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Original Article

Stochastic Modelling of Respiratory System Elastance for Mechanically Ventilated Respiratory Failure Patients

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Abstract—While lung protective mechanical ventilation (MV) guidelines have been developed to avoid ventilator-induced lung injury (VILI), a *one-size-fits-all* approach cannot benefit every individual patient. Hence, there is significant need for the ability to provide patient-specific MV settings to ensure safety, and optimise patient care. Model-based approaches enable patient-specific care by identifying time-varying patient-specific parameters, such as respiratory elastance, E_{rs}, to capture inter- and intra-patient variability. However, patient-specific parameters evolve with time, as a function of disease progression and patient condition, making predicting their future values crucial for recommending patient-specific MV settings. This study employs stochastic modelling to predict future E_{rs} values using retrospective patient data to develop and validate a model indicating future intra-patient variability of E_{rs}. Cross validation results show stochastic modelling can predict future elastance ranges with 92.59 and 68.56% of predicted values within the 5–95% and the 25–75% range, respectively. This range can be used to ensure patients receive adequate minute ventilation should elastance rise and minimise the risk of VILI should elastance fall. The results show the potential for model-based protocols using stochastic model prediction of future E_{rs} values to provide safe and patient-specific MV. These results warrant further investigation to validate its clinical utility.

Keywords—Mechanical ventilation, Stochastic modelling, Respiratory mechanics, Patient-specific ventilation, Elastance, Critical care.

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INTRODUCTION

Optimal mechanical ventilation (MV) settings are patient-specific and evolve with time as treatment continues.[42] Landmark trials helped establish guidelines on optimal ranges of mechanical ventilator settings for all patients based on observational data.[7,9,43,44,61] However, a *one-size-fits-all* approach may benefit many or most patients, but may cause harm to others, failing to cater to individual patient-specific needs.[2,11,28,32,46]

Non-optimal MV settings carry high risks for patients, such as ventilator-induced lung injury (VILI), which exacerbates patient condition, inhibits or delays recovery, and in the worst case, results in organ failure.[30,56] These risks combined with patient variability require patient-specific MV settings and care. One approach is *via* personalised, model-based medicine to create adaptive protocols directly managing inter- and intra-patient variability,[14,27,42] as already emerging in other areas of care.[13,57] These methods focus on identifying a key patient-specific and clinically relevant "sensitivity" parameter at clinically relevant time intervals, and using it, and its variability, to personalise and guide care.[14]

Patient-specific respiratory system elastance, E_{rs}, is one such sensitivity,[14] and is a time-varying measure of the elastic properties of the respiratory system, capturing volume response to controlled pressure input or vice versa[65] E_{rs} thus provides insight into evolving patient condition. Before directly utilising E_{rs}, one method used to help determine the optimum positive

end expiratory pressure (PEEP) setting was by using the static pressure–volume (PV) curve. Studies showed that setting PEEP between the upper inflection point (UIP) and lower inflection point (LIP) was associated with improved survival among patients.[1,66] However, obtaining the static PV curve of each individual patient is cumbersome, requires patient sedation, and is a significant interruption to patient care.[42] Thus, many works have recommended patient-specific MV settings based on E_{rs} or a surrogate.[10,18,47,49,58,70] In fact, the work of Goligher *et al.*[32] most recently showed low tidal volume ventilation strategies resulted in significantly different mortality benefits based on patient-specific E_{rs}. This important outcome indicates the clear potential to optimise MV based on individual, time-varying patient-specific elastance, E_{rs}. Hence, identifying minimum E_{rs} through model-based methods can potentially provide the means to non-invasively assess patient lung condition without increased risk or clinical workload.[10,14,16]

