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Improving breathing effort estimation in mechanical ventilation via optimal experiment design

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ABSTRACT

Estimation of the breathing effort and relevant lung parameters of a ventilated patient is essential to keep track of a patient's clinical condition. The aim of this paper is to increase estimation accuracy through experiment design. The main method is an experiment design approach across multiple breaths within a linear regression framework to accurately identify the patient's condition. Identifiability and persistence of excitation are used to formulate an estimation problem with a unique solution. Furthermore, Fisher information is used for assessing the parameters sensitivity to slight changes of the ventilator settings to improve the variance of the estimation. The estimation method is applied to simulated patients who breathe regularly but also to patients who have variable breathing patterns. A virtual experiment is conducted for both situations to generate estimation results. The results are analyzed using mathematical tools and show that uniquely estimating the lung parameters and breathing effort over multiple breaths for both regularly and variably breathing patients is possible in the presented framework. The proposed estimation method obtains clinically relevant estimates for a large set of breathing disturbances from the simulation case-study.

1. Introduction

Mechanical ventilators are mechatronic systems utilized in Intensive Care Units (ICUs) to provide life-saving therapy to support patients who cannot fully breathe independently. Especially during the flu season or a world-wide pandemic such as the SARS or COVID-19 pandemic, mechanical ventilation has emerged as a vital lifeline for many patients worldwide (Wunsch, 2020). The primary goal of mechanical ventilation is to ensure oxygenation and carbon dioxide elimination for the patient as stated in Warner and Patel (2013). Patients that are fully sedated rely entirely on mechanical ventilation, while patients that are spontaneously breathing receive only ventilatory support.

Gaining information about the patient's clinical condition is crucial to achieve the most effective patient treatment. For tailoring individualized treatment plans, it is necessary to monitor the patient's condition continuously over time. Directly assessing the patient's clinical state through measurements is challenging. Insight into the patient's condition can be inferred indirectly from measurements using parametric patient models of the lungs. In particular, parametric patient models, such as the one-compartmental lung model (Bates, 2009), allow for insightful qualification of key factors affecting the patient's condition, including lung compliance and airway resistance. Both these parameters are important in a clinical context (Brochard et al., 2012). In practice, these estimates are readily obtained for fully sedated patients using recursive least squares algorithms (Avanzolini, Barbini, Cappello, Cevenini, & Chiari, 1997; Borrello, 2001) or through static estimates based on delta-pressure/delta-volume and peak-flows. These methods are readily available in commercial ventilators. However, these methods produce inaccurate results for the parameter estimation when applied to spontaneously breathing patients. These inaccuracies arise from omission of the patient's breathing as stated by Redmond, Chiew, Major, and Chase (2019).

From an estimation perspective, it is essential to include the unknown spontaneous breathing effort of the patient in the estimation problem to obtain accurate estimates of the patient parameters (van de Kamp, Hunnekens, van de Wouw, & Oomen, 2023). In addition, information about the patient's breathing effort also represents intrinsic value from a clinical perspective. It contributes to patient monitoring and to the weaning process, i.e., gradually reducing ventilatory support. Simultaneously estimating patient parameters and breathing effort is possible if prior knowledge on the breathing effort is imposed (van de Kamp et al., 2023). Imposing such prior knowledge in parameter estimation

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approaches is challenging since the estimated parameters highly depend on the prior which is often uncertain and too patient- and ventilator-specific.

A set of requirements for uniquely estimating the patient's condition and breathing effort are defined. These requirements include the following:

i Simultaneously and uniquely estimating the patient's condition and the breathing effort with a maximum error in the accuracy of 20%.[1]
ii While the patient's breathing effort shape is considered to be free, the variability of the patient's breathing effort across breaths can be captured by additive disturbances on top of the breathing effort.
iii The estimation method is allowed to only minimally intervene with the treatment and thereby not decrease the patient's comfort.

Breathing effort estimation has received considerable research interest given its importance and inherent challenges. In Petersen, Graßhoff, Eger, and Rostalski (2020), Reinders, Hunnekens, van de Wouw, and Oomen (2022), Schauer and Simanski (2021) and Vicario et al. (2016), a specific breathing effort shape is enforced via parameterization or regularization of the breathing effort. These methods conflict with requirement (ii), because a breathing effort shape is enforced, which results in a loss of generality. In Navajas et al. (2000), a different approach is pursued, where it is assumed that the breathing effort is identical across breaths. By adjusting the ventilator settings over those breaths, the lung compliance and resistance are estimated accurately. This deteriorates the patient's comfort, hence, this violates requirement (iii).

Although important progress has been made to estimate the patient parameters and the patient breathing effort, at present the required estimation accuracy is not achievable while simultaneously satisfying requirements i-iii.

The main contribution of this paper is the presentation of a framework that is used to improve patient parameter estimation over multiple breaths by selecting appropriate target pressures for the ventilator. Theory from the field of system identification is applied to the case of mechanical ventilation, which is to the best of our knowledge, not yet done to this extent. To this end, an optimal experiment design approach is developed that integrates clinical knowledge to determine inputs that are comfortable for the patient and result in accurate estimates. The method presented is a step towards improved patient estimation by understanding the problem better and offering valuable future research directions.

The outline of this paper is as follows. First, in Section 2, the considered patient and breathing effort model together with the regression framework is presented. Subsequently, in Section 3, a linear regression framework for multi-breath estimation is introduced. In Section 4, optimal experiment design tools are used to find the optimal ventilator target pressure for estimation of the lung resistance, lung compliance, and breathing effort under the condition that the breathing effort is equal across patient's breaths. Thereafter, in Section 5, a theoretical analysis together with a simulation case study is conducted on a multi-breath estimation approach with a variable breathing effort across breaths. Finally, in Section 6, conclusions and recommendations for future work are presented.

[1] The 20% maximum error represents an indicative threshold established through consultations with medical professionals and hospitals. While this specific value may not be explicitly supported or refuted in existing literature, it serves as a practical guideline and makes the methodology explicit. It is important to note that the threshold indicates that large changes over time are more important for ensuring patient comfort and treatment than exactly knowing the patient's condition.

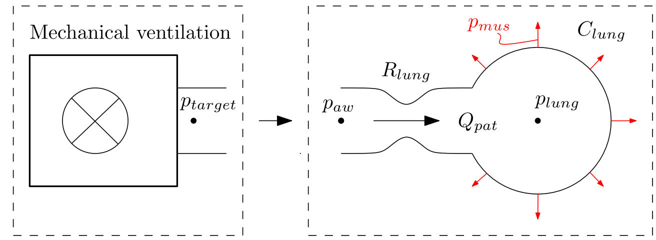

Fig. 1. Schematic representation of a mechanical ventilator that generates the target pressure p_{target} on the left and the linear one-compartmental lung model on the right. The schematic representation of the interconnection between ventilator and patient is omitted for simplicity.

2. Breathing effort estimation in a linear regression framework

In this section, a linear regression framework that uses multiple breaths to estimate the patient parameters and breathing effort is introduced. In Section 2.1, a patient model is presented that contains the important patient parameters. Subsequently, in Section 2.2, the linear regression framework is introduced.

2.1. Patient modeling

The patient model utilized in this paper is the linear one-compartmental lung model as described in Bates (2009). This model presents a simplified representation of pulmonary and airway dynamics and stands out for its clinical applicability due to the physiological parameters: the lung resistance R_{lung} and lung compliance C_{lung} (Brochard et al., 2012). Fig. 1 provides a schematic overview that includes all signals and parameters associated with the model. The model is a gray box model with certain patient parameters, which are derived below. Finally, an input–output model is presented, where the inputs, outputs, and exogenous disturbance are defined.

