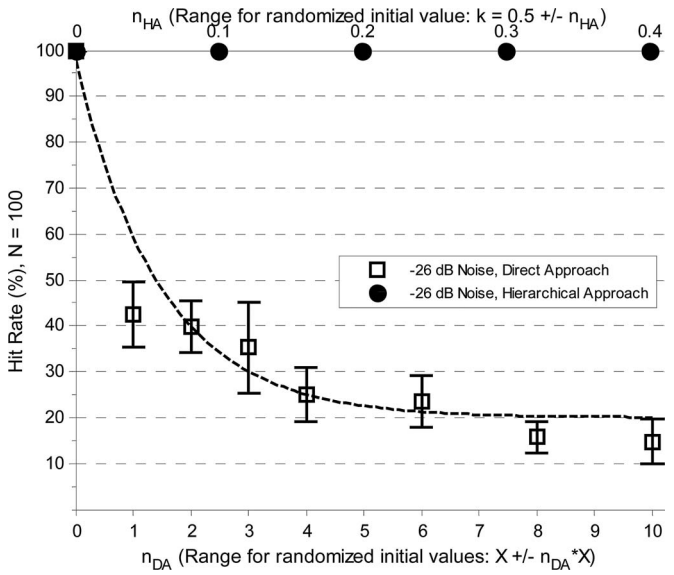

Fig. 3. Hit Rates of the *Direct Approach* and *Hierarchical Approach* with randomized initial values in an extending range around the original values. The bottom x-axis denotes the interval boundaries around the original parameters for the *Direct Approach* and the top x-axis denotes the interval boundaries of factor *k* around the value 0.5 of the *Hierarchical Approach*. The y-axis corresponds to the number of results matching the original values within 100 trials. Four different datasets were evaluated (Table I).

$\mathrm{SSE}_{\mathrm{DA},n}$ denotes the SSE of the *n*th DA. To capture the variation of the parameters over all attempts, mean parameter scattering was calculated according to (8):

$$\bar{s} = \frac{1}{4}\sum_{i=1}^{4}\frac{s_{X_n}(i)}{\bar{X}_n(i)} \tag{8}$$

with $\bar{X}_n(i)$ and $s_{X_n}(i)$ being the mean and standard deviation of a single parameter *i* within *N* runs.

Hierarchical Approach: In contrast to the *Direct Approach*, the *Hierarchical Approach* operates in a hierarchical model structure where simpler models with lesser degrees of freedom, i.e., less parameters are identified first. The obtained intermediate parameter values are then incorporated in guidelines (9–12) to set the initial estimates for the parameter estimation process of the models in the next, more complex level. In case of identifying the VEM, the approach is illustrated in Fig. 1 and works as follows: In a first step, the parameters of the FOM are identified. As this parameter estimation problem is uniquely solvable, the method of linear regression can be applied without needing to estimate initial parameter values. In parallel, the time constant of the pressure relaxation phase during the zero-flow situation is estimated. Therefore, the corresponding interval of measured airway pressure is selected omitting the resistive pressure drop during valve closure [14]. Logarithmizing the selected samples linearizes the problem in order to estimate the time constant by linear regression. In an error-free model structure this time constant equals the viscoelastic time constant of R_2 and C_2 of the VEM (11).

TABLE II
PARAMETER VALUES FOR DIFFERENT PROBLEM CLASSES

Param.[a]	Orig. Value	Global Min. (-26 dB noise)	Local Min. Class 1	Local Min. Class 2
R_1	0.0114	0.0117	0.0132	0.0120
C_1	24.89	24.97	31.38	70.37
R_2	0.0081	0.0082	-7.9710	0.8701
C_2	90.44	106.39	107.38	33.68

Original parameter values of the viscoelastic model (VEM_1) that generated the data and three exemplary solutions of identification processes: the global minimum and two exemplary local minima. [a]Units for resistances are $\mathrm{cmH_2O{\cdot}s/mL}$ and $\mathrm{mL/cmH_2O}$ for compliances. [b]By adding –26 dB white noise the global minimum changes because the mean value of the noise signal is not exactly 0. Class 1 solutions include non-physiological parameter values. Class 2 solutions are physiological plausible but not correct.

With respect to the model structure of the VEM, the following guidelines were developed:

$$R_1 = k \cdot R, 0 < k < 1 \tag{9}$$

$$R_2 = R - R_1 \tag{10}$$

$$C_2 = \frac{\tau}{R_2} \tag{11}$$

$$C_1 = (C^{-1} - C_2^{-1})^{-1}. \tag{12}$$

Obviously just one parameter (k) remains to be chosen prior to identification. The resistance R and the compliance C in the FOM are divided into the serial-like arrangement of R_1 and R_2, C_1 and C_2, respectively (neglecting the frequency dependence). The remaining tuning factor k can be defined by the user within the constraints, i.e., the sum of R_1 and R_2 should not exceed R.

III. RESULTS

A. Parameter Identification Using Simulation Data

Using simulation data meaningful investigations regarding the robustness of both approaches can be performed. The initial values for the *Direct Approach* are chosen randomly ($N = 100$) in a defined interval around the original values $X_{\mathrm{VEM}} \pm n_{\mathrm{DA}} * X_{\mathrm{VEM}}$ which is extendable by the variable $n_{\mathrm{DA}} = 0, 1, 2, \ldots, 10$. Within these intervals negative initial values are allowed assuming bias-free comparison without relying on specific *a priori* knowledge of the user. Since the *Hierarchical Approach* has only one degree of freedom (k) in the range of 0 to 1, the scenario of testing the robustness has changed to the following: k is set to 0.5 and the interval boundaries for randomized initial values ($N = 100$) are extending stepwise according to $k = 0.5 \pm n_{\mathrm{HA}}$ with $n_{\mathrm{HA}} = 0, 0.1, 0.2, \ldots, 0.4$.

Table II exemplarily shows the original parameter values of VEM_1 generating one dataset. The given values also correspond to the global minimum of the identification process within a noise-free setting. By adding -26 dB of white noise to the simulated pressure signal, the values of the global minimum change because the mean value of the added noise is not exactly zero.

Since the Hit Rate of the *Direct Approach* is dropping with the increasing range of possible initial values (Fig. 3), local minima with different parameter constellations from the original model were found. Two solutions of local minima that were found even

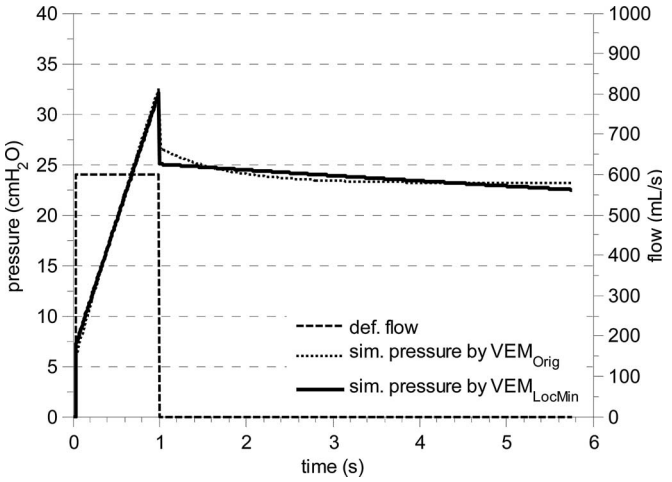

Fig. 4. Resulting pressure response of a viscoelastic model. The model parameters correspond to a local minimum that was found by the *Direct Approach*. The parameter values are physiological plausible but not correct (Table II).

under noise-free conditions, are given exemplarily in Table II. They were classified into two different classes: Class 1 includes solutions with parameter values that are not physiologically plausible. Class 2 includes solutions with parameter values in a physiological range, which are not matching the original values. The resulting pressure response of the given Class 2 problem is plotted in Fig. 4. For n_{DA} being 1 or larger, parameter constellations related to Class 1 are found in 50% of the attempts. Thus they appear more often than Class 2 solutions.

The *Hierarchical Approach* always hits the original parameter values, no other local minima were found, leading to a Hit Rate of 100%.

B. Parameter Identification Using Clinical Data

The initial estimates required by the *Direct Approach* were randomly chosen within an interval covering the physiological range of the parameters including possible pathological changes (Table III). A random search process based on $N = 16$ attempts of *Direct Approaches* was used to fit a single breathing cycle (Fig. 5) of a patient (Patient 5). The global minimum corresponds to the solution with the lowest SSE (7) and was hit nine times leading to a success rate of 56%. The resulting parameters scatter within the analysis of a single cycle on average about $\bar{s} = 44\%$ around their mean values (8).

The average computing time of a single *Direct Approach* equals 4.77 s on a standard desktop PC (2.5 GHz Dual Core Processor) (Table III).

The *Hierarchical Approach*, with k varying between 0.2 and 0.8, found the global minimum in each attempt leading to a success rate of 100%. Thus the resulting SSE of each run was always smaller or at least equal to the SSE of the *Direct Approach* ($\mathrm{SSE_{HA}} \leq \mathrm{SSE_{DA}}$). The scattering of the resulting parameters within the 16 runs is eliminated by the *Hierarchical Approach*. The averaged required computing time equals 2.62 s (Table III).

Extending this comparison to 13 patients with five breathing cycles each, resulted in the average parameter variation shown in Fig. 6. The *Direct Approach* involves four degrees of freedom (DOF) and showed an average parameter variation of 58%. The *Hierarchical Approach* was first performed with a randomized k in the range of 0.2 and 0.8 reducing the DOF to 1. This leads to an overall average scattering of the resulting parameters of 6%. Obviously, with constant $k = 0.5$, i.e., zero DOF, no variation occurs. By comparing the results based on $k = 0.5$ to the results of the random search process and to the *Hierarchical Approach* with randomized k, it was confirmed that the global minimum was found in each dataset. Due to the occurrence of several local minima using the *Direct Approach*, the average SSE over all datasets is higher than with the *Hierarchical Approach* (Table III).

TABLE III
RESULTS OF PARAMETER IDENTIFICATION USING CLINICAL DATA

Parameter[a]	Direct Approach		Hierarchical Approach[d]
	Range of initial estimates	Results	Results
R_1	[0.001, 0.1]	0.0137 ± 0.0003	0.0135 ± 0.0000
C_1	[10, 250]	36.51 ± 7.81	30.83 ± 0.00
R_2	[0.001, 0.1]	0.0946 ± 0.1100	0.0165 ± 0.0000
C_2	[20, 1000]	114.78 ± 40.58	148.15 ± 0.00
mean($s_{X,rel}$)[b]		(43.74 ± 3.14)%	(0.00 ± 0.00)%
t_{Comp}[c]		(4.77 ± 1.32) s	(2.62 ± 0.33) s
mean(SSE)		389.30 ± 10.75	228.35 ± 34.72

Resulting parameters of $N = 16$ attempts using the *Direct Approach* and the *Hierarchical Approach* to identify the VEM using clinical data of a single breathing cycle of one patient (Patient Nr. 5). Mean SSE over all data sets of all patients and standard deviation of mean value (P = 68%).
[a]Units for resistances are $\mathrm{cmH_2O{\cdot}s/mL}$ and for compliances $\mathrm{mL/cmH_2O}$. [b]mean value of the relative standard deviation of all parameters (7). [c]Required computing time to identify the parameters for one attempt. [d]randomized k within the interval [0.2, 0.8].

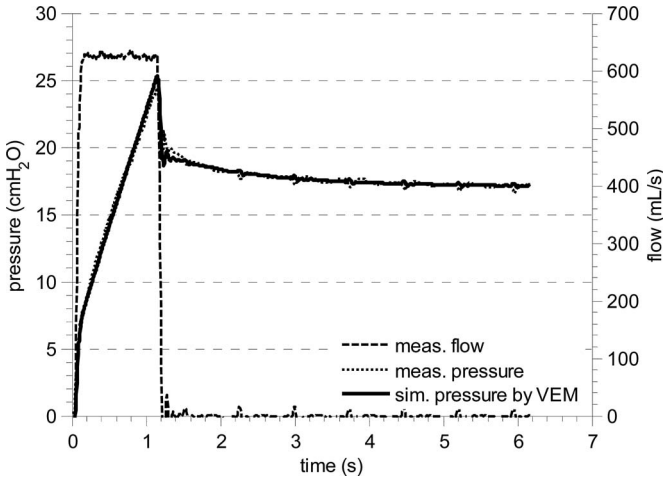

Fig. 5. Exemplary measurement set of pressure and flow of a patient and the simulated pressure response of the identified VEM.

IV. DISCUSSION

A. Simulation Data

The simulation experiment creates a controlled, ideal setting that allows a comparison of the identified parameters with the original ones used in data generation. It is obvious that the

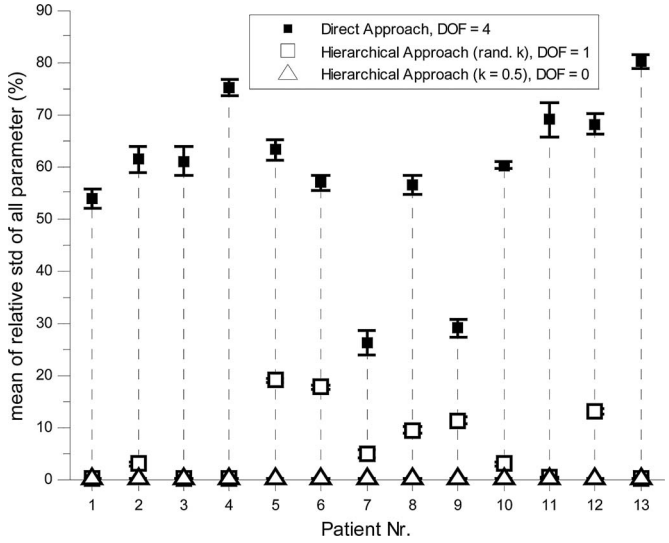

Fig. 6. Average relative standard deviation over all parameter values by applying the *Direct-* and *Hierarchical Approach* implying various numbers of degrees of freedom (DOF). *The Hierarchical Approach* was performed with a randomized k between 0.2 and 0.8 and a constant k at 0.5. All approaches were applied to measure data of 13 ARDS patients with five breathing cycles. Each breathing cycle with randomized initial values was evaluated 16 times.

Direct Approach always found the correct solution in 100 attempts when the initial parameters were matching the original ones. With a stepwise extension of the range of possible initial values around the original parameters the Hit Rate dropped. Spurious Class 1 results with partly nonphysiological values can easily be detected and removed. More difficult to handle are results of Class 2, containing wrong parameters in a physiological range. In the example depicted in Table II, parameters C_1, C_2, and R_2 are badly estimated leading to a different relaxation behavior (see Fig. 4). This mismatch is almost undetectable by a qualitative analysis of the plot. Knowing the correct parameter values in advance in this evaluation with simulation data, we were able to detect spurious but physiological plausible solutions. In a clinical application, a model-based decision support system whose advice is based on values of the estimated parameters, might mislead to wrong therapeutically decisions.

Besides the Simplex-Search algorithm, other nonlinear optimization algorithms such as Levenberg-Marquardt algorithm and Trust-Region algorithm were evaluated. Differences in the required number of iterations and function evaluations were found. The Trust-Region method showed to be the fastest converging LSE method in this particular situation [18].

In contrast to the *Direct Approach,* the developed *Hierarchical Approach* reaches a 100% Hit Rate independent of initial values within the defined range of valid guidelines. Due to the *Hierarchical Approach*, with simple identification processes at the beginning, the influence of the initial estimates on the results can be decoupled. The results of the simpler identification processes are then incorporated as guidelines (9–12), which sets appropriate initial estimates for the identification of the VEM.

B. Clinical Data

Similar behavior could be seen when applying these approaches to clinical data where an error-free model structure is not given any more and the original values are unknown. Within this experimental setting, higher scattering of the parameter values were observed with the *Direct Approach* compared to the *Hierarchical Approach.*

The gained improvement regarding robustness can be illustrated by testing both approaches using ventilation cycles of various patients (Fig. 6). Minimal variation (Patient 7 in Fig. 6) indicates a good agreement of the lung properties to the chosen lung model. In patients with higher variations nonlinear effects may be present that are not represented in the VEM, such as alveolar recruitment, flow depending resistances, etc.

The observed scattering of the *Direct Approach* is depending on the range of possible initial values and might be reduced by applying other optimization methods, e.g., genetic algorithms.

Local minima even occur using the *Hierarchical Approach* if k is set to extreme values in the range between 0.2 and 0.8., e.g., with k being 0.8, close to 1, R_2 approaches 0 (9, 10). This initialization carries the risk to reduce the model structure from a VEM to an FOM by an iterative decrease of R_2, which corresponds to a local minimum of the parameter optimization process that should be avoided. It seems that within the investigated datasets, $k = 0.5$ is a good choice to determine the global minimum without any exception.

Comparing the computing time as a measure of effectiveness, the *Hierarchical Approach* is superior to the *Direct Approach*. Even if the *Hierarchical Approach* consists of three identification steps, it is almost twice as fast as the *Direct Approach*. That becomes possible because basic optimization methods, like linear regression are applied in the first level of the hierarchy (Fig. 1). These methods consist basically of a single operation and their results lead to new initial estimates close to the global minimum. This feature avoids complex search processes in regions of wrong attractor fields like in case of the *Direct Approach*.

C. Limitations

Parameter identification based on simulated data allows straightforward verification of the results. The datasets include viscoelasticity and white noise. Additional effects and disturbances as seen in patients' data, such as nonlinear properties of resistance and compliance, cardiogenic oscillations and influences of the ventilator are not considered. Nevertheless, it is an important step in the evaluation of a novel approach showing that the method is correct.

In parameter identification based on patients' data, no gold standard is currently available to verify the results in the discussed application. If an acceptable agreement between model prediction and patient is a good indicator of model fit, a low SSE could be used as a quality measure to guide the identification process. Care has to be taken that noise in the data has no important influence on the accuracy of the parameter estimation.

D. Further Potential of the Approach

The applicability of the VEM model with respect to healthy lungs and ARDS lungs has been principally demonstrated [19], [20]. Nevertheless patient data revealed, depending on the severity of the disease, curved deviations to the VEM predictions. Especially during inspiration, nonlinear effects suggesting alveolar recruitment and distention appear that cannot be captured by the VEM.

The presented investigations based on the example of the VEM are only one potential application of hierarchical parameter identification. In case of a mismatch of the model due to the pathological state or in case of a different modeling focus, e.g., considering recruitment effects, the model hierarchy can be extended by including additional models [21].

Application in different fields with viscoelastic properties seems possible as long as appropriate measurement data are available. In the same way, hierarchical parameter identification could be a suitable approach to identify hierarchical models of cardiovascular dynamics [22].

V. Conclusion

By using the *Hierarchical Approach,* a decoupling of the results from initial estimates can be achieved. The implemented guidelines allow robust parameter identification and the hierarchical structure leads to significant reduction in computing time. Thus, these investigations based on the example of the VEM confirm that a *Hierarchical Approach* may be beneficial with respect to robustness and efficiency using computed and clinical data. With this breath-to-breath identifiability, the *Hierarchical Approach* is applicable at the bedside as an online tool for the clinician. Optimal ventilation management and continuous patient monitoring may profit from further investigations in this technique.

Acknowledgment

The authors express their gratitude to Prof. M. P. Saccomani from the University of Padua for the kind support regarding the identifiability theory, and to the McREM Study Group and Dräger Medical for providing the clinical data for the evaluation.

References

[1] J. D. Ricard, D. Dreyfuss, and G. Saumon, "Ventilator-induced lung injury," *Curr. Opin. Crit. Care.*, vol. 8, pp. 12–20, 2002.

[2] A. S. Slutsky, "Lung injury caused by mechanical ventilation," *Chest.*, vol. 116, pp. 9–15, 1999.

[3] S. Lozano, K. Möller, A. Brendle, D. Gottlieb, S. Schumann, C. A. Stahl, and J. Guttmann, "AUTOPILOT-BT: A system for knowledge and model based mechanical ventilation," *Technol. Health Care.*, vol. 16, pp. 1–11, 2008.

[4] S. E. Rees, C. Allerød, D. Murley, Y. Zhao, B. W. Smith, S. Kjaergaard, P. Thorgaard, and S. Andreassen, "Using physiological models and decision theory for selecting appropriate ventilator settings," *J. Clin. Monit. Comput.*, vol. 20, pp. 421–429, 2006.

[5] C. E. Hann, J. G. Chase, T. Desaive, C. B. Froissart, J. Revie, D. Stevenson, B. Lambermont, A. Ghuysen, P. Kolh, and G. M. Shaw, "Unique parameter identification for cardiac diagnosis in critical care using minimal data sets," *Comput. Methods Programs Biomed.*, vol. 99, pp. 75–87, 2010.

[6] A. G. Polak, "Analysis of multiple linear regression algorithms used for respiratory mechanics monitoring during artificial ventilation," *Comput. Methods Programs Biomed.*, vol. 101, pp. 126–134, Feb 2011.

[7] L. Ljung, *System Identification—Theory for the User*. Englewood Cliffs, NJ: Prentice-Hall, 1999.

[8] B. Diong, H. Nazeran, P. Nava, and M. Goldman, "Modeling human respiratory impedance," *IEEE Eng. Med. Biol. Mag.*, vol. 26, pp. 48–55, 2007.

[9] C. Schranz, J. Guttmann, and K. Möller, "Fitting respiratory mechanics in ARDS by a nonlinear recruitment model with viscoelastic component," *Biomed. Tech.*, vol. 55 (Suppl. 1), 2010. DOI: 10.1515/BMT.2010.437.

[10] J. H. Bates, *Lung Mechanics: An Inverse Modeling Approach*, 1st ed. Cambridge U.K.: Cambridge University Press, 2009.

[11] G. Bellu, M. P. Saccomani, S. Audoly, and L. D'Angiò, "DAISY: A new software tool to test global identifiability of biological and physiological systems," *Comput. Methods Programs Biomed.*, vol. 88, pp. 52–61, 2007.

[12] K. R. Lutchen and K. D. Costa, "Physiological interpretations based on lumped element models fit to respiratory impedance data: use of forward-inverse modeling," *IEEE Trans Biomed Eng.*, vol. 37, pp. 1076–1086, 1990.

[13] M. P. Saccomani, S. Audolyand, G. Bellu, and L. D'Angiò, "Examples of testing global identifiability of biological and biomedical models with the DAISY software," *Comput. Biol. Med.*, vol. 40, pp. 402–407, 2010.

[14] S. Ganzert, K. Möller, D. Steinmann, S. Schumann, and J. Guttmann, "Pressure-dependent stress relaxation in acute respiratory distress syndrome and healthy lungs: an investigation based on a viscoelastic model," *Crit. Care.*, vol. 13, p. R199, 2009.

[15] C. A. Stahl, K. Möller, S. Schumann, R. Kuhlen, M. Sydow, C. Putensen, and J. Guttmann, "Dynamic versus static respiratory mechanics in acute lung injury and acute respiratory distress syndrome," *Crit. Care Med.*, vol. 34, pp. 2090–2098, 2006.

[16] M. Sydow, H. Burchardi, J. Zinserling, H. Ische, T. A. Crozier, and W. Weyland, "Improved determination of static compliance by automated single volume steps in ventilated patients," *Intensive Care Med.*, vol. 17, pp. 108–114, 1991.

[17] J. C. Lagarias, J. A. Reeds, M. H. Wright, and P. E. Wright, "Convergence properties of the Nelder-Mead Simplex method in low dimensions," *SIAM J. Optim.*, vol. 9, pp. 112–147, 1998.

[18] C. Knöbel, C. Schranz, and K. Möller, "Identification of models of respiratory mechanics—Influence of parameter estimation techniques," in *BMT 2011*, Freiburg, Germany, *Biomech. Tech.* (to appear).

[19] B. Jonson, L. Beydon, K. Brauer, C. Mansson, S. Valind, and H. Grytzell, "Mechanics of respiratory system in healthy anesthetized humans with emphasis on viscoelastic properties," *J. Appl. Physiol.*, vol. 75, pp. 132–140, Jul. 1993.

[20] L. Beydon, C. Svantesson, K. Brauer, F. Lemaire, and B. Jonson, "Respiratory mechanics in patients ventilated for critical lung disease," *Eur. Respir. J.*, vol. 9, pp. 262–273, Feb. 1996.

[21] C. Schranz and K. Möller, "Model-based quantification of pressure and time depending effects in ARDS patients," in *5th Int. Conf. Bioinformatics Biomed. Eng., (iCBBE) 2011*, Wuhan, China, May 10–12, pp. 1–4.

[22] J. Kretschmer and K. Möller, "A hierarchical model family of cardiovascular dynamics," in *Proc. 5th Eur. Conf.*, Budapest, Hungary, 2011, vol. 37, pp. 295–298.

C. Schranz was born in Feldkirch, Austria, on July 30, 1984. He received the Dipl. Ing. (FH) degree in system engineering, in 2007, from the Interstate University of Applied Sciences NTB, Buchs, Switzerland, and the M.Sc. degree in biomedical engineering, in 2010, from Furtwangen University, Villingen-Schwenningen, Germany.

His current research interests include physiological modeling, parameter identification, and respiratory mechanics.

C. Knöbel was born in Villingen-Schwennigen, Germany, on July 4, 1986. He received the B.Sc. degree in medical engineering, in 2011, from Furtwangen University, Villingen-Schwenningen, Germany.

His current research interests include physiological modeling, parameter identification and respiratory mechanics.

J. Kretschmer was born in Speyer, Germany, on November 3, 1982. He received the M.Sc. degree in biomedical engineering, in 2009, from Furtwangen University, Villingen-Schwenningen, Germany.

His current research interests include hierarchical model families and model interactions in complex model systems.

Z. Zhao was born in Guangzhou, China, on November 24, 1982. He received his M.Sc. degree in biomedical engineering, in 2008, from Furtwangen University, Villingen-Schwenningen, Germany.

His current research interests include electrical impedance tomography, respiratory mechanics, and lung protective ventilation strategies.

K. Möller was born in Hamburg, Germany, on March 11, 1960. He received the M.S. and Ph.D. degrees in computer science, and the M.S. degree in medical science from the University of Bonn, Bonn, Germany, in 1986, 1991, and 1996, respectively.

From 1991 to 1997, he was an Assistant Professor in the Department of Computer Science, at Bonn University, Bonn, Germany, where he was involved in the fields of machine learning, robotics, and image processing. In 1998, he became a Professor of medical informatics at Furtwangen University, Villingen-Schwenningen, Germany, where currently he is Vice Dean of the Faculty "Mechanical and Process Engineering," Director of the Institute for Technical Medicine (ITeM), and the Head of the Biomedical Engineering Division. His research interests include decision support systems, modeling, and signal analysis with the application to lung protective mechanical ventilation.

Prof. Möller is a member of the German Society of Biomedical Engineering (DGBMT) and of the German Association for Electrical, Electronic, and Information Technologies (VDE).