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Functional Residual Capacity Predictions through Three Personalized Basis Functions in a Virtual Patient Model for VCV

Trudy Caljé-van der Klei*; Qianhui Sun; Cong Zhou*; Geoff Chase*; Thomas Desaive****

**Department of Mechanical Engineering, Centre for Bio-Engineering, University of Canterbury, New Zealand (e-mail: trudy.calje-vanderklei@pg.canterbury.ac.nz; geoff.chase@canterbury.ac.nz; cong.zhou@canterbury.ac.nz)*

***University of Liege, Liege, Belgium (e-mail: qianhui.sun@uliege.be; tdesaive@uliege.be)*

Abstract: The current approach to invasively mechanically ventilating a patient is generalized, and determining a patient-specific positive-end-expiratory-pressure (PEEP) is not standardized. This raises issues not only around the efficiency of ventilation but the safety of such. The inclusion of recruitment maneuvers with subsequent PEEP in mechanical ventilation has proven highly effective in recruiting lung volume and preventing alveolar collapse. The introduction of patient-specific, personalized monitoring enables a more appropriate delivery of ventilation that evolves as the patients condition does. In this study, function residual capacity has been analysed using hysteresis loop analysis (HLA) and three separate potential basis functions, Exponential (EXP), Parabolic (PARA) and Cumulative (CUMU). These basis function sets were compared based on their performance in predicting functional residual capacity (V_{frc}). Additional components of lung mechanics have been previously analysed and compared, however this particular study prioritized the accuracy of V_{frc} predictions. Data was provided from the McREM trial which spanned across 19 patients and 7 different baseline PEEP levels ranging from 0 cmH_2O through 12 cmH_2O. Up to 6 prediction steps were analysed from each baseline PEEP to determine the accuracy across a range of information yielding 623 cases. The results showed that all three basis function sets displayed the highest R^2 values for cumulative prediction steps 1-6. All three had a final R^2 of 0.84, however the PARA set showed higher R^2 over each prediction step, yielding it the most efficient as the higher PEEP levels are the more clinically relevant ones for invasive mechanical ventilation (IMV).

Keywords: Digital Twin, Virtual patient, Mechanical ventilation, critical care, prediction, identification

1. INTRODUCTION

Ventilator induced lung injury (VILI) is caused due to suboptimal ventilation of a patient resulting in the overdistension of the lungs. This type of injury is unintended and is often a result of overloaded ventilator support (high driving pressures or delivered volume) causing over-inflation of the alveoli (Bugedo, Retamal and Bruhn, 2017; Tonetti *et al.*, 2017). This type of injury increases the duration of invasive mechanical ventilation (IMV) alongside, additional health complications and mortality (Major *et al.*, 2018). Protective mechanical ventilation (MV) strategies have proven effective in limiting tidal volumes and driving pressures (Arcelo *et al.*, 1998). The inclusion of patient-specific IMV strategies could significantly advance care and improve the outcomes of ventilator complications by using models and evolve as a patients condition does.

There are current models that are effective in capturing lung mechanics, however few can accurately predict pulmonary response over different PEEP and ventilator modes/types. Alongside this, no standardised patient-specific MV strategies are available for clinicians to use that are effective in accurately predicting the optimal PEEP for an individual.

There is a variety of mechanical ventilation types and modes, each having a different set of parameters and risks to consider. Though there are various modes and types of MV, this study analysed IMV using volume controlled ventilation (VCV). This specific type of ventilation sets the patients tidal volume by controlling the flow of air into the lungs.

Recruitment manoeuvres are used to open collapsed alveolar using a temporary increase in airway pressure. Following this, PEEP is set to maintain recruited lung volume and avoid lung/alveolar collapse. The addition of functional residual capacity (V_{frc}) is to also aid in this as it assists in alveolar recruitment/derecruitment. The value of V_{frc} defines the volume of air remaining in the lungs after exhalation. There are methods to accurately measure V_{frc}, such as wash in/wash out method. However, this is only available for use on specific ventilators (Turbil *et al.*, 2020). V_{frc} can also be easily influenced by MV mode and PEEP, so non-invasive, continuous estimates allow for a patient-specific approach to treatment including lung recruitment modelling.