However, E_{rs} evolves significantly with time, patient condition, and ventilator settings, such as PEEP.[8,17,47,69] A better understanding of the variability of E_{rs} between patients and over time is vital to enable selection of optimal patient-specific MV settings at any current time. Ideally, a deterministic model capturing the entirety of pulmonary mechanics would allow accurate prediction of future lung parameters, if it was accurate and able to be identified, neither of which has been demonstrated due identifiability and validation issues.[14] Equally, lack of information results in unavoidable simplifications.[55] This missing data can manifest as unpredictable variability, which cannot be ignored.[21] To this end, stochastic modelling might hold the solution by grouping indeterminable randomness into a stochastic variable to provide a better picture of system, which has become an increasingly preferred tool to describe biological dynamics.[21,68] Clinically, one and two variable stochastic models have demonstrated clinical impact and potential in managing variability in glycemic control in the intensive care unit.[22,39,41]

Finally, E_{rs} has shown to vary significantly with patient condition and ventilator settings.[9,17,44] Hence, the idea of incorporating a stochastic model to predict future respiratory system mechanics could be explored to potential benefit. In this research, we aim to investigate the feasibility of a stochastic model to capture the variability of mechanically ventilated patients' respiratory system elastance. Specifically, the stochastic model used in this study is generated *via* model-based estimated respiratory elastance from airway pressure and flow data of 24 mechanically ventilated patients. This research will provide potential insight to the viability of using a stochastic model to predict fu-

ture elastance variation, which can be pre-calculated for computational simplicity to ensure effective, potential clinical implementation. Such an accurate, validated stochastic model could enable risk-based, patient-specific care, as seen in glycemic control.[57,64]

METHODS

The Single Compartment Linear Lung Model

The single compartment linear lung model is the most commonly used model to describe mechanically ventilated patient respiratory mechanics[65]:

$$P_{aw}(t) = E_{rs}V(t) + R_{rs}\dot{V}(t) + P_0 \qquad (1)$$

where P_{aw} represents the airway pressure (cmH_2O), V represents the volume of air delivered to the lungs (L), $\dot{V}$ is the air flow delivered by the ventilator (L/s) and P_0 is the offset pressure (cmH_2O) or positive end-expiratory pressure (PEEP) applied by the ventilator if there is little or no intrinsic PEEP.[65] Respiratory system elastance (cmH_2O/L) and respiratory system resistance (cmH_2Os/L) are represented by E_{rs} and R_{rs}, respectively.

Airway pressure, flow and volume can be used to identify E_{rs} and R_{rs} using integral-based parameter identification[17,26,53] in an identifiable problem,[25] where E_{rs} is defined as the average elastance of a single breath.[16]

Patient Data and Processing

This study used the airway pressure-flow data from 24 MV patients prospectively recruited at the International Islamic University Malaysia (IIUM) Medical Centre as part of an observational study under informed consent.[15] Ventilator data was recorded using the CURE soft system[59] connected to a Puritan Bennet PB980 ventilator (Covidien, Boulder, CO, USA). Airway pressure (cmH_2O) and flow (L/min) are recorded at a sampling rate of 50 Hz. The collection and use of this data is approved by the IIUM research ethics committee (Ethics Approval Number IREC666).

Recorded data is separated into individual breaths. To mitigate small fluctuations in data, breath filtering criteria are included to ensure an individual breath is a full breath. The criteria are based on the work of Kim *et al.*,[35] modified to suit the adult cohort in this research, and defined for each breath:

- Start of inspiration is defined as the first overall increase in flow (flow rate > 0.1 L/s) and pressure (Pressure $> $ (PEEP $+ 2$ cmH_2O)). Data is checked

over the next 8 data points (0.16 s) to ensure constant positive flow.
- Start of expiration is defined as the first overall decrease in flow (flow rate < -0.1 L/s). Data is checked over the next 8 data points to ensure constant negative flow.
- Peak Inspiratory volume reaches a significant value (Peak inspiratory volume > 40 mL which is $\sim 10\%$ of typical tidal volume).
- Peak Inspiratory Pressure (PIP) is in the inspiratory phase and is of significant value (PIP $>$ (PEEP $+ 1$ cmH$_2$O), where typical PIP is $\sim$ PEEP $+ 10$–14 cmH$_2$O).
- Expiration is detected within 4.125 s of calculated onset of inspiration as defined above, matching the expected respiratory rate in this cohort.