The patient model consists of two components: the airway and the lungs. The airway model describes the pressure drop over the airway based on the airflow in and out of the lungs. The lung model describes the change in lung pressure due to the volume change inside the lungs together with the patient's breathing effort. The pressure inside the patient's lungs is modeled as

$$p_{lung}(t) = \frac{1}{C_{lung}} V_{pat}(t) + p_{lung}(t_0) + p_{mus}(t), \tag{1}$$

where $V_{pat}(t) = \int_{t_0}^{t} Q_{pat}(\tau)d\tau + V_{pat}(t_0)$ represents the current volume inside the patient's lungs, C_{lung} the constant lung compliance, $Q_{pat}(t)$ the flow towards the patient's lungs, $p_{lung}(t_0)$ the initial lung pressure, and $p_{mus}(t)$ denotes the patient's time-varying breathing effort. The breathing effort p_{mus} affects the lung pressure p_{lung} due to contraction and relaxation of the respiratory muscles and is modeled as an additive exogenous disturbance in (1). In practice, the initial lung volume is assumed to be zero at the start of a mechanical breath. Therefore, $V_{pat}(t)$ represents the additional air volume relative to the start of a mechanical breath.

The patient's airway is represented by a linear resistance R_{lung}, establishing the relation between the airway pressure, lung pressure, and the patient flow as

$$Q_{pat}(t) = \frac{p_{aw}(t) - p_{lung}(t)}{R_{lung}}. \tag{2}$$

The ventilator on the left side of Fig. 1 produces a target pressure p_{target} that affects the airway pressure p_{aw}, which leads to changes in the patient flow Q_{pat}. The pressure difference between the target pressure and the airway pressure is predominantly determined by the hose characteristics (that connect the patient and ventilator) and the internal pressure control loops of the ventilator. The hose configuration determines the (non-linear) hose resistance, hose compliance, and leakage which results in a pressure drop. Two common hose configurations are the single hose system with a passive leak for expiration (Reinders et al., 2022) and the double hose system with an active expiration valve (van Diepen et al., 2022).

Combining the expressions of the lung pressure (1) and the patient flow (2) results in

$$p_{aw}(t) = \frac{1}{C_{lung}} V_{pat}(t) + R_{lung} Q_{pat}(t) + p_{lung}(t_0) + p_{mus}(t). \tag{3}$$

The lung compliance C_{lung}, the lung resistance R_{lung}, the initial lung pressure $p_{lung}(t_0)$, and the breathing effort $p_{mus}(t)$ are unknown in practice. The signals that are in general measured are the airway pressure $p_{aw}(t)$, the patient flow $Q_{pat}(t)$, and the volume $V_{pat}(t)$. Discretization of (3) results in

$$p_{aw}(k) = \frac{1}{C_{lung}} V_{pat}(k) + R_{lung} Q_{pat}(k) + p_{lung}(1) + p_{mus}(k), \tag{4}$$

where k is the discrete sampling number and $p_{lung}(1)$ the initial lung pressure. The model (4) is used in the estimation problem as presented in Section 2.2. The model is cast in the following generic form:

$$y(k) = G(\xi)u(k) + d(k), \tag{5}$$

where for the model as described in (4), $y(k) := p_{aw}(k)$ is a measured output, $G(\xi) = \begin{bmatrix}\xi_1 & \xi_2\end{bmatrix} := \begin{bmatrix}1/C_{lung} & R_{lung}\end{bmatrix} \in \mathbb{R}^{1\times 2}$ the (static) transfer function from u to y, which includes the patient parameters, $u(k) := \begin{bmatrix}V_{pat}(k) & Q_{pat}(k)\end{bmatrix}^\top$ the measured input signals, and $d(k) := p_{lung}(1) + p_{mus}(k)$ the unknown exogenous disturbance. In the next section, an estimation perspective is developed to identify the patient parameters in $G(\xi)$ and the exogenous disturbance $d(k)$ simultaneously. It is important to note that more complex lung models (as long as they are linear in their parameters) can be utilized with the following estimation method or with an extension thereof.

2.2. Linear regression framework for breathing effort estimation

In this section, an estimation perspective on spontaneously breathing patients is presented, where a linear regression framework based on a single breath is introduced and analyzed.

2.2.1. Introduction to the estimation problem

The primary objective is to achieve accurate estimates of both patient parameters and the exogenous disturbances within the gray box model as presented in (5). These estimates are important for adjusting the treatment in response to the patient's evolving condition. Ideally, this goal is accomplished by only using the readily available measured signals, i.e., the airway pressure $p_{aw}(k)$, the patient $Q_{pat}(k)$, and the patient volume $V_{pat}(k)$. These signals are measured for multiple breaths m of length N.

Parameter estimation over multiple breaths instead of a single breath enables us to formulate less restrictive constraints on the breathing effort. In a multi-breath approach, constraints over multiple breaths are formulated for the variation between breaths, hence, the shape of a single patient breathing effort is completely free. Furthermore, enforcing constraints on the variability of the breathing effort aligns with clinical perspective. The breathing effort variation is seen as a potential marker for the patients to start breathing independently again (El-Khatib, Jamaleddine, Soubra, & Muallem, 2001).

A multiple breath estimation approach leads to the following model structure:

$$\mathcal{M}_\beta : X \to Y, \quad Y = X\beta \tag{6}$$

with

$$\begin{aligned} Y &= \begin{bmatrix} p_{aw}(1) & \cdots & p_{aw}(mN) \end{bmatrix}^\top, \\ X &= \begin{bmatrix} V_{pat}(1) & Q_{pat}(1) & \\ \vdots & \vdots & I_{mN\times mN} \\ V_{pat}(mN) & Q_{pat}(mN) & \end{bmatrix}, \\ \beta &= \begin{bmatrix} \xi_1 & \xi_2 & d(1) & \dots & d(mN) \end{bmatrix}^\top \in \mathbb{R}^{mN+2} \\ &= \begin{bmatrix} \frac{1}{C_{lung}} & R_{lung} & \bar{p}_{mus}(1) & \dots & \bar{p}_{mus}(mN) \end{bmatrix}^\top. \end{aligned} \tag{7}$$

Here, $\bar{p}_{mus}(k) = p_{mus}(k) + p_{lung}(1)$ denotes the sum of the patient effort and the initial lung pressure, N denotes the number of samples within a single breath, and m denotes the number of breaths. The data acquired during multiple breaths m is captured by $\mathcal{D} = \{X, Y\}$.

In the estimation procedure, the aim is to select the member from the model set $\mathcal{M}_\beta$ that best reflects the patient given the dataset $\mathcal{D}$. Assume that the true system is given by the parameter vector β_o. Hence, measurements of the true system are expressed as:

$$Y = X\beta_o + v, \tag{8}$$

where X and Y are the regressor and output, respectively, that are related through the exact parameters β_o. The measured output Y is available being contaminated with noise vector v. The noise vector v is i.i.d. normally distributed with mean 0 and variance σ_v^2. To estimate the parameters, the least-squares cost function

$$J(\hat{\beta}) = \sum_{k=1}^{mN} \left(p_{aw}(k) - \hat{p}_{aw}(k)\right)^2 = \|Y - X\hat{\beta}\|_2^2 \tag{9}$$

is considered. Here, $p_{aw}(k)$ corresponds to the measured airway pressure generated by (8) and $\hat{p}_{aw}(k)$ corresponds to the estimated airway pressure generated by the model (4) with the estimated lung resistance $\hat{R}_{lung}$, the estimated lung compliance $\hat{C}_{lung}$, and the estimated breathing effort $\hat{p}_{mus}(k)$. The parameter vector that minimizes the cost function is found analytically (Hastie, Tibshirani, & Friedman, 2009) and is given by

$$\hat{\beta} = (X^\top X)^{-1} X^\top Y. \tag{10}$$

It is important to note that the solution $\hat{\beta}$ is only unique if $(X^\top X)$ is invertible, which is not the case for the estimation problem as defined above. By definition, the system is underdetermined, i.e., X is a wide matrix ($X \in \mathbb{R}^{mN\times mN+2}$), meaning that $\hat{\beta}$ is non-unique.