Basis functions have been used and proven effective for modelling in lung mechanics (Sundaresan *et al.*, 2011; Chiew *et al.*, 2012). They can simulate and predict targeted biomedical information such as lung elastance and resistance using a linear single compartment model. This study analyses three basis functions. These were chosen based on prior work (Laufer *et al.*, 2016; Morton *et al.*, 2018, 2019) and compatibility with the identification model, hysteresis loop

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model (HLM). Though basis functions have proven accurate in predicting resistance and lung elastance, they have proven ineffective in capturing other lung mechanics characteristics in inspiration and expiration.

The main framework of this model uses a non-linear hysteresis loop model to identify and predict the evolution of lung mechanics (Zhou *et al.*, 2021). However, it was unable to comparatively analyse which basis function was most accurate.

2. METHODOLOGY

2.1 HLM

Equation 1 refers to the dynamic equation of motion of the HLM lung mechanics model.

$$M\ddot{V}(t) + R\dot{V}(t) + K_e V(t) + K_{h1}V_{h1} + K_{h2}V_{h2} = f_V(t) + PEEP \quad (1)$$

Where M is the normalised mass, R is the airway resistance, K_e represents the alveolar resistance i.e. k_2 in this approach, K_{h1} is defined as $k1 - k4$ and K_{h1}as $k2 - k4$ which are the alveolar hysteresis elastances for inspiration and expiration respectively.$V$is the volume of air delivered to the lungs where $\dot{V}$ and $\ddot{V}$ are its relative derivatives. PEEP is as previously defined and $f_V(t)$ represents a steady state input.

2.2 Identification and prediction

Hysteresis loop analysis (HLA) is used initially to identify the various elastance parameters as defined in Figure 1 $k1_1$, $k2_1$ and $k2end_1$ are all elastance parameters representing three different stages within the inspiration cycle. $k3_1$ and $k4_1$ are the defined elastances for expiration. Following this, the basis functions are then input to predict $k2_i$. Final two stages are dependent on the mode of ventilation under analysis, in this stance for VCV, $k2end_i$ and *LIP* are predicted using equations 11-14

In this study, 7 baseline PEEPs were analysed ranging from 0 cm H_2O to 12cm H_2O (2 cmH_2O increments in between each). For each one, lung mechanics were analysed up to 6 prediction steps ahead (6 x 2 cmH_2O or 12 cmH_2O) as outlined in Table 1.

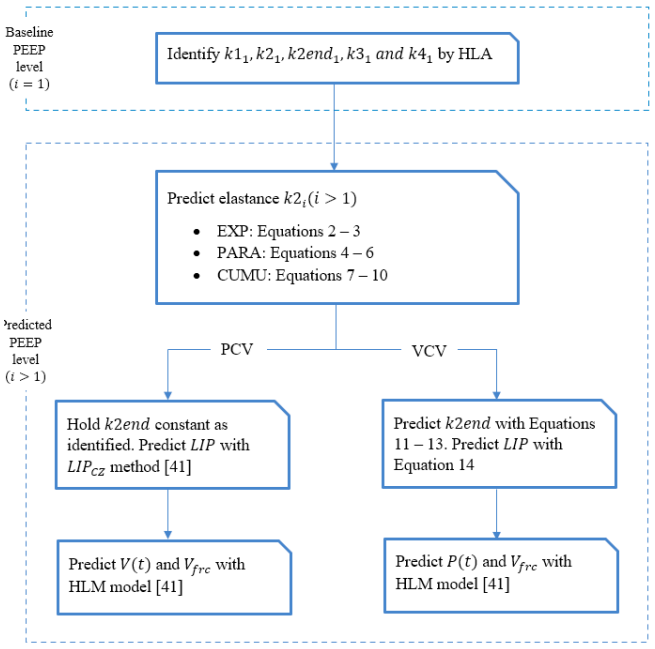


Figure 1. Identification and prediction procedure

2.3 Basis Functions

2.3.1 EXP function set

$$k2_i = \left(\frac{PEEP_i}{k1} + \frac{k2_1}{k1} * e^{b*\frac{PEEP_i}{k1}}\right) * k1 \quad (2)$$

$$b = \frac{k1}{PEEP_1} * \log\frac{k2_1 - PEEP_1}{k2_1} \quad (3)$$

EXP basis function set assumes elastance has a bowl shape across PEEP levels. Where, $k2_i$ is the elastance determined in inspiration during the highest rate of volume recruitment. $PEEP_i$ represents that of the prediction step under analysis verses $PEEP_1$ which is the baseline PEEP given during the identification process. $k1$ is the elastance determined from the initial recruitment of air during inspiration, both elastance values are measured as cmH_2O/L. Finally, b is the exponential rate of recruitment.