Lower boundaries for typical values for tidal volume and maximum flow rate are roughly 400 mL and 60 L/min respectively.[34,67] As for PIP, which is essentially the inspiratory pressure setting in addition to PEEP, typical values for inspiratory pressure vary greatly depending on patient condition and clinician preference, with the general aim of keeping plateau pressures under 30 cmH$_2$O. Thus, some guidelines recommend initial inspiratory pressure settings as low as 5–10 cmH$_2$O.[4] To help filter noise and fluctuating data, 10% of these values are used as the threshold to define what constitutes a 'true' breath. Hence, 10% of 400 mL (40 mL), 60 L/min (6 L/min) and 10 cmH$_2$O (1 cmH$_2$O) are listed as these criteria, which set very low thresholds and thus exclude relatively few breaths while ensuring those breaths captured are not influenced by partial breaths or coughs and asynchrony.

While recording, patients can exhibit asynchronous events or patient effort during breathing. These asynchronous breaths do not accurately reflect the underlying patient-specific pulmonary mechanics as the pressure and flow waveforms are distorted.[19,20] As this study aims to capture the underlying patient-specific pulmonary mechanics, breaths considered asynchronous are eliminated. As the previously mentioned, the criterion defining a 'true' breathing cycle are generally lenient, and additional criteria are added to further filter noise and asynchronous breathing cycles, which may obscure the process of obtaining the respiratory system elastance. These further criteria indicating an asynchronous breath are also based on the work of Kim *et al.*,[35] and defined:

- Median model-fit error for a breathing cycle $> 15\%$
- Model-based estimated $E_{rs} \leq 0$

- Model-based estimated E_{rs} outside 5th and 95th percentile of collected patient-specific data for that patient

Model-fit for the first criteria is calculated using the median absolute percentage error (APE) between the model's estimated airway inspiration pressure (P_{sim}) and measured airway inspiration pressure (P_{mea}) shown in Eq. 2. Note, P_{sim} is calculated using the identified model-based E_{rs}. If P_{mea} deviates from P_{sim} too much, its *APE* will exceed the threshold, indicating too

$$\text{APE} = \text{Median}\left(\left|\frac{P_{sim_i} - P_{mean_i}}{P_{sim_i}}\right|\right) \times 100 \quad (2)$$

much noise or asynchrony. These breaths are thus not included in this study.

E_{rs} is identified and recorded for all remaining breaths, and averaged into mean values over clinically relevant intervals, $E_{rs,N}$, where N is a selected time interval. For this research, N is arbitrarily chosen as 10 min as a clinically relevant proof-of-concept, and this interval could be varied or changed. The E_{rs} data is then sorted into data pairs over this interval of $E_{rs,N}$ and the subsequent interval, $E_{rs,N+1}$. Thus, $E_{rs,N}$ defines the mean respiratory elastance of the current 10-min interval, and $E_{rs,N+1}$ defines the mean respiratory elastance of the next subsequent 10-min interval. These data pairs across all time sampled, and across all patients, form the basis of the stochastic model. This process is illustrated in Fig. 1.

Stochastic Model Development

Stochastic modelling is used to approximate potential outcomes for a process showing a random element. To deal with stochastic processes, probability densities can be created by recording stochastic variables as a function of time.[55] In this research, a stochastic model of $E_{rs,N}$ against $E_{rs,N+1}$ is developed. This stochastic model uses conditional kernel density estimation.[5,23] $E_{rs,N}$ is assumed to be a Markov process, in which the probability distribution of future values of $E_{rs,N}$ can be predicted given the current $E_{rs,N}$ value only and no past values of E_N are required.[55] This situation is defined:

$$P\left(E_{rs,N+1}|E_{rs,1}, E_{rs,2}, E_{rs,3}\ldots E_{rs,N}\right) = P\left(E_{rs,N+1}|E_{rs,N}\right) \quad (3)$$

According to Bayes Theorem, the conditional probability has the following property:

