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# Real-Time Noninvasive Estimation of Intrapleural Pressure in Mechanically Ventilated Patients: a Feasibility Study

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*Abstract*— **A method for real-time noninvasive estimation of intrapleural pressure in mechanically ventilated patients is proposed. The method employs a simple first-order lung mechanics model that is fitted in real-time to flow and pressure signals acquired non-invasively at the opening of the patient airways, in order to estimate lung resistance ($R_L$), lung compliance ($C_L$) and intrapleural pressure ($P_{pl}$) continuously in time. Estimation is achieved by minimizing the sum of squared residuals between measured and model predicted airway pressure using a modified Recursive Least Squares (RLS) approach. Particularly, two different RLS algorithms, namely the conventional RLS with Exponential Forgetting (EF-RLS) and the RLS with Vector-type Forgetting Factor (VFF-RLS), are considered in this study and their performances are first evaluated using simulated data. Simulations suggest that the conventional EF-RLS algorithm is not suitable for our purposes, whereas the VFF-RLS method provides satisfactory results. The potential of the VFF-RLS based method is then proved on experimental data collected from a mechanically ventilated pig. Results show that the method provides continuous estimated lung resistance and compliance in normal physiological ranges and pleural pressure in good agreement with invasive esophageal pressure measurements.**

## I. Introduction

Monitoring of intrapleural pressure ($P_{pl}$) in actively breathing ventilated patients provide instantaneous information on patients' efforts during spontaneous and machine-aided breaths. Several indices that reflect patients' energy expenditure while breathing, such as Pressure-Time Product (PT product) or Work of Breathing (WOB), can be derived from intrapleural pressure [1]. Moreover, $P_{pl}$ is required to compute transpulmonary pressure, the latter being essential to ensure optimal lung protective ventilation strategies and avoid over-distention of the lungs.

Direct measurement of intrapleural pressure (pleural manometry) requires an invasive procedure to place needles, catheters, or transducers. The risk of infection and other complications makes this approach unattractive in the clinical setting. For this reason, the pressure into the esophagus ($P_{es}$) is typically used as a surrogate of $P_{pl}$, with the esophageal balloon technique being the most popular method for $P_{es}$ measurement. This technique, however, not only requires the patient to swallow a balloon-tipped catheter, but it also requires expert operators for correct placement and inflation of the balloon, special equipment and particular attention to avoid errors and artifacts [2]. These drawbacks have limited the use of esophageal manometry as a way of monitoring $P_{pl}$ and have prevented its adoption into standard clinical practice. A real-time, continuous and noninvasive way to estimate intrapleural pressure in mechanically ventilated patients would hence be highly desirable.

In the present work we propose to estimate $P_{pl}$ using a first-order lung mechanics model and a modified Recursive Least Squares (RLS) approach that fits the model in real-time to flow and pressure signals measured non-invasively at the airway opening of the patient. The first-order lung mechanics model and RLS algorithm with exponential forgetting (EF) have been extensively applied for on-line parameter estimation of lung mechanics in both human and animal studies in the last decades [3]–[8]. However, in all the previous studies, intrapleural pressure was never considered as one of the model's parameters to be estimated. The goal was to achieve tracking of the time-varying lung resistance and compliance using a surrogate measurement of $P_{pl}$, typically esophageal or central venous pressure, as input to the parameter estimation algorithm. The purpose of the present study is to investigate if the use of the simple first-order lung mechanics model and the RLS technique can be extended to real-time estimation of intrapleural pressure, in addition to lung resistance and compliance, in actively breathing mechanically ventilated patients.

## II. Methods

### A. The Lung Mechanics Model

Several lumped-parameter models have been proposed in the past to represent breathing mechanics. These models range from the simple first order resistance-compliance model to higher-order models that account for inhomogeneity of the lungs. Attempts to use high-order models have not provided satisfactory results [3] because the performances of recursive algorithms for online parameter estimation sharply deteriorate as the number of parameters increases [9]. For this reason, the first order single-compartment model, whose electrical analogue is shown in Fig. 1, has been chosen for this study. In this model, the resistive properties of the conductive airways and the viscosity of the lung tissue are lumped into a single resistance ($R_L$), whereas the elastic properties of the lungs are described by a single compliance ($C_L$). The lung is surrounded by the pleural space, represented as a pressure source ($P_{pl}$). When the