Table 1. Schematic representation of the identification levels (orange) and the prediction steps for the McREM trial

Test group	PEEP level [cmH_2O]									
1st	0	2	4	6	8	10	12	14	16	18
2nd	0	2	4	6	8	10	12	14	16	18
3rd	0	2	4	6	8	10	12	14	16	18
4th	0	2	4	6	8	10	12	14	16	18
5th	0	2	4	6	8	10	12	14	…	20
6th	0	2	4	6	8	10	12	14	…	22
7th	0	2	4	6	8	10	12	14	…	24

2.3.2 PARA function set

$$k2_i = \left(\frac{PEEP_i}{k1 * \beta1} + \beta2 * \left(\beta1 - \frac{PEEP_i}{k1}\right)^2\right) * k1 \quad (4)$$

$$\beta1 = 2 - \frac{\widehat{k1}}{k1} \quad (5)$$

$$\beta2 = \frac{\frac{k2_1}{k1} - \frac{PEEP_1}{k1 * \beta1}}{\left(\beta1 - \frac{PEEP_1}{k1}\right)^2} \quad (6)$$

Where, all parameters are previously defined, $\beta1$ and $\beta2$ are arbitrary parameters and $\widehat{k1}$ is the average value of alveolar elastance for the first inspiration segment, with an estimated value of 130.

2.3.3 CUMU function set

$$k2_i = \left(\begin{array}{l} \frac{\delta1}{k1} * \sum_{j=2}^{j=i} \Phi_j + \delta2 * PEEP_1 \\ * \sum_{j=2}^{j=2} \Phi_j * \sum_{j=2}^{j=3} \Phi_j * \ldots * \sum_{j=2}^{j=i} \Phi_j \end{array}\right) * k1 \quad (7)$$

$$\delta1 = \left(\frac{k2_1}{k1} - \frac{PEEP_1}{k1 - k2_1}\right) * k1 \quad (8)$$

$$\delta2 = \frac{1}{k1 - k2_1} \quad (9)$$

$$\Phi_i = \begin{cases} \left(1 + PIP_{fit_{error}}\right)^{-1} & , \quad i = 2 \\ \vartheta_1 * (PEEP_i - PEEP_{i-1}) & , \quad i > 2 \end{cases} \quad (10)$$

Φ_j, $\delta1$ and $\delta2$ which are all arbitrary parameters. $PEEP_{i-1}$ is the PEEP level from one step prior to the identified. Finally, $\vartheta_1 = 0.0087$ and $PIP_{fit_{error}} = \frac{fitted\ PIP - clinical\ PIP}{clinical\ PIP}$. All other parameters are previously defined.

2.4 k2end prediction

$$k2end_i = \left(\frac{PEEP_i}{k2_i} + \frac{k2end_1}{k2_1} * (\theta1 + (\Delta PEEP * \theta2)^2)\right) * k2_i \quad (11)$$

$$\theta1 = \frac{k2end_1 - PEEP_1}{k2end_1} \quad (12)$$

$$\theta2 = \frac{EELV_1}{PIV_1 - EELV_1} \quad (13)$$

$k2end_i$ captures any overdistension that occurs at the end of inspiration which is clinically relevant as it indicates excessive pressure and alterations required to minimise occurrence VILI. All parameters are previously defined except $EELV_1$ is the end expiratory volume and PIV_1 is the peak inspiratory volume.