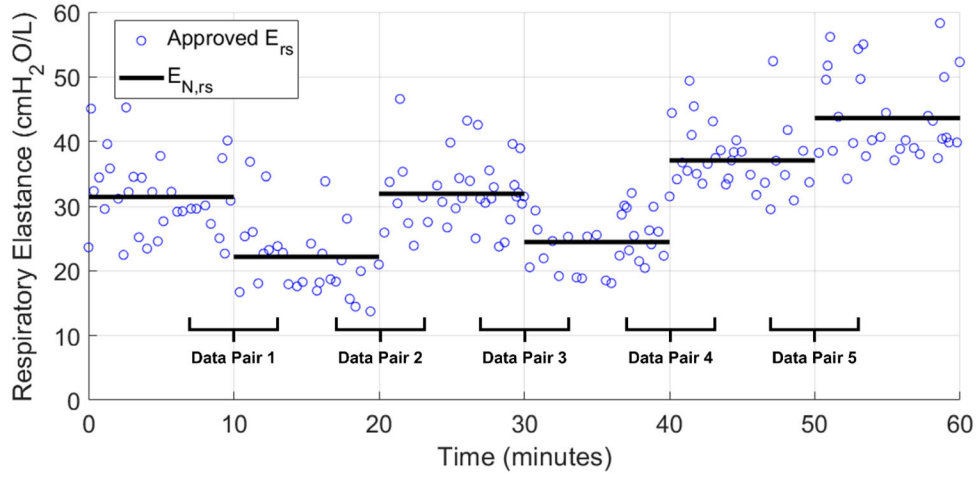$$P(A|B) = \frac{P(A,B)}{P(B)} \quad (4)$$

FIGURE 1. Simplified illustration of the obtaining $E_{N,rs}$ from the approved breaths and sorting into data pairs.

Hence, $P(E_{rs,N+1}|E_{rs,N})$ can be written:

$$P\left(E_{rs,N+1} = x|E_{rs,N} = y\right) = \frac{P\left(E_{rs,N+1} = x, E_{rs,N} = y\right)}{P\left(E_{rs,N} = x\right)}$$

(5)

Equation 5 is the conditional probability function that provides the stochastic information on the potential variation of E_{rs} which can be obtained using kernel density estimation.[33] This specific technique of computing conditional probability was adopted from the work of Lin *et al.*[40] where this technique was first used to create a stochastic model of insulin sensitivity variation. The right-hand side numerator of Eq. 5 is the kernel density estimated joint probability $P(x,y)$ and can be calculated using the available patient data:

$$P(x,y) = \frac{1}{n}\sum_{i=1}^{n}\frac{\phi\left(x;x_i,\sigma_{x_i}^2\right)}{p_{x_i}}\frac{\phi\left(y;y_i,\sigma_{y_i}^2\right)}{p_{y_i}}$$

(6)

where

$$p_{x_i} = \int_{0}^{\infty}\phi\left(x;x_i,\sigma_{x_i}^2\right)$$

(7)

$$p_{y_i} = \int_{0}^{\infty}\phi\left(y;y_i,\sigma_{y_i}^2\right)$$

(8)

and x_i and y_i are the coordinates of each E_N data pair which can be seen later in Fig. 5a. Each $\phi(x;x_i,\sigma^2_{x_i})$ and $\phi(y;y_i,\sigma^2_{y_i})$ is a normal probability distribution function centred at a corresponding x_i and y_i. Equations 7 and 8 are used to ensure that the probability distributions are properly normalised, where p_{x_i} and p_{y_i} represent the area under each normal distribution between zero and infinity and are therefore chosen to be non-negative.

The right-hand side denominator of Eq. 5 can be calculated by obtaining the marginal probability of $P(x)$ from $P(x,y)$ and is done by integrating Eq. 6.

$$P(x) = \int P(x,y)\mathrm{d}y$$

$$= \frac{1}{n}\sum_{i=1}^{n}\frac{\phi\left(x;x_i,\sigma_{x_i}^2\right)}{p_{x_i}}\int\frac{\phi\left(y;y_i,\sigma_{y_i}^2\right)}{p_{y_i}}\mathrm{d}y$$

(9)

$$= \frac{1}{n}\sum_{i=1}^{n}\frac{\phi\left(x;x_i,\sigma_{x_i}^2\right)}{p_{x_i}}\cdot 1$$