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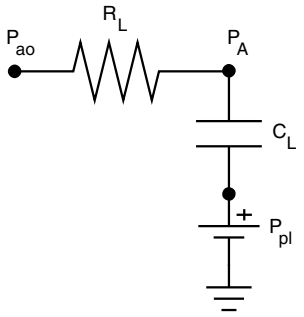


Fig. 1. Electrical analog of the single-compartment lung mechanics model. $P_{ao}$, airway pressure; $R_L$, lung resistance; $P_A$, alveolar pressure; $C_L$, lung compliance; $P_{pl}$, intrapleural pressure.

patient is under mechanical ventilation, the pressure at the airway opening ($P_{ao}$) depends on a balance between the intrapleural pressure, the pressure across the compliance (elastic recoil pressure) and the pressure drop across the resistance (resistive pressure). The mathematical equation describing the model, known as "equation of motion of the lung", is then:

$$P_{ao}(t) = R_L(t)\,\dot{V}(t) + \frac{1}{C_L(t)}V(t) + P_{pl}(t) + P_0 \quad (1)$$

where $\dot{V}$ is the air flow, $V$ is the lung volume above functional residual capacity (FRC) and $P_0$ is a constant added to account for the fact that at FRC, when both the resistive and elastic pressure terms in (1) are zero, $P_{ao}$ is not equal to $P_{pl}$.

### *B. The Parameter Estimation Algorithm*

Using continuous measurements of airway pressure $P_{ao}(t)$ and flow $\dot{V}(t)$ (from which, the volume $V(t)$ can be computed by numerical integration), (1) has been extensively applied to assess lung mechanics in both human and animal studies [3], [5], [8]. In these studies, surrogate measurements of $P_{pl}$ were also used to compute transpulmonary pressure $P_{tp} = P_{ao} - P_{pl}$ and recast (1) into a standard linear regression problem:

$$y(t) \equiv P_{tp}(t) = \underbrace{\begin{bmatrix} R_L(t) & \frac{1}{C_L(t)} & P_0 \end{bmatrix}}_{\theta^T(t)} \underbrace{\begin{bmatrix} \dot{V}(t) \\ V(t) \\ 1 \end{bmatrix}}_{x(t)} \quad (2)$$

where $x(t)$ is the vector containing the input variables, $y(t)$ is the output variable and $\theta(t)$ is the parameter vector containing the unknown parameters $R_L(t)$, $C_L(t)$ and $P_0$. Note that, when trying to fit (2) to experimental data, an extra term $w(t)$ needs to be considered to model the presence of process as well as measurement error:

$$y(t) = \theta^T(t)\,x(t) + w(t) \quad (3)$$

For on-line applications, the classical RLS algorithm with EF has been advocated to achieve continuous estimate of the time-varying parameter vector $\hat{\theta}(t)$, according to the general scheme:

$$\hat{\theta}(t) = \hat{\theta}(t-1) + G(t)n_o(t) \quad (4)$$

$$n_o(t) = y(t) - \hat{\theta}^T(t-1)x(t) \quad (5)$$

$$G(t) = \frac{P(t-1)x(t)}{\lambda + x^T(t)P(t-1)x(t)} \quad (6)$$

$$P(t) = \frac{\left[\mathbb{I} - G(t)x^T(t)\right]P(t-1)}{\lambda} \quad (7)$$

where $n_0(t)$ is the a priori model prediction error, $G(t)$ is the algorithm gain vector, $P(t)$ is a matrix proportional to the parameter covariance matrix, $\mathbb{I}$ is the identity matrix and $\lambda$ is a number between 0 and 1 commonly referred to as the "forgetting factor" (or design variable). The choice of the forgetting factor is critical as it determines the memory of the estimation procedure by defining the effective number and weight of past data points to which the model is being fitted. Small values of $\lambda$ reduce the memory of the algorithm, thus allowing for tracking of rapid parameter variations but result in high noise sensitivity. On the other hand, higher values of $\lambda$ provide better filtering of the noise but reduce the algorithm alertness. Hence, when choosing the value of $\lambda$, a trade-off between noise sensitivity and tracking capability must be sought.

In the present work, we propose to use (1) and extend the above RLS technique such that $P_{pl}(t)$, instead of being measured (or inferred), becomes one of the parameters to be estimated in addition to $R_L(t)$ and $C_L(t)$. A more challenging task since in order to recast (1) into a linear regression problem, the constant $P_0$ in (2) is substituted by a time-varying term ${P_0}^*(t)$:

$$y(t) \equiv P_{ao}(t) = \underbrace{\begin{bmatrix} R_L(t) & \frac{1}{C_L(t)} & {P_0}^*(t) \end{bmatrix}}_{\theta^T(t)} \underbrace{\begin{bmatrix} \dot{V}(t) \\ V(t) \\ 1 \end{bmatrix}}_{x(t)} \quad (8)$$

where, in comparison to (2), the output variable $y(t)$ is no longer $P_{tp}(t)$, and the third component of the parameter vector ${P_0}^*(t)$ now includes the constant term $P_0$ plus the time-varying term $P_{pl}(t)$. Hence, by estimating ${P_0}^*(t)$, we are actually estimating $P_{pl}(t)$ plus an offset term whose value can be obtained by evaluating (1) at the end of exhalation. Namely,

$$P_0 = P_{ao}(t_{EE}) - P_{pl}(t_{EE}) = PEEP - P_{pl}(t_{EE}) \quad (9)$$

where $PEEP$ is the positive end-expiratory pressure value and $t_{EE}$ is the end-expiratory time instant. Substituting $P_0$ back into ${P_0}^*(t)$ yields:

$$P_{pl}(t) - P_{pl}(t_{EE}) = {P_0}^*(t) - PEEP \quad (10)$$

which means that by estimating ${P_0}^*(t)$ and knowing $PEEP$ we only obtain an estimate of the intrapleural pressure variations with respect to its baseline value. Note that this does not constitute a limitation of the proposed method, as

in order to asses patients' breathing effort the baseline value of $P_{pl}$ is not required. Keeping this in mind, for simplicity, it will be assumed in the remaining part of the paper that the result of the estimation algorithm is an estimate of $P_{pl}(t)$ directly, neglecting the presence of the offset term $P_0$.

The problem we are trying to solve is hence estimating the parameter vector $\theta$, which contains 3 time-varying parameters: $P_{pl}(t)$, $R_L(t)$ and $C_L(t)$. Among these, $P_{pl}$ is certainly varying at a much different rate than the other two. $R_L$ and $C_L$ have indeed slower intra-breath variability compared to $P_{pl}$. It is well known in the literature that the conventional RLS with exponential forgetting (EF-RLS) is not suitable when the parameters to be estimated have different temporal variation rates. Using a single scalar forgetting factor $\lambda$ the algorithm applies forgetting equally over the whole parameter space. As a result, if there is a drift in one of the parameters, the same correction will be applied to all parameters, a fact that leads to overshoot or undershoot in the estimates when the parameters change at different rates. In these cases, a modification of the general RLS scheme, where the covariance matrix is scaled using a diagonal matrix with different forgetting factors corresponding to the parameters being estimated, can be more effective. This concept has already been proposed in the literature under different names [10]–[12], but to our knowledge has never been applied to lung mechanics studies. The proposed modified RLS algorithm, which in the following will be referred to as RLS with Vector-Type Forgetting Factor (VFF-RLS), is very similar to the general scheme in (4-7) and takes the following form:

$$\hat{\theta}(t) = \hat{\theta}(t-1) + G(t)n_o(t) \tag{11}$$

$$n_o(t) = y(t) - \hat{\theta}^T(t-1)x(t) \tag{12}$$

$$G(t) = \frac{P(t-1)x(t)}{1 + x^T(t)P(t-1)x(t)} \tag{13}$$

$$P(t) = \Lambda^{-1}\left(\mathbb{I} - G(t)x^T(t)\right)P(t-1)\Lambda^{-1} \tag{14}$$

where $\Lambda$ is the diagonal matrix that scales the covariance matrix $P(t)$ and contains the different forgetting factors:

$$\Lambda = \text{diag}\left[\sqrt{\lambda_1}\,\sqrt{\lambda_2}\,\sqrt{\lambda_3}\,\right] \tag{15}$$

In the next section, we will show first via simulation studies how the performances of the VFF-RLS algorithm are superior to those of the conventional RLS with EF. Finally, the potential of the proposed method will be proven using experimental data collected from a pig under mechanical ventilation.

### C. Animal Experiment

Preliminary results of our proposed technique have been obtained using experimental data collected during an animal test performed at the Pulmonary Research and Animal Laboratory of Duke University Medical Center on a 30 Kg adult male pig. The experimental protocol was approved by the local institutional committee. The pig was anaesthetized, intubated and connected to an Esprit ventilator with NM3 respiratory monitor (Philips-Respironics). Airway pressure and flow were measured at the Y-piece, between the breathing circuit and the endotracheal tube. The pressure inside the esophagus was measured using an esophageal balloon connected to a differential pressure transducer (Model PS309D, Validyne Engineering, Northridge, CA). Occlusion test was performed to assess the correct positioning of the balloon as described in [2]. Data were acquired and collected at 100Hz using a dedicated system for real-time data acquisition and computation. The test was performed for approximately 7 hours, during which the pig was subject to different ventilator modes and maneuvers. When the pig was completely anaesthetized, pressure control ventilation (PCV) and volume control ventilation (VCV) in assist/control (A/C) mode were used. When the effects of the anesthetics were vanishing, the ventilator was switched to continuous positive airways pressure (CPAP) with variable levels of pressure support (PSV).

## III. Results and Discussion

The feasibility of the proposed method was investigated via a two-stage process. In the first stage, we evaluated the performance of both the conventional EF-RLS and modified VFF-RLS estimation algorithms on simulated data. In the second stage, we evaluated the performance of the VFF-RLS algorithm on the real animal data.

### A. Algorithm evaluation on simulated data - Stage 1

A simulated airway pressure signal $\tilde{P}_{ao}$ was first generated by solving (1) and using the experimental flow ($\dot{V}$) and esophageal pressure ($P_{es}$) collected during the animal test ($P_{es}$ was used in place of $P_{pl}$ and the volume $V$ was obtained by numerical integration of the flow waveform). While solving (1) for $\tilde{P}_{ao}$, the values of $R_L$, $C_L$ and $P_0$ were kept constant and fixed to 10 $\frac{\text{cmH}_2\text{O}}{\text{L/s}}$, 0.08 $\frac{\text{L}}{\text{cmH}_2\text{O}}$ and 5 $\text{cmH}_2\text{O}$, respectively. The RLS estimation algorithm (EF or VFF) was then run according to (4-7) or (11-14), using the experimental $\dot{V}$ and $V$ to construct the input vector, $x(t)$, and the simulated $\tilde{P}_{ao}$ as output variable, $y(t)$. The resulting estimated time-varying parameters ($\hat{R}_L$, $\hat{C}_L$ and $\hat{P}_{pl}$) were finally compared with their respective true values. Note that this simulation approach is equivalent to assuming that the model fits the data perfectly without the presence of process or measurements noise. Since we want the estimation algorithm to cope with drastic variations in pleural pressure, we used as our input dataset a portion of data related to a transition between high level to low level of ventilator support. Particularly, we choose a 2-minute window (see Fig. 2) during which the pig was subject to CPAP with PSV level from 10 to 0 $\text{cmH}_2\text{O}$. As shown in Fig. 2 (see red line), when the PSV level is reduced, the shape of the esophageal pressure changes drastically due to the increase in the respiratory effort as dictated by the absence of ventilator support and reflected by negative deflections in $P_{es}$ with respect to its baseline value.

The results of the RLS with scalar EF on the above mentioned dataset are shown in Fig. 3. The value of the

forgetting factor was set to 0.95, which is in the range of values typically used in the literature. The parameter vector $\theta$ was initialized to 0, assuming that no prior knowledge about the true parameter values is available, and the covariance matrix $P$ was initialized to $10^6 \cdot \mathbb{I}$ to reflect the low confidence in the initial parameter guess. To quantitatively assess how well the model fits the data, the coefficient of determination (CD) was computed as:

$$CD = 1 - \frac{SSR}{\sum_i \left(y(i) - \overline{y}\right)^2} \tag{16}$$

where $\overline{y}$ represents the mean value of the real output variable and $SSR$ is the sum of squared residuals between the real output, $y(t)$, and the model predicted output, $\hat{y}(t)$. Results (Fig. 3) show that despite the small amplitude in the residuals, and hence the high value of CD (0.9771), large breath-by-breath fluctuations in $\hat{R}_L$ and $\hat{C}_L$ and poor matching of the $P_{pl}$ waveform are obtained. Further tuning of the forgetting factor did not improve the results: it was observed that by decreasing $\lambda$, the accuracy of the fit improved and hence the value of CD increased, but at the same time the level of fluctuation in the parameter estimates also increased. As mentioned in the $Methods$ section, we believe that the poor performance of the RLS with EF is essentially due to the inadequacy of the estimation algorithm to cope with parameters that change at different rates.

On the other hand, the results of the VFF-RLS algorithm on the same dataset, shown in Fig. 4, clearly prove the superior performances of the modified RLS algorithm. The coefficient of determination is still high (CD=0.9762) , the amplitude of the residuals is comparable with the results obtained using the conventional EF-RLS algorithm, but the large variations in the estimated resistance and compliance that characterize the results of the previous algorithm are no longer present. Furthermore, small biases in $\hat{R}_L$ and $\hat{C}_L$, compared to their true values, and good matching of the pleural pressure signal are observed. The values of the different forgetting factors $\lambda_i$ were chosen in order to maintain small residuals and keeping in mind that the parameters that change the most need to be assigned smaller forgetting factors. Particularly, the results in Fig. 4 were obtained using $\lambda_1$=0.9999, $\lambda_2$=0.9999 and $\lambda_3$=0.85. They show that the introduction of the diagonal matrix $\Lambda$ in the RLS formulation allows for tracking of parameters that change at different rates and, more importantly, of a highly time-varying signal such as $P_{pl}$.

### *B. Algorithm evaluation on real data - Stage 2*

The performances of the VFF-RLS algorithm were finally evaluated on the real data without using the simulation approach described in the previous section. In this case, the experimental airway pressure signal ($P_{ao}$) was used as output for the estimation algorithm, flow ($\dot{V}$) and volume ($V$) were used as input and the resulting estimated pleural pressure signal ($\hat{P}_{pl}$) was compared to the esophageal pressure measurements ($P_{es}$) collected during the animal test. To account for the presence of the offset in the estimated $P_{pl}$ signal

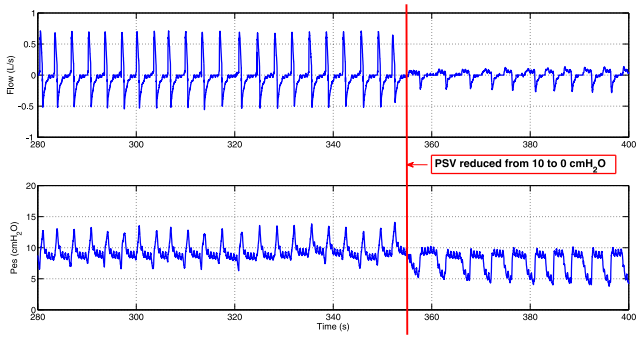


Fig. 2. Flow and esophageal pressure data used to test the estimation algorithm.

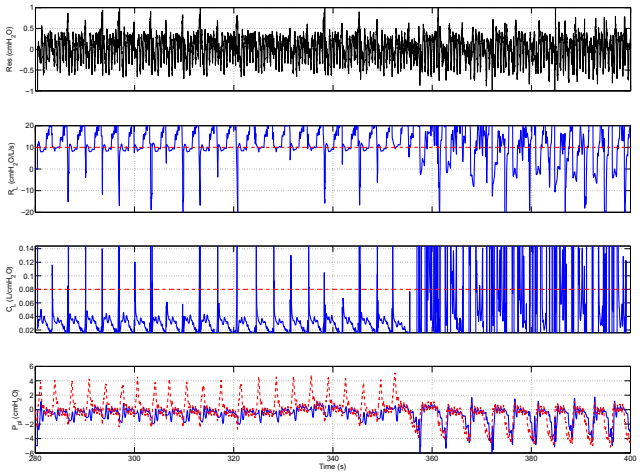


Fig. 3. Stage 1 results: EF-RLS algorithm on simulated data. Estimation residuals (Res) are shown in the top plot. Estimated (blue continuous line) versus actual (red dotted line) parameters are shown in the remaining bottom plots.

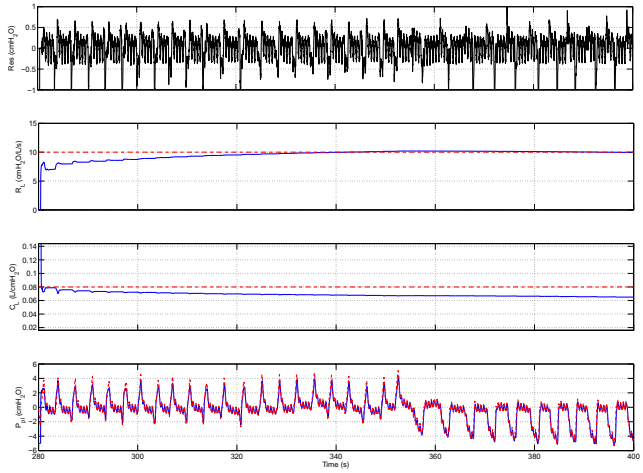


Fig. 4. Stage 1 results: VFF-RLS algorithm on simulated data. Estimation residuals (Res) are shown in the top plot. Estimated (blue continuous line) versus actual (red dotted line) parameters are shown in the remaining bottom plots.

(see $Methods$ section), the baseline value was subtracted from $P_{es}$. The forgetting factors $\lambda_i$ were given the same values used in the simulation study. Results related to the same dataset considered in the previous section are shown

in Fig. 5. Compared to the results from the simulation study, the residuals appear to be more deterministic, reflecting the fact that the error term $w(t)$ in (3) is not simple white noise. This contradicts the general Least Square assumptions and suggests that the simple first-order lung mechanics model is not able to explain the data very accurately. This is certainly due to the simplicity of the model and the fact that the real lungs are far from being a simple resistance-compliance model. Nevertheless, the coefficient of determination is still high (CD=0.9716) and the estimated parameters appear to make sense. Particularly, the estimated $R_L$ and $C_L$ converge over time to values within the normal physiological ranges and, more importantly, the estimated $P_{pl}$ signal matches quite well the experimental esophageal measurements, even when the transition in the PSV level changes the shape of the real signal. The accuracy of the proposed algorithm in tracking the pleural pressure signal is reflected by the low value of Root Mean Square Error (RMSE) between the estimated $P_{pl}$ and the experimental $P_{es}$: RMSE=0.8904 $cmH_2O$, corresponding to 8.7% of the range of the measured signal.

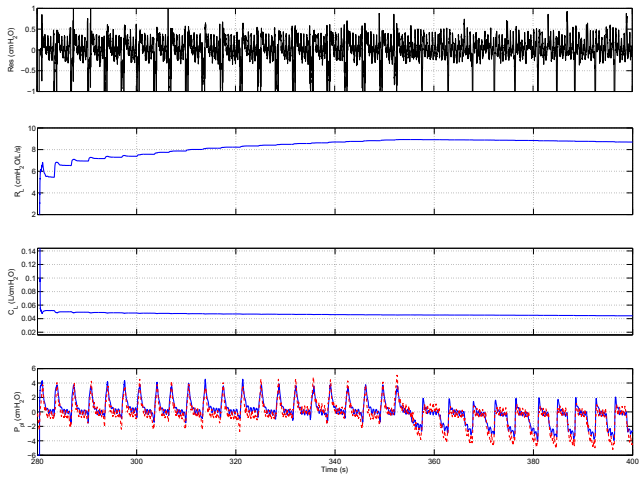


Fig. 5. Stage 2 results: VFF-RLS algorithm on real data. Estimation residuals (Res) are shown in the top plot. Estimated lung resistance and compliance are shown in the middle plots. Estimated $P_{pl}$ (blue continuous line) versus measured $P_{es}$ (red dotted line) is shown in the bottom plot.

## IV. Conclusion

The results of this study suggest that a simple first order lung mechanics model with RLS technique can achieve simultaneous estimation of intrapleural pressure, lung resistance and lung compliance in mechanically ventilated patients, provided airway pressure and flow are available. These are routinely monitored non-invasively when using a ventilator. Hence, our findings demonstrate the feasibility of a novel method for continuous real-time noninvasive estimation of intrapleural pressure without requiring additional instrumentation.

The superiority of the VFF-RLS algorithm, against the conventional EF-RLS algorithm, was proven via a two-stage validation process performed using simulated and real animal data.

However, despite these promising preliminary results, several limitations exist and will be object of further investigation. First, the estimation algorithm is very sensitive to the value of the forgetting factors. Optimal values for $\lambda_i$ have been selected by trial and error for the specific dataset used in this study and this does not guarantee the algorithm giving satisfactory results on different datasets. Furthermore, the results presented pertained only to one dataset, obtained from a single animal under specific ventilator mode and settings. Hence, the performance of the algorithm will need to be evaluated on multiple datasets from multiple subjects (animals or humans) spanning a wider variety of ventilator modes and settings. Also, changing the initial conditions of the parameter vector $\theta$ and covariance matrix $P$ will change the convergent behaviour of the estimation algorithm. A rigorous sensitivity analysis need be performed in order to quantify the effects of these design variables on the estimator's performance. Finally, it would be interesting to evaluate the capability of the algorithm not only to track the fast variations of $P_{pl}$ but slower changes in $R_L$ and $C_L$ as well. To this end, further animal testing using techniques to alter the mechanical properties of the lung in a predictable way during the experiment (such as saline washing and methacoline/histamine challenges) is envisioned.

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