2.4 LIP and V_{frc} prediction

In this approach, the lower inflection point (LIP), defined as V_{m1} in (Zhou *et al.*, 2021) and marked in Figure 1, is predicted for VCV patients (only) using an evolution equation defined:

$$LIP_i = LIP_1 * \left(\begin{array}{c} \min\left(\frac{P_r}{PEEP_{max}}, \frac{PEEP_{max}}{P_r}\right) \\ -\left(\frac{\Delta PEEP}{PEEP_{max}}\right)^2 \end{array}\right) \quad (14)$$

Where $P_r = \max(P(t)) - \min(P(t))$ at baseline $PEEP_1$. LIP prediction for PCV patients uses the procedure from(Zhou *et al.*, 2021) , named as LIP_{cz} in this approach (not shown here). V_{frc} prediction for both VCV and PCV trials is the same as presented in (Zhou *et al.*, 2021).

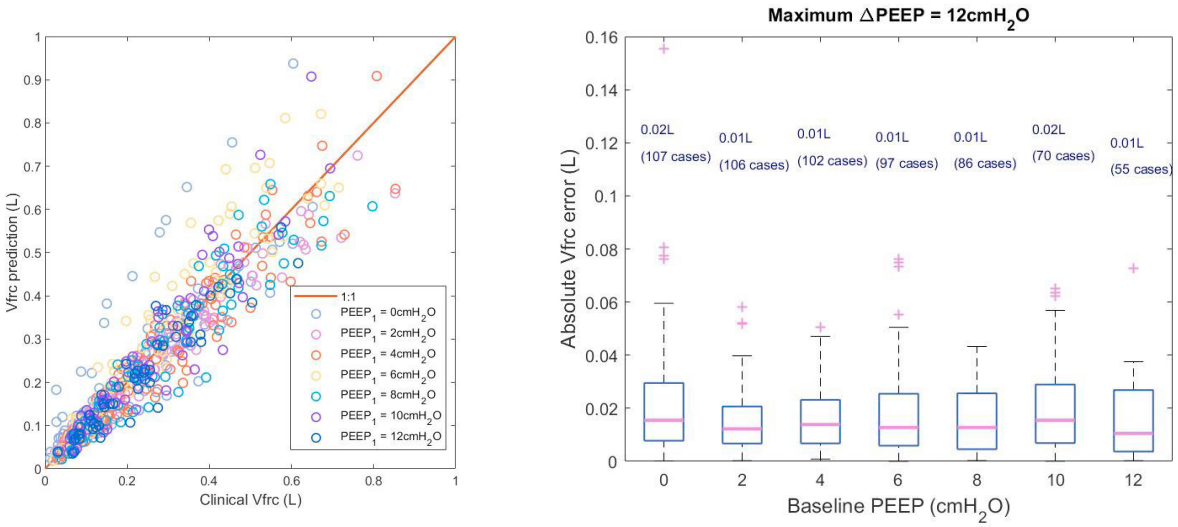
3. RESULTS

3.1 Clinical vs prediction

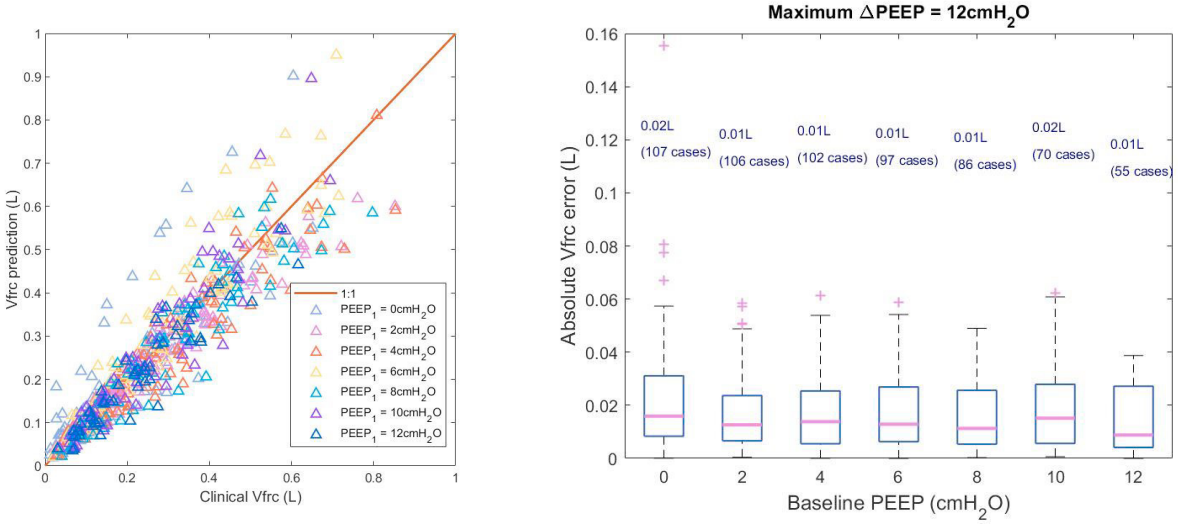
The functional residual capacity was predicted across 7 different baseline/identified PEEP levels ranging from 0 cmH_2O through to 12 cmH_2O with 2 cmH_2O increments. For each baseline PEEP level, up to 6 predictions were conducted in 2 cmH_2O increments (6 x 2 cmH_2O or 12 cmH_2O) up to a maximum difference of 12 cmH_2O. This yielded a total of 623 cases, further outlined in Table 2. Scatter plots were generated inFigure 1 (left) comparing the clinical data obtained from the McREM trial to the predicted data from the model. This is done across the three different basis function sets, (a) EXP, (b) PARA and (c) CUMU. In the same figure (right), boxplots were generated to display the absolute error from this information and the relative median errors for each baseline PEEP level across all 6 prediction steps for each.

Table 2. R^2 values across different cumulative collections of prediction steps intervals for all three basis function shapes for V_{frc} prediction from any baseline PEEP level.

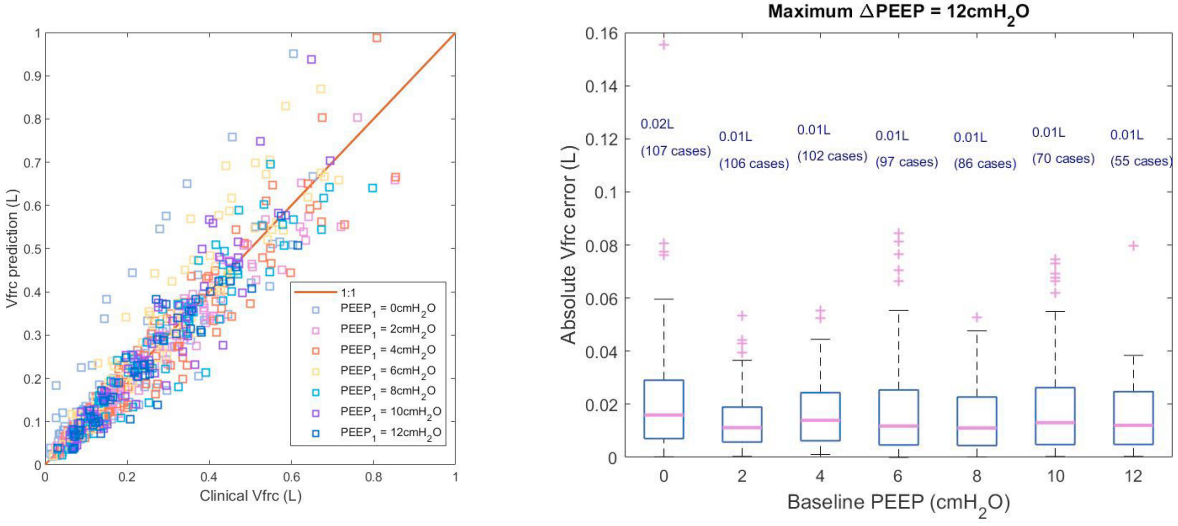
McREM trial	**R^2 value of V_{frc} prediction**			Prediction Cases
	EXP	PARA	CUMU	
1 step ahead	0.40	0.41	0.41	122
1-2 steps ahead	0.69	0.71	0.68	241
1-3 steps ahead	0.77	0.79	0.77	356
1-4 steps ahead	0.81	0.82	0.81	460
1-5 steps ahead	0.83	0.84	0.83	550
1-6 steps ahead	0.84	0.84	0.84	623



(a) EXP



(b) PARA



(c) CUMU

Figure 2. Correlation plots of clinical vs predicted Vfrc (left) and their respective boxplots (right) for absolute prediction errors including noted median errors for each across all three basis function sets (a) EXP, (b) PARA and (c) CUMU

In

Figure 2 (left), perfect match lines give a general idea of the overall correlation of the information. Further, Table 2 states the R^2 calculations for each cumulative step ahead. These

Figure 2 boxplots. From these R^2 values, it's clear that the model works more effectively as the prediction step range increases, with the highest R^2 values returning from 1-6 predictive steps ahead.