Thus, Eq. 5 can be calculated from Eqs. 6 and 9:

$$P\left(E_{rs,N+1} = x|E_{rs,N} = y\right) = \frac{\sum_{i-1}^{n}\left(\frac{\phi\left(x;x_i,\sigma_{x_i}^2\right)}{p_{x_i}}\right)\left(\frac{\phi\left(y;y_i,\sigma_{y_i}^2\right)}{p_{y_i}}\right)}{\sum_{j=1}^{n}\frac{\phi\left(x;x_j,\sigma_{x_j}^2\right)}{p_{x_j}}}$$

(10)

Hence Eq. 10 defines the two-dimensional kernel density estimation for the conditional variation of E_{rs} where E_{rs} depends on its own prior state. Thus, knowing E_{rs} at any given interval N ($E_{rs,N} = x$), the probability of E_{rs} at interval $N+1$ ($E_{rs,N+1} = y$) can be calculated from Eq. 10. A further step-by-step description of how $P(y|x)$ is computed can be found in the work of Lin *et al.*[40]

Once $P(E_{rs,N+1}|E_{rs,N})$ is generated using kernel density estimation, it can be plotted and presented as a stochastic model of elastance variability. Subsequently, the 5th, 25th, 50th, 75th and 95th percentiles lines can be plotted. These percentile lines represent the probability interval for potential $E_{rs,N+1}$ values. The stochastic model then can be used as a look up table to predict a potential range of $E_{rs,N+1}$ values given the

current $E_{rs,N}$ value, and these ranges can be subsequently used to assess the potential and risk of changes in MV settings and care. Limits of the generated model have been chosen to be 10–100 cmH$_2$O/L, based on ranges reported in a range of clinical literature[7] and the data provided from this patient cohort.

Model Validation

Model development from data requires both self-validation for the best case result, and cross-validation to assess the likely performance and ensure the model is robust to the amount of data and patients used. First, the self-validation process is summarised:

1. Build a stochastic model from all data.
2. Generate probability intervals of potential interval elastance ($E_{rs,N+1,sim}$) from the identified $E_{rs,N}$ values using the developed stochastic model.
3. Compare predicted $E_{rs,N+1,sim}$ probability intervals with actual $E_{rs,N+1}$ measurements.

The data used to create the model is also the same data as used to test it, providing a best-case estimate.

Second, a 5-fold cross validation is employed, which separates the model creation data and model test data. Data from the entire cohort is randomly divided into 5 groups with approximately equal numbers of data pairs. A stochastic model is then created with 4 of the 5 groups (training sets) with the remaining independent data group is the test set used for validation. This approach creates five validation tests using independent data. Variable outcomes in cross validation would indicate the amount of data used is potentially too low or reliant on specific patients. A schematic of the cross-validation process is shown in Fig. 2.

For each test, the percentage of predictions within the 25–75th percentile range and those within the 5–95th percentile range are compared to the ideal values of 50% and 90%. A good model will have results near the ideal values. Consistency across test sets in cross-validation will also validate the amount of data used as appropriate.

RESULTS

Patient Demographics, Breath Data, and Model-Based Lung Mechanics

From a total of 2,086,646 breaths, 2,000,140 (95.85%) were identified as true breaths and 1,671,519 (80.1%) remain after filtering asynchronous breaths (19.9% asynchrony rate). Individual patient details and demographics are presented in Table 1. Figure 3 shows example breaths failing the initial true breath criteria, while Fig. 4 shows examples of breaths meeting all criteria.

Stochastic Model

After 10-min averaging, a total of 10,218 values of $E_{rs,N}$ were obtained, yielding 10,071 pairs of ($E_{rs,N}$, $E_{rs,N+1}$). Table 1 shows the number of data pairs contributed by each patient. Figure 5a shows the collected mean elastance data sorted into pairs of $E_{rs,N}$ and $E_{rs,N+1}$. Figure 5b shows the conditional probability density created from the data. The resulting stochastic model for interval elastance is shown in Fig. 5c, and can be now be used as a look-up table to predict future elastance values, as illustrated in Fig. 5d. The coloured lines in Figs. 5b and 5c represent the Nth percentile for the $E_{rs,N+1}$ given $E_{rs,N}$. For example, in Fig. 5d, if $E_{rs,N} = 50$ cmH$_2$O/L, the values of $E_{rs,N+1}$ over the 5th to 95th probability interval are 44.0–54.5 cmH$_2$O/L, while the 25th to 75th probability interval covers the range 47.6–51.2 cmH$_2$O/L. Figure 5e shows