2.2.2. Non-uniqueness of parameter estimates

A non-unique solution of the parameter estimates is due to identifiability of the model structure and/or informativeness of the inputs (Ljung, 1999). Given the underdetermined system, the initial emphasis is on the model structure and the relation with to the (lack of the) model property of identifiability.

Definition 1. The parameterization $\mathcal{M}_\beta$ is identifiable if for all β_1 and β_2 it holds that

$$\mathcal{M}_{\beta_1} = \mathcal{M}_{\beta_2} \Rightarrow \beta_1 = \beta_2, \tag{11}$$

where the model equality is defined as

$$\mathcal{M}_{\beta_1} = \mathcal{M}_{\beta_2} \Leftrightarrow \mathcal{M}_{\beta_1}(X) = \mathcal{M}_{\beta_2}(X), \quad \forall X. \tag{12}$$

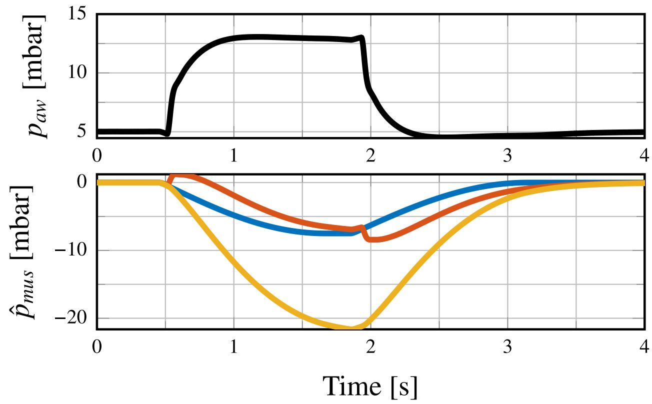

Fig. 2. Three combinations of $\hat{C}$, $\hat{R}$, ($\hat{C}$ = 80 [ml/mbar], $\hat{R}$ = 0.083 [mbar s/ml](blue line)), ($\hat{C}$ = 80 [ml/mbar], $\hat{R}$ = 0.042 [mbar s/ml](red line)), ($\hat{C}$ = 40 [ml/mbar], $\hat{R}$ = 0.083 [mbar s/ml](yellow line)) with accompanying breathing effort $\hat{p}_{mus}$ leading to the same airway pressure p_{aw} (black line). This illustrates that the model structure in (7) is not identifiable.

Identifiability is a property of the model structure and remains independent of the data. In this case, the model structure is not identifiable, because multiple regressor vectors produce identical input–output pairs, which is caused by the size of X. A physical interpretation of the lack of identifiability is given using (4). It is observed that for a combination of $\hat{C}_{lung}$ and $\hat{R}_{lung}$, a breathing effort exists $\hat{p}_{mus}(k)$ such that $p_{aw}(k) = \hat{p}_{aw}(k)\ \forall k \in [1, N]$, namely $\hat{p}_{mus} = p_{aw}(k) - \left(\frac{1}{\hat{C}_{lung}} V_{pat}(k) + \hat{R}_{lung} Q_{pat}(k) + \hat{p}_{lung}(1)\right)$. This holds true even if the parametric estimates $\hat{R}_{lung}$ and $\hat{C}_{lung}$ are incorrect. In Fig. 2, this is illustrated by showing three different parameter combinations that yield the same airway pressure. This further underscores that the parameterization lacks identifiability. Thus, the model structure requires adjustments to overcome the identifiability challenge. An option often used in practice is to assume that a patient is not actively breathing; hereby, reducing the parameter vector significantly because a large part is known, i.e., $p_{mus}(k) = 0\ \forall k$. This leads to an identifiable model structure as shown in Example 1.

Example 1. Assume that the patient is fully sedated such that there is no breathing effort, i.e., $p_{mus}(k) = 0\ \forall k$. In this scenario, the regression problem simplifies to:

$$\underbrace{\begin{bmatrix} p_{aw}(1) \\ \vdots \\ p_{aw}(N) \end{bmatrix}}_{Y} = \underbrace{\begin{bmatrix} V_{pat}(1) & Q_{pat}(1) \\ \vdots & \vdots \\ V_{pat}(N) & Q_{pat}(N) \end{bmatrix}}_{X} \underbrace{\begin{bmatrix} \frac{1}{C_{lung}} \\ R_{lung} \end{bmatrix}}_{\beta}. \tag{13}$$

In the modified regression problem, it is observed that the model structure is identifiable, because the system is overdetermined, resulting in a tall $X \in \mathbb{R}^{N \times 2}$ matrix. Each parameter vector β produces a distinct output Y for inputs X under the assumption that the columns of $X^\top X$ are linearly independent.

The case of Example 1 is straightforward. Hence, an extended solution is developed. An identifiable model structure for actively breathing patients can be achieved by imposing constraints on the breathing effort over a single breath or by imposing constraints on the breathing effort over multiple breaths instead of leaving $\hat{p}_{mus}(k)$ completely free.

An identifiable model structure is shown in Fig. 3, where the parameter vector β is reduced to $\bar{\beta}$ by including prior knowledge on a single breathing effort, i.e., the breathing effort estimate $\hat{p}_{mus}$ is not described at every sampling instant k, but parameterized by a functional description with a lower number of parameters. A different identifiable model structure is shown in Fig. 4 where the length of $\breve{X}$ is increased while not increasing or only slightly increasing the parameter vector $\breve{\beta}$. In the context of breathing effort estimation, this is accomplished by estimating multiple breaths while parameterizing the variability of the breathing effort.

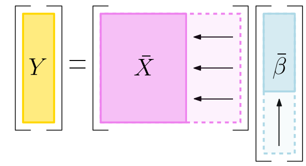

Fig. 3. Enforcing constraints on the breathing effort shape reduces the amount of parameters to be estimated $\bar{\beta}$, e.g., basis functions, sparse estimation.

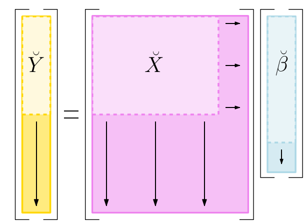

Fig. 4. Estimation over multiple breaths with constraints over subsequent breaths to increase information, e.g., a breath does not vary from the previous breath(s).

The options visualized in Figs. 3 and 4 result in an overdetermined system, i.e., in tall X-matrices and identifiable model structures. Another model property that is crucial for obtaining unique solutions is informativeness, which is made explicit by the condition of persistence of excitation.

Definition 2. A dataset $\mathcal{D}$ is persistently exciting with respect to the identifiable parameterization $\mathcal{M}_\beta$ if, for any two realizations $\mathcal{M}_{\beta_1}$, $\mathcal{M}_{\beta_2}$ satisfying

$$\mathcal{M}_{\beta_1}(X) - \mathcal{M}_{\beta_2}(X) = 0, \tag{14}$$

it holds that $\beta_1 = \beta_2$.

Informativeness is a property of the model that is directly linked to the data. Non-informative input data result in a column rank drop in X, which leads to non-unique estimates.

Remark. Note that the uniqueness properties; identifiability and informativeness, are respectively linked to structural identifiability and practical identifiability which might be more known in the field of mechanical ventilation (Schranz, Docherty, Chiew, Chase, & Möller, 2012).

2.2.3. Solutions for multi-breath estimation

In multi-breath estimation, four solutions result in unique parameter estimates. These possibilities are shown in Fig. 5 and below all possibilities are discussed briefly in terms of their model assumptions and properties.

Starting in the top left of Fig. 5, quadrant I, it shows that there are no variations in the breathing effort and target pressure. Therefore a multi-breath approach is redundant. To obtain an identifiable model structure, it is necessary to parameterize the shape of the breathing effort to decrease the parameter vector. Informativeness of the input data is guaranteed as long as the target pressure is not constant during a breath (van de Kamp et al., 2023).

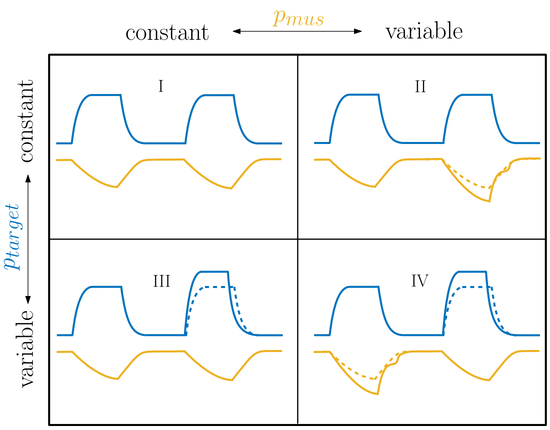

Fig. 5. Diagram that shows four different possibilities regarding multiple breath estimation. The division is made based on target pressure and patient breathing effort.

In quadrant II, the top right of Fig. 5, the breathing effort is variable across breaths. In this situation, a multi-breath approach is employed where a parameterization of the breathing effort variability is used to make the model structure identifiable. Informativeness of the input data cannot be enforced because the patients control their own breathing. A unique estimate is found when the patient is breathing with a large (enough) variability; however, this variability is unknown, making it inherently challenging to conclude whether estimates are accurate in practice in quadrant II.

In the bottom left of Fig. 5, quadrant III, the target pressure of the ventilator varies over breaths while the patient effort does not vary over breaths. The model structure is made identifiable by the model assumption that the breathing effort is equal across breaths, which is discussed in further detail in Section 3. Informativeness of inputs can be guaranteed by designing target pressure variations across breaths. Hereby, tools from experiment design can be used to design a target pressure signal that guarantees both patient's comfort and persistence of excitation of specific order.

In quadrant IV, the bottom right of Fig. 5, both the target pressure and breathing effort are varying across breaths. Identifiability is guaranteed by the model assumption that the variation of breathing effort over multiple breaths is parameterized. Note that guaranteeing persistence of excitation is more challenging compared to quadrant III because a patient, which cannot be manipulated, can counteract the designed inputs, which results in information loss.

In practice, it is challenging to derive which quadrant scenario is occurring between patient and ventilator. Information about the ventilator settings, the airway pressure, and patient flow are necessary to make a distinction between the different quadrants. Adjustments to the ventilator settings induce changes to the airway pressure and patient flow, while a different breathing effort mainly induces a change in patient flow. If the ventilator settings remain unchanged, but the patient flow differs, then the breathing effort is varying, hence, quadrant II is occurring. The distinction between quadrant III and quadrant IV is more challenging and requires analysis over sets of multiple breathing cycles.

In remainder of this paper, quadrant III is further analyzed in Sections 3 and 4. In Section 5, an analysis is conducted for quadrant IV where the breathing effort and the target pressure are both varying. Quadrant II is left as future research due to the challenging nature of the estimation regarding informativeness of the data.

3. Linear regression framework for multi-breath estimation

In this section, the model structure of the multi-breath estimation approach is introduced and their model properties, identifiability and informativeness are discussed.

The multi-breath model structure in (7) is made identifiable by assuming that the breathing effort stays equal across breaths. Note that the model assumption (equal breathing efforts across breaths denoted by the double I_N) is more restrictive for larger values of m; therefore, the emphasis lies on the estimation over two breaths ($m = 2$). This leads to the following model structure:

$$\mathcal{M}_{\breve{\beta}} : \breve{Y} = \breve{X}\breve{\beta} \tag{15}$$

with

$$\begin{aligned} \breve{Y}^\top &= \begin{bmatrix} p_{aw}(1) & \cdots & p_{aw}(2N) \end{bmatrix}, \\ \breve{X} &= \begin{bmatrix} V_{pat}(1) & Q_{pat}(1) & \\ \vdots & \vdots & I_N \\ V_{pat}(N) & Q_{pat}(N) & \\ V_{pat}(N+1) & Q_{pat}(N+1) & \\ \vdots & \vdots & I_N \\ V_{pat}(2N) & Q_{pat}(2N) & \end{bmatrix}, \\ \breve{\beta}^\top &= \begin{bmatrix} \frac{1}{C_{lung}} & R_{lung} & \bar{p}_{mus}(1) & \ldots & \bar{p}_{mus}(N) \end{bmatrix} \in \mathbb{R}^{N+2}. \end{aligned} \tag{16}$$

The optimal parameter estimates are computed with the least squares solution:

$$\hat{\breve{\beta}} = \left(\breve{X}^\top \breve{X}\right)^{-1} \breve{X}^\top \breve{Y}, \tag{17}$$

where $\breve{Y}$ is the measured output from the noiseless data-generating system,

$$\breve{Y} = \breve{X}\breve{\beta}_o + v, \tag{18}$$

where $\breve{\beta}_o$ is denoted as the true parameter vector. The noise vector v is i.i.d. normally distributed with mean 0 and variance σ_v^2. Additional noise use cases are considered in Section 5. The size of $\breve{X}$ is tall, meaning that there are more data points than parameters to be estimated. Thus, the model structure is identifiable. To guarantee unique parameter estimates, it is necessary to also check the informativeness of the input. It can be shown that for two subsequent breaths with equal patient breathing efforts (quadrant III in Fig. 5), a unique solution can be found if the patient flow is different across breaths. First, let us introduce an assumption before the condition for a unique estimate is mathematically formalized in a theorem.

Assumption 1. The patient flow and volume satisfy the inequality

$$V_{pat}^i \neq c Q_{pat}^i$$

with c being a constant and the subscript i standing for the ith breath.

Remark. The patient flow assumption in Assumption 1 is not stringent because practically valid breathing cycles satisfy the inequality.

The uniqueness of the estimation problem is formalized in the following theorem:

Theorem 1. *Consider the nominal data generating system in (18) together with the proposed estimation model structure in (15) and (16) and Assumption 1. If*

$$Q_{pat}^1 - Q_{pat}^2 \neq 0,$$

where Q^1_{pat} is the flow of the first breath and Q^2_{pat} of the second breath, then the estimation problem in (15) and (16) with the data generating system (18) results in a full column rank matrix $\breve{X}$. This ensures persistence of excitation of sufficient order and results in unique parameter estimates.

A proof of Theorem 1 is provided in Appendix. Thus, theoretically a unique solution is found if the norm condition is satisfied, i.e., the flow of the first and second breath is different ($Q^1_{pat} \neq Q^2_{pat}$). In practice, a small deviation might raise numerical issues due to ill-conditioning of the matrix $\breve{X}^\top \breve{X}$; therefore, it is convenient to bound the condition in Theorem 1 from below by α. Furthermore, it is crucial to note that only the target pressure p_{target} influences the patient flow Q_{pat} when the breathing effort p_{mus} stays the same across breaths. The target pressure can be manipulated by the user, which makes quadrant III in Fig. 5 an experiment design problem that is tackled in the upcoming section.

4. Optimal experiment design of the target pressure for mechanically ventilated patients

In this section, the optimal experiment design framework is introduced for the patient estimation problem as introduced in Section 3. In Section 4.1, the criteria for the optimal experiment design are introduced. Thereafter, in Section 4.2, the optimization problem for the Fisher information matrix is introduced.

4.1. Experiment design problem definition

In the multiple breath estimation approach, the goal is to find accurate estimates of the breathing effort and the patient parameters simultaneously. A unique solution exists if Theorem 1 holds, which can be realized by designing two ventilator targets that are different from each other while the breathing effort stays equal across breaths. Here, it assumed that the patient does not react to changes in ventilator settings on a time-scale of one breath. A latency of few breaths exists before the patient starts adapting to the new situation (Viale et al., 1998). A high estimation accuracy for an unbiased estimator corresponds to a low covariance of the parameter estimates. Therefore, we strive to minimize the covariance. Below, the covariance of the estimation problem is introduced and translated to scalar optimality measures via the Fisher Information matrix (FIM). This enables us to formulate an optimization problem that designs ventilator targets that lead to accurate estimates.

The sample covariance matrix of the unique solution is given by

$$\operatorname{cov}\left(\hat{\breve{\beta}}\right) := \mathbb{E}\left[\left(\breve{\beta}_o - \hat{\breve{\beta}}\right)\left(\breve{\beta}_o - \hat{\breve{\beta}}\right)^\top\right] = \left(\breve{X}^\top \breve{X}\right)^{-1} \hat{\sigma}_v^2, \tag{19}$$

where $\hat{\sigma}_v^2$ is the estimated sample variance

$$\hat{\sigma}_v^2 = \frac{1}{mN - z - 1} \|\breve{Y} - \breve{X}\hat{\breve{\beta}}\|_2^2 \tag{20}$$

with z the amount of parameters that need to be estimated, i.e., the length of $\breve{\beta}$. let ψ be the estimator of a multi-parameter estimation problem then the covariance is bounded from below by the Cramer–Rao lower bound (Rao, 1992)

$$\operatorname{cov}_{\breve{\beta}}(\psi(\breve{\beta})) \geq \frac{\partial \psi}{\partial \breve{\beta}} I(\breve{\beta})^{-1} \frac{\partial \psi}{\partial \breve{\beta}}^\top, \tag{21}$$

where $I(\breve{\beta})$ is the Fisher Information Matrix. Let ψ be an unbiased estimator, i.e., $\psi(\breve{\beta}) = \breve{\beta}_o$, then the bound simplifies to

$$\operatorname{cov}_{\breve{\beta}}(\psi(\breve{\beta})) \geq I(\breve{\beta}_o)^{-1}. \tag{22}$$

This shows that instead of minimizing the covariance, it is possible to maximize the information content within the FIM. Maximizing in terms of optimality conditions is discussed below. The data generating system in (18) and the module structure in (15) and (16) result in an unbiased estimate. The fisher information matrix for the formulated regression problem with (18), (15), and (16) is given by

$$I = \breve{X}^\top \breve{X} / \hat{\sigma}_v^2. \tag{23}$$

This result shows that the information matrix solely depends on the inputs $\breve{X}$ and not on the parameter vector $\breve{\beta}$ or the output $\breve{Y}$. Hence, the covariance can be minimized by optimally designing the inputs $\breve{X}$ without having knowledge about the outputs $\breve{Y}$.

The information content within the FIM (see (23)) can be maximized via scalar optimality measures, including:

- **A-optimality:** minimize the trace of $(\breve{X}^\top \breve{X})^{-1}$.
- **D-optimality:** minimize the determinant of $(\breve{X}^\top \breve{X})^{-1}$.
- **E-optimality:** maximize the minimum eigenvalue of $(\breve{X}^\top \breve{X})^{-1}$.

Throughout this paper, the A-optimality measure is used as an example. Hereby, the aim is to reduce covariance of the estimated parameters by minimizing the average variance of the estimated parameters, i.e., minimizing the trace of $\left(\breve{X}^\top \breve{X}\right)^{-1}$.

4.2. FIM optimization in mechanical ventilated patients

The Fisher information matrix $I(\breve{X})$ consists of the patient flow and the volume response. These signals are a result of the induced pressure difference between ventilator and patient and the patient characteristics itself. In a general experiment design problem, first an optimal spectrum of inputs is found via optimization (Rojas, Welsh, Goodwin, & Feuer, 2007), and subsequently, viable inputs according to time constraints are sampled from the optimal spectrum. In the case of breathing effort estimation, optimization of the target pressure's spectrum is redundant, because the signal is constraint tightly by a set of parameters. Furthermore, there are limits to adjusting the ventilator settings due to patient comfort and treatment. This leads to the following constrained optimization problem:

$$\begin{aligned} \min_{\text{IPAP}, t_{rise}} \quad & \operatorname{tr}\left\{(\breve{X}^\top \breve{X})^{-1}\right\}, \\ \text{s.t.} \quad & \alpha < \|Q^1_{pat} - Q^2_{pat}\| \leq \gamma, \\ & Q^i_{pat} = f_1(p^i_{target}, p^i_{aw}, p^i_{lung}), \\ & p^i_{target} = f_2(\text{PEEP}, \text{IPAP}, t_{rise}, t_{fall}, T_{insp}, T_{exp}). \end{aligned} \tag{24}$$

The target pressure p_{target} is modeled as a first-order filtered block wave, as shown in Fig. 6, defined by six parameters, where PEEP, IPAP are the low and high pressure levels, respectively, t_{rise} the ramp rise time of the target pressure from PEEP to IPAP, t_{fall} the ramp fall time of the target pressure from IPAP to PEEP, T_{insp} the time at which the inspiration is triggered, and T_{exp} the time when the expiration is triggered. In supportive modes, T_{insp} and T_{exp} can be adjusted by respectively changing the (flow) inspiration and expiration triggers. Furthermore, patients on a ventilator are only able to handle inputs within a patient-specific range. This is quantified by enforcing addition bounds on the identifiability condition in Theorem 1. We only have to check the norm condition of two subsequent breaths, where γ is a bound to limit the difference between the first and second ventilator breath. The norm must be greater than α where $\alpha \in \mathbb{R}_{\geq 0}$ to not have conditioning problems computing the inverse of $\breve{X}^\top \breve{X}$. The difference between the flow of two subsequent breaths, associated to Q^1_{pat} and Q^2_{pat} in (24), is a result of the pressure difference,

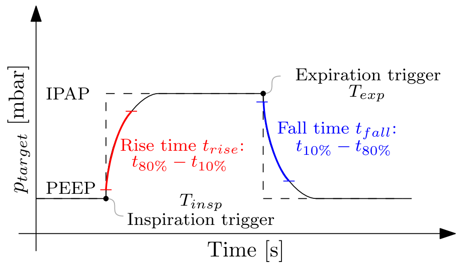

Fig. 6. Parameterization of the input signal p_{target}. The input signal is a blockwave defined by the PEEP and IPAP level together with the inspiration and expiration trigger. The blockwave is filtered with a first order filter, which determines the rise and fall time.

which can quantified by the patient-hose model as described in Reinders, Hunnekens, Heck, Oomen, and Van De Wouw (2021).

In a clinical setting, the inspiration and expiration trigger (and thus T_{insp} and T_{exp}) should preferably not be adjusted, because this could induce patient-ventilator asynchrony, which can be detrimental for the patient's health (Blanch et al., 2015). Furthermore, the IPAP level and the rise time t_{rise} are most convenient to adjust; therefore, these are the only two remaining parameters that are considered for optimization of the information content in this paper. Adjustments to the IPAP levels between breaths is similar to a manoeuvre called variable PSV, which improves oxygenations and lung protection (Spieth et al., 2011).

5. Application of optimal experiment design in multi-breath estimation: a case study

In this section, an optimal experiment design case-study is conducted for two scenarios. The first scenario describes a patient that has a non-varying breathing effort across breaths, i.e., quadrant III in Fig. 5. The second scenario describes a patient with a varying breathing effort across breaths, i.e., quadrant IV in Fig. 5. In Section 5.1, the data generating system and the estimation problem formulation with non-varying breathing effort across breaths are introduced. Subsequently, in Section 5.2, a simulation case study is conducted to investigate the estimation accuracy of the multi-breath estimation of quadrant III. In Section 5.3, the data generating system and the estimation problem formulation with varying breathing effort across breaths are introduced. Subsequently, in Section 5.4, a simulation case study is conducted to investigate the estimation accuracy of the multi-breath estimation approach with varying breathing effort. The ventilatory data in this section is generated using a data-driven ventilator model, a realistic and measured single hose configuration, and a single compartmental lung model (Reinders, 2022, p. 197).

5.1. Parameter estimation of multiple patient breaths with non-varying breathing efforts

The data generating system for non-varying breathing effort across breaths containing measurement noise is:

$$\breve{Y} = \breve{X}\breve{\beta}_o + v, \tag{25}$$

where $\breve{\beta}_o$ is denoted as the true parameter vector. The noise vector v is i.i.d. normally distributed with mean 0 and variance σ_v^2.

An unbiased estimate is expected within the ordinary least squares solution, because the expected value of (17) is

$$\mathbb{E}\left[\hat{\breve{\beta}}\right] = \breve{\beta}_o + \left(\breve{X}^\top\breve{X}\right)^{-1}\mathbb{E}\left[v\right], \tag{26}$$

where v is a disturbance vector with zero mean. In the upcoming section, this is further analyzed with a simulation case study.

5.2. Results of the simulation case-study with non-varying breathing efforts

In this section, we focus on changing two parameters of the target pressure, the IPAP level and the rise time, to minimize the covariance of the parameter estimates for non-varying breathing efforts. For this simulation case study, we use the data-generating system in (18) and the estimation module structure in (15), and (16). In Section 5.2.1, estimation results of different IPAP levels are presented. Thereafter, in Section 5.2.2, a comparison of the information gain obtained by changing both target pressure parameters is presented based on the A-optimality design criterium, i.e., solving the constrained optimization problem in (24).

5.2.1. Results of variable pressure support ventilation

Increasing the inspiratory positive airway pressure (IPAP) of the second breath, the patient flow of this second breath is higher during inspiration and lower during expiration compared to the first breath resulting in a unique estimate according to Theorem 1. The larger we make the difference in IPAP level (ΔIPAP) between subsequent breaths, the larger the difference in flows between the subsequent breaths becomes. In Fig. 7, parameter estimates and their 95% confidence bounds for the patient parameters and breathing effort for different ΔIPAP levels are shown. The approximate confidence set for the entire parameter vector $\breve{\beta}_o$ are defined as (Hastie et al., 2009)

$$C_{\breve{\beta}_o} := \left\{\breve{\beta}\left|(\hat{\breve{\beta}} - \breve{\beta}_o)^\top\breve{X}^\top\breve{X}(\hat{\breve{\beta}} - \breve{\beta}_o) \leq \hat{\sigma}_v^2\chi_{z+1}^{2,(1-\phi)}\right.\right\}, \tag{27}$$

where $\chi_{z+1}^{2,(1-\alpha)}$ is the $1-\phi$ percentile of the chi-squared distribution on $z+1$ degrees of freedom. The confidence bounds on the parameter estimates are plotted by using an eigenvalue decomposition of the covariance matrix.

We conclude that a larger ΔIPAP results in a smaller variance on the parameter estimates based on Fig. 7. Furthermore, it is observed that the estimated values do not perfectly coincide with the true parameter values (black cross). In the case study, only one double breath is evaluated resulting in a small mismatch of the estimates. Evaluating multiple double breaths for different noise configurations eventually leads to averaged estimate of the breathing effort and the patient parameters that is unbiased because $\mathbb{E}\left[v\right] = 0$.

In Sections 5.3 and 5.4, an extension of this case is further analyzed. There the variability in the breathing effort is added to the output noise.

5.2.2. Optimal experiment design based on A-optimality

In this section, A-optimality is employed as a measure to find the target pressure parameter that results in the most accurate patient parameter estimates. Hereby, we solve the optimization problem in (24) for a certain parameter range such that the flow difference is bounded by $\alpha = 15$ and $\gamma = 220$. The values for α, γ are chosen for demonstration and should be clinically validated. A-optimality enables us to quantify the information gain that certain target pressure parameter adjustments induce. This allows for better comparison between different parameters of the target pressure p_{target}. Fig. 8 shows the A-optimality measure versus the norm of the difference in patient flow between the two breaths for changes in IPAP level and rise time t_{rise}. From this figure, it is concluded that within the given parameter sets, ΔIPAP variations result in a lower trace compared to Δt_{rise} variations for a given difference in flow between breaths. This shows that adjustments of ΔIPAP are more effective to minimize the variance of the estimates for the currently tested parameter set.

To find the optimal ΔIPAP while ensuring $\Delta t_{rise} = 0$, a clinician should determine what is still allowed to not compromise the patient comfort and treatment, hereby adjusting the γ

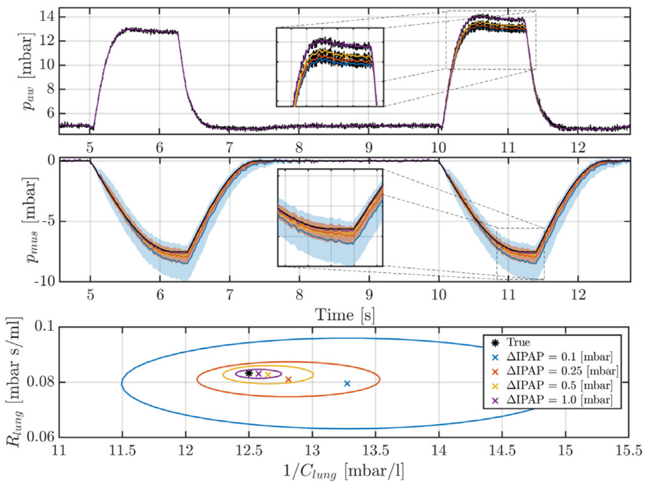

Fig. 7. Simulation results of the estimated airway pressure $\hat{p}_{aw}$ (colored lines), patient parameters $\hat{R}_{lung}$ and $\hat{C}_{lung}$ and the breathing effort $\hat{p}_{mus}$ for 2 subsequent breaths with different IPAP levels are displayed. An increase in the IPAP level of the target pressure between subsequent breaths, i.e., a larger ΔIPAP, results in more accurate estimates of the true airway pressure and breathing effort (—) and true patient parameters ($*$) regarding their estimated values and variances. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

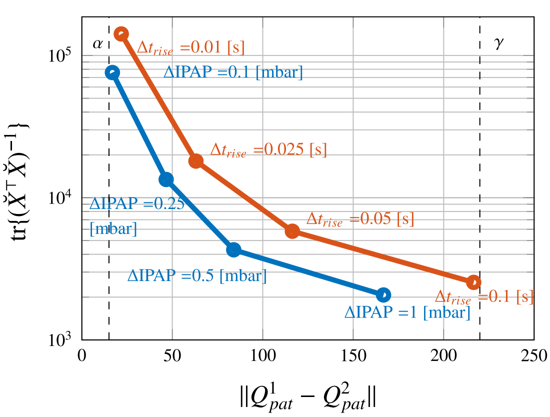

Fig. 8. A-optimality versus the norm of the difference between the patient flows of the first and second breath. While varying the ΔIPAP levels, the difference in rise time between breaths Δt_{rise} is set to zero seconds and vice versa. The chosen parameter set for the experiment stays within the bounds of α and γ (- - -). The same patient parameters and breathing efforts from Fig. 7 are used.

bound in (24). The overall estimation approach of Section 4 shows promising results; however, it is important to note that within this approach restrictive assumptions are made that the patient breathing effort does not change across breaths. In the upcoming section, the influence of a varying patient breathing effort on the estimation approach is analyzed, i.e., going from quadrant III to quadrant IV in Fig. 5.

5.3. Parameter estimation of multiple patient breaths with varying breathing efforts

The data-generating system for a double breath with variable breathing effort is defined as:

$$\breve{Y} = \breve{X}\breve{\beta}_o + v + w \tag{28}$$

with

$$w := \begin{bmatrix} 0_{2N\times 2} & \begin{bmatrix} 0_{N\times N} & \kappa I_{N\times N}\end{bmatrix}^\top \end{bmatrix} \breve{\beta}_o, \tag{29}$$

where $\kappa \sim \mathcal{N}(0, \sigma_\kappa^2)$ is the variation on the breathing effort amplitude. An assumption is made that the patient is breathing with a constant duration and interval, while the amplitude of the breathing effort is varying with a variance of σ_κ^2 across breaths. Patients on support ventilation breathe regularly with small variations (El-Khatib et al., 2001) that can be captured by a stochastic parameter. There is no clear consensus on how the breathing effort varies, therefore, it is chosen to model the variability of the breathing effort by an amplitude variation. In general, all additive variations on top of the breathing effort fit the current data generating system.

For the estimation model, the breathing effort is assumed to be constant across breaths because the variations are typically unknown, resulting in (15) and (16). In other words, it is assumed that there is no disturbance κ. This leads to the least squares solution

$$\begin{aligned}\hat{\breve{\beta}} &= (\breve{X}^\top\breve{X})^{-1}\breve{X}^\top\breve{Y} \\ &= (\breve{X}^\top\breve{X})^{-1}\breve{X}^\top\left(\breve{X}\breve{\beta}_o + v + w\right).\end{aligned} \tag{30}$$

The estimator is unbiased, i.e., $\mathbb{E}\left[\hat{\breve{\beta}}\right] = \breve{\beta}_o$, in case the estimation model is perfect because the disturbance vectors v and w are independent and have zero mean. Therefore, if enough sets of double breaths are taken into account, the average estimate converges to the true parameter vector. In the upcoming section, the performance of the estimation model in (15) and (16) is evaluated while the data is generated with system (28).

5.4. Results of simulation case study with varying breathing efforts

In this section, the estimation results for a single set of double breaths are discussed first. Afterwards, the analysis is extend to a set of 300 double breaths. The variation of the target pressure between two breaths is set to ΔIPAP $= 1$ [mbar] for all simulations.

A single set of a double patient and ventilator breath is simulated in Fig. 9. The second breathing effort is smaller compared to the first breathing effort ($\kappa = -0.74$ [mbar]), hereby violating the estimation model assumption of equal patient breathing efforts. As a result, the parameter estimates are not accurate.

Although, a modeling error is present, let us simulate a set of 300 double breaths with variable breathing effort and investigate the average estimated parameters. In Fig. 10, the results of estimation lung parameters from 300 sets of double breaths of a single patient are shown. The average parameter estimates (black cross) do no converge to the true parameter values (black asterix) for a patient amplitude variance of 0.14 mbar^2. The extent of convergence to the true parameter estimates is related to the variation of the breathing effort amplitude variability σ_κ^2. The larger the amplitude variability σ_κ^2, the larger the mismatch with the estimation model assumption of equal breathing efforts, the larger the bias of the parameter estimates. This statement is substantiated by Fig. 11, which displays the relative error of the average parameter estimates under different levels of breathing effort amplitude variance. Higher variance levels yield larger relative error, i.e., larger biases.

Finally, in Fig. 12, the average patient parameters are used to compute the breathing effort for different variance levels. Increasing the variance leads to larger biases, which results in accurate estimation of the patient breathing effort if its variation is small over breaths and in inaccurate breathing effort estimates if the variation of the patient breathing effort is large.

From a clinical perspective, a small bias in the lung parameter estimates is allowed because parameter trends over time are more important. Therefore, it is allowed to have a relative

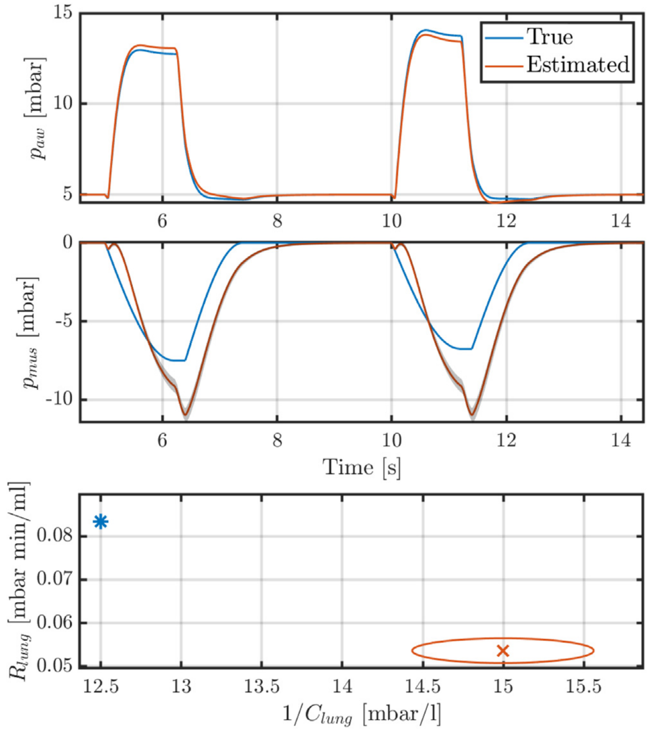

Fig. 9. Estimation results of the lung resistance, lung compliance, and the breathing effort with estimation model (15) and (16), while the data is generated with a varying breathing effort. The gray area around the breathing effort p_{mus} represents the 95% confidence bounds of the breathing effort estimate.

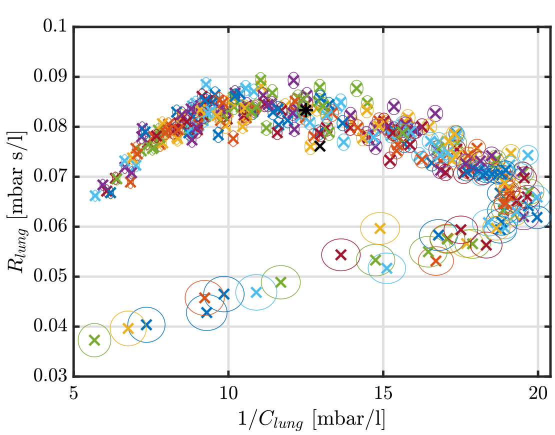

Fig. 10. Simulation results that contains the lung resistance and compliance estimates for 300 double breaths where the breathing effort amplitude variance is 0.14 [mbar^2] and ΔIPAP is 1 [mbar]. The estimates together with their 95%-confidence intervals are shown. The true parameter values are displayed with (✱) and the estimate average is displayed with the black cross (✖). The difference between the true parameters values and the average estimated parameters indicate that a bias is present.

error on the patient parameters of maximum 20% as stated in requirement (i). This is shown by the marked green area in Fig. 11. From this figure, it is concluded that the allowed variance on the breathing effort amplitude is 0.32 [mbar^2] for the tested variants based on the 2-norm. The 2-norm of the estimated patient parameters reflect for which level of variance the breathing effort estimates comply with requirement (i).

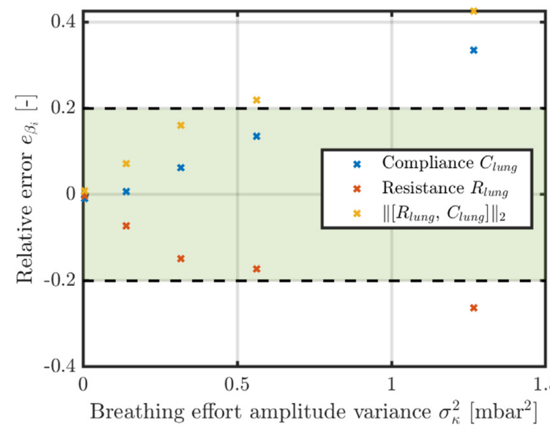

Fig. 11. Relative error of the average estimated lung compliance and resistance for different levels of breath effort variance α. An increase in the breathing effort amplitude variance σ_b results in a larger bias for the average lung compliance and resistance estimates. The green area represents a 20% error band for the patient parameter estimates. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

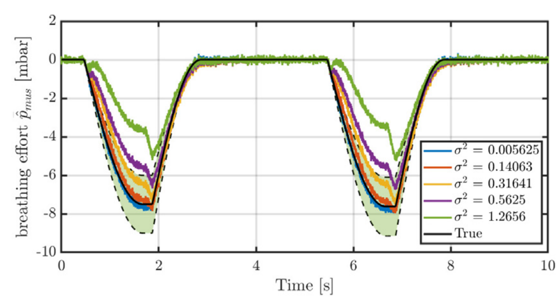

Fig. 12. The average breathing effort $\bar{\hat{p}}_{mus}$ is computed using the linear one-compartmental lung model and the average estimated lung resistance and compliance. The higher the variance of the breathing effort amplitude, the less accurate the average breathing effort becomes. The green area is a 20%-error bound on the true breathing effort, which is the maximum allowable error for the breathing effort estimates. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

6. Conclusion and recommendations

6.1. Conclusions

In this paper, a new perspective on the simultaneous estimation of patient breathing effort and lung parameters is studied in the scope of mechanical ventilation. Simultaneous estimation of lung parameters and breathing effort results in non-unique estimates if no additional prior knowledge about the breathing effort is taken into account. Therefore, a framework is presented that helps to solve the non-uniqueness by analyzing the identifiability and persistence of excitation. A persistence of excitation analysis in the proposed multi-breath estimation problem reveals that these unique parameter estimates are only found if the first and second ventilator breath are not identical. Finally, experiment design tools are leveraged to obtain accurate estimates of the breathing effort and lung parameters for both regularly breathing patients and patients that have a variable breathing pattern.

6.2. Recommendations

Further improvements regarding accurate and unique estimate for both regularly and variably breathing patients include choice of prior knowledge and formulation of the estimation problem. The assumption that the breathing effort only varies in amplitude over multiple breaths is a stringent assumption that does not occur frequently in practice. Therefore, to extend this method by incorporating the fact that the breathing effort can also vary in shape and timing, which is a necessary step for implementation in practice. This leads to an error-in-variables estimation model, that requires a different set of analysis tools. Future research includes testing the framework in a clinical setting with real patient data, that contains ground truth data of the lung resistance, lung compliance, and breathing effort. Furthermore, the designed estimator in this paper can potentially be improved by using instrumental variable estimation. Lastly, it is also interesting to look beyond the parameters of target pressure for increasing the information content, such as adding a signal on top of the target pressure.

CRediT authorship contribution statement

Lars van de Kamp: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bram Hunnekens:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Nathan van de Wouw:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Tom Oomen:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix. Proof of Theorem 1

The proof for Theorem 1 is provided below.

Proof. The proof is given for two breaths, i.e., $m = 2$ in (15), but can easily be extended to a general proof. Let column rank$(\check{X}) = N + 2$, then we know that all columns are linearly independent and that the column space is given by

$$\text{span}\left\{\begin{bmatrix} V_{pat}(1) \\ V_{pat}(2) \\ V_{pat}(3) \\ \vdots \\ V_{pat}(N) \\ V_{pat}(N+1) \\ V_{pat}(N+2) \\ V_{pat}(N+3) \\ \vdots \\ V_{pat}(2N) \end{bmatrix}, \begin{bmatrix} Q_{pat}(1) \\ Q_{pat}(2) \\ Q_{pat}(3) \\ \vdots \\ Q_{pat}(N) \\ Q_{pat}(N+1) \\ Q_{pat}(N+2) \\ Q_{pat}(N+3) \\ \vdots \\ Q_{pat}(2N) \end{bmatrix}, \begin{bmatrix} 1 \\ 0 \\ 0 \\ \vdots \\ 0 \\ 1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ 1 \\ 0 \\ \vdots \\ 0 \\ 0 \\ 1 \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \ldots, \begin{bmatrix} 0 \\ 0 \\ \vdots \\ 0 \\ 1 \\ 0 \\ 0 \\ \vdots \\ 0 \\ 1 \end{bmatrix}\right\}. \tag{A.1}$$

Let $\exists k \in [1, N]$ s.t. $Q^1_{pat}(k) \neq Q^2_{pat}(k)$. Then the vector $\begin{bmatrix}(Q^1_{pat})^\top & (Q^2_{pat})^\top\end{bmatrix}^\top$ cannot be in the column space spanned by the last N columns of $\check{X}$. This result can be simplified even further to $Q^1_{pat} - Q^2_{pat} \neq 0$. Furthermore, the vector $\begin{bmatrix}(V^1_{pat})^\top & (V^2_{pat})^\top\end{bmatrix}^\top$ is not in the column space spanned by the last N columns of $\check{X}$ because there is a difference in the flow between breaths, i.e., $Q^1_{pat} - Q^2_{pat} \neq 0$, and it holds that $V^i_{pat} = \int_{t_{(i-1)N}}^{t_{iN}} Q_{pat}(\tau)d\tau$. Lastly, the volume and flow vectors are linearly independent due the flow condition in Assumption 1, hence, the vectors span the full space of $\mathbb{R}^{N+2}$. □

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