All three basis functions show similar growth in R^2 values as more cases are included, however the PARA basis function set displays a slightly higher rate of increase in these values compared to the others. From the boxplots, it is also clear that the PARA set yields the fewest amount of outliers of the three boxplots. Despite this, the EXP set yields the most stable in terms of steady median error across all 7 baseline PEEP levels where the PARA and CUMU sets both have an increased median error at baseline PEEP level 10 cmH_2O.

5. DISCUSSION

Protective MV strategies have been previously used to assist in defining more accurate and effective ventilation methods using identification manoeuvres (Arcelo *et al.*, 1998; Amato *et*

Figure 2, there is a typical trend where the lower baseline PEEP levels (namely 0 cmH_2O) predictions overshoot the clinical information. This could be due to various reasons including an issue with this particular dataset. To further understand why this occurs, the model needs to be analysed through another set of data. However, the higher baseline PEEP levels show a tighter correlation between the predicted and clinical data which is preferrable as these are our more clinically relevant PEEP levels for invasive mechanical ventilation.

Similarly, calculated R^2 values are higher with increased prediction steps. Though this is likely due to a higher number of cases allowing more corrections in the model, it is again Figure 2. However, this does not reflect on the prediction status of this model, therefore the PARA set has yielded the most accurate predictions of functional residual capacity in Figure 2.

Given the predictive accuracy across all three basis function sets, this model would be effective in aiding clinical decisions around IMV. The primary benefactor is to provide clinicians with a monitoring tool that can accurately predict the lung mechanics under various circumstances throughout the delivery of ventilation. However, before such can be implemented, further analysis must be completed to determine and resolve weak points in the model.

6. CONCLUSIONS

In this study, three basis functions were compared based on their performance in predicting V_{frc}. All three showed promise and performed relatively equally yielding a final R^2 value of

values include cases across all baseline PEEPs and analyses them as predictive steps as opposed to baseline level groups as in

al., 2015). However, few effective predictive models exist that are able to not only accurately predict initial MV states, most of which are standardized (Briel *et al.*, no date; Chase *et al.*, 2018; Major *et al.*, 2018). Alongside this, there are no active patient-specific MV modes that use the likes of digital twins to simulate lung mechanics. The introduction of such is not only critical in determining an accurate initial level of treatment but also enabling MV to accurately evolve with a patients condition through continuous monitoring and modelling. These aspects are vital in ensuring patients aren't at risk of insufficient or excessive ventilation where VILI can occur. Insufficient ventilation (low driving pressure or volume delivered) can induce risks around under inflation and collapse of the alveolar, minimising the rate of oxygen/carbon dioxide diffusion. Conversely, excessive ventilation (high driving pressures or delivered volume) incurs overdistension of the lungs, putting strain on the alveolar and risking permanent damage (Ricard, Dreyfuss and Saumon, 2003; Pavone *et al.*, 2007; Major *et al.*, 2018).

From the correlation plots in

preferable as these are the clinically relevant PEEP levels for IMV with the minimum PEEP level at the 6th prediction step = 12 cmH_2O.

Looking further into a comparison of the basis function sets, all three are operating at an effective and acceptable level displaying prediction accuracy of 84%. However, from Table 2, the PARA function set did show a higher increasing rate in the R^2 values as prediction steps increased. This correlates to the models adaptability at an earlier stage, requiring less information to achieve an accurate prediction. As previously stated, the CUMU set does have more stability in the median errors across all baseline PEEP levels as seen in

this data set. This is backed up by the fewest number of outliers seen in the boxplots in

0.84 each for all predictive steps (1-6) and across all 7 baseline PEEP levels (0 cmH_2O to 12 cmH_2O). However, the PARA set proved more effective at early prediction steps with fewer case numbers. There was also a correlation between the higher prediction steps yielding higher R^2 values. This is preferable as these higher PEEP levels are more clinically relevant to invasive mechanical ventilation. Though this study has shown promise in accurately predicting V_{frc}, it stills requires further validation by testing it through different datasets to interpret any recurring issues.

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