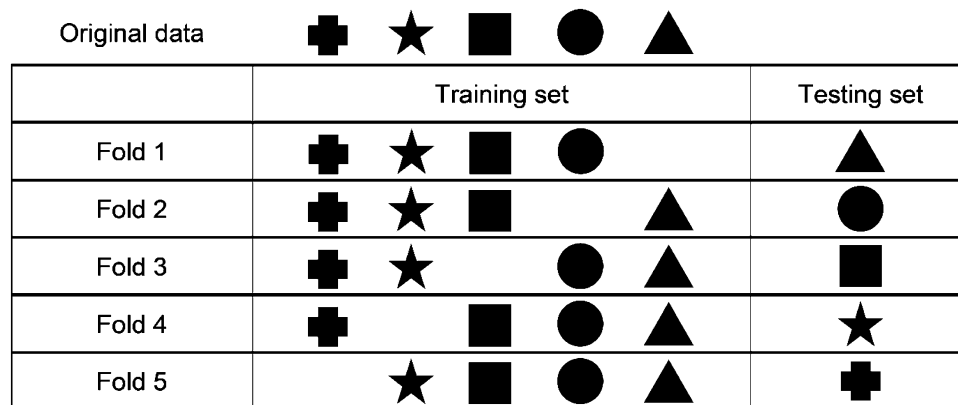|	Training set				Testing set
Original data	✚ ★ ■ ● ▲				
Fold 1	✚	★	■	●	▲
Fold 2	✚	★	■	▲	●
Fold 3	✚	★	●	▲	■
Fold 4	✚		■ ● ▲		★
Fold 5		★	■ ● ▲		✚

FIGURE 2. Illustration of 5-fold cross validation with five groups delineated by shapes and the combinations used in 5-fold cross validation of model creation and independent test sets.

TABLE 1. Patient demographics and data summary, including identified elastance and resistance values.

Patient	Gender	Age	Hours of recording	Number of readings	Number of breaths	Number of breaths after filtering	Number of E_N data pairs	Median [IQR] E_{rs} (cmH$_2$O/L)	Median [IQR] R_{rs} (cmH$_2$Os/L)	Median [IQR] APE (%)
1	F	43	168	236,400	233,452	188,980	850	38.7 [31.7–46.4]	5.7 [1.5–7.1]	4.0 [2.5–6.7]
2	M	54	59	61,790	58,160	50,360	343	21.2 [16.4–69.0]	11.0 [2.0–14.0]	1.7 [0.9–2.8]
3	M	52	44	46,070	45,508	40,864	259	54.8 [49.9–60.1]	20.4 [18.6–21.7]	7.0 [3.9–8.0]
4	M	64	20	21,289	21,234	19,038	117	29.1 [26.6–32.0]	12.2 [9.9–13.8]	2.5 [1.5–3.9]
5	F	63	139	152,474	151,141	112,056	811	29.0 [23.9–36.4]	7.3 [5.8–8.5]	2.8 [2.3–3.6]
6	F	73	5	6,054	4,922	3,571	29	10.1 [6.5–14.3]	16.7 [14.4–18.9]	4.8 [3.7–6.3]
7	F	64	34	38,869	38,435	29,401	199	21.6 [15.8–28.4]	10.2 [8.6–12.3]	2.6 [1.8–3.7]
8	M	48	35	36,987	35,459	26,498	209	33.6 [26.8–39.1]	5.9 [3.8–10.7]	2.9 [1.8–5.0]
9	M	42	5	19,200	18,689	16,409	117	27.4 [22.3–33.2]	6.8 [4.7–8.8]	4.0 [2.7–5.4]
10	F	60	3	2,901	2,746	2,308	21	11.8 [9.0–16.9]	9.2 [7.6–10.5]	2.1 [1.4–3.4]
11	M	64	3	86	809	445	3	21.3 [16.4–28.1]	10.0 [6.0–20.9]	3.7 [3.0–4.8]
12	M	74	3	3,636	3,535	1,933	12	19.5 [12.1–27.0]	6.2 [5.1–13.5]	3.3 [1.9–8.8]
13	M	63	14	13,213	13,061	10,278	57	29.9 [25.8–34.2]	7.9 [6.3–12.3]	2.7 [2.1–4.4]
14	M	53	49	38,911	38,467	33,370	293	21.1 [19.0–23.3]	8.1 [6.7–9.8]	1.1 [0.6–2.4]
15	F	62	55	83,388	82,362	72,987	323	47.7 [39.8–56.0]	4.9 [3.7–6.5]	1.4 [0.9–2.2]
16	F	34	112	120,179	118,826	103,280	664	31.4 [24.1–39.8]	7.3 [6.1–10.9]	2.0 [0.9–3.9]
17	M	43	42	52,963	52,195	45,076	247	22.7 [19.8–35.3]	10.5 [9.2–12.3]	2.7 [1.8–4.5]
18	F	61	64	62,150	58,912	52,594	388	37.2 [30.6–42.3]	11.4 [8.5–15.3]	2.0 [1.3–3.3]
19	M	48	303	368,703	362,283	298,839	1,795	41.4 [29.8–48.6]	6.9 [5.8–9.2]	2.0 [1.5–2.9]
20	F	53	156	216,992	215,992	194,099	923	38.3 [32.9–45.3]	10.4 [5.2–12.3]	2.2 [1.7–2.8]
21	F	65	119	169,658	116,503	102,246	702	60.7 [50.4–121.9]	19.5 [18.3–74.4]	3.6 [2.9–10.8]
22	M	48	113	128,561	127,242	106,099	749	31.0 [27.4–34.4]	5.8 [4.7–7.6]	2.1 [1.5–3.3]
23	F	66	114	149,166	144,351	127,042	671	47.7 [25.2–52.1]	14.4 [13.4–15.8]	2.7 [1.8–3.9]
24	M	53	49	56,230	55,856	33,746	289	11.3 [9.8–12.9]	6.5 [4.8–10.0]	2.3 [1.9–3.0]
Overall	–	–	1,708	2,086,646	2,000,140	1,671,519	10,071	–	–	–
Median		60	49	54,597	54,026	42,970	291	36.8	8.0	2.5
[IQR]		[48–64]	[17–114]	[20,245–138,864]	[19,962–123,034]	[17,724–104,690]	[117–687]	[27.3–47.4]	[5.6–12.6]	[1.7–3.8]

*IQR – Interquartile range, APE–Model Fitting Absolute Percentage Error.
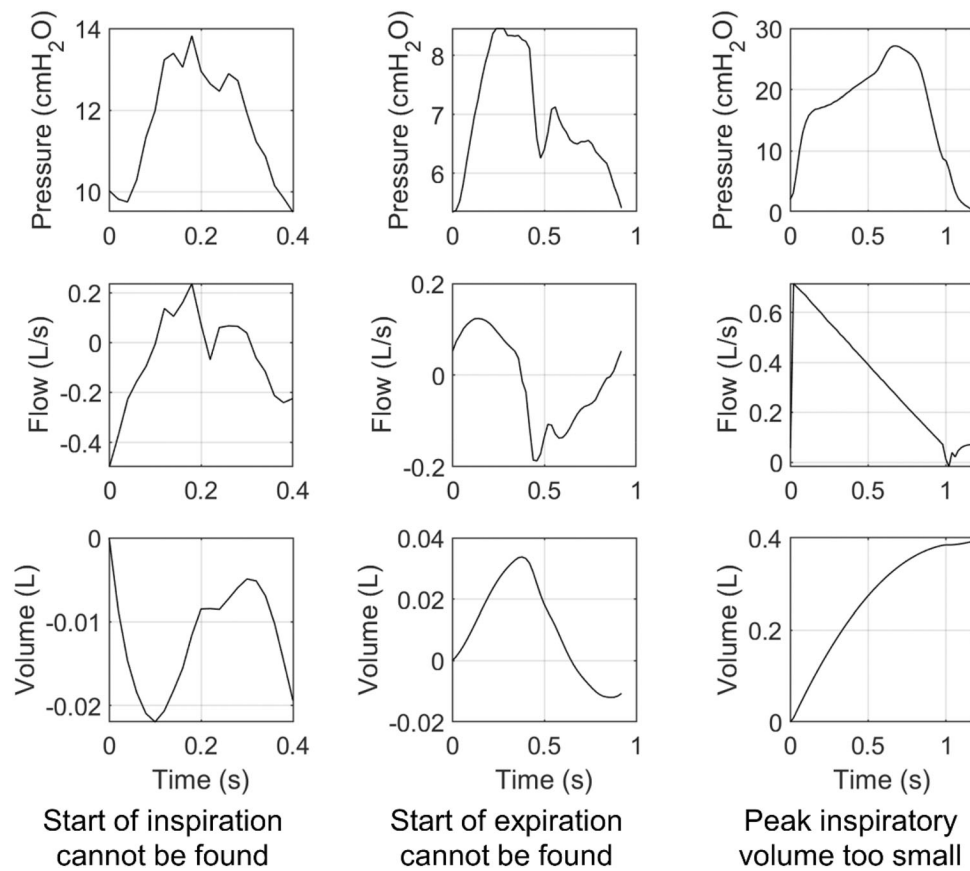
FIGURE 3. Examples of breaths that fail true breath criteria.

a cascade plot of conditional probability functions over a number of possible values of $E_{rs,N}$.

Self- and Cross-Validation

Using the stochastic model in Fig. 5c, the data pairs are self-validated against the same data for a best-case result, with results in Fig. 6. Table 2 shows the cross validation results, where the overall results, particularly for the clinically relevant 5–95th percentile range are near 90%. There is modest variability by group indicating the total amount of data might need to be larger considering the 5–95th interval results, even though these results show a very good proof of concept. The strong consistency between self- and cross-validation results shows the amount of data is more than adequate, as there is no loss in performance.

Figure 7 shows an example of the evolution of $E_{rs,N}$ over 10-min intervals, with the actual measured $E_{rs,N}$ shown by the red line and the shaded areas representing the probability intervals of probable $E_{rs,N+1}$ values generated using the developed stochastic model shown in Fig. 5c. The 5–95% range is the range between the 5th and 95th percentile prediction of $E_{rs,N+1}$ ($E_{rs,N+1,5th}$–$E_{rs,N+1,95th}$) and the 25–75%

range is the range between the 25th and 75th percentile prediction of $E_{rs,N+1}$ ($E_{rs,N+1,25th}$–$E_{rs,N+1,75th}$).

DISCUSSION

Table 1 shows elastance and resistance values for the entire cohort. The elastance values of patients vary substantially with most patient-specific E_{rs} values lying within ranges reported in literature[7,9,43] and a few having exceptionally high elastance values. The ranges show the significant inter-patient variability in lung mechanics, and the ranges per-patient show the significant intra-patient variability.

The asynchrony rate calculated using the filtering criteria is 19.9%, which agrees with manual inspection on a portion of this cohort.[15] Fluctuation, asynchronies, patient effort, and other causes of unreliable data disrupt the ability to identify accurate values of respiratory elastance and resistance. For example, for Patients 6, 11 and 12, almost half the identified breaths are removed due to unidentifiable readings or breaths with *APE* values far too high to be considered as unaffected breaths without asynchrony or patient effort. Consequently, Patient 11 is unable to contribute

any E_N data pairs as the little E_N data it has are non-subsequent. In this study, non-subsequent data occurs when either E_N or E_{N+1} is missing from the data pair. This result can arise when, within an entire interval from a mechanical ventilated patient, the breaths are noisy, asynchronous, and, as a result, none have passed the filtering criteria. Hence, a data pair cannot be formed, which typically occurs due to significant patient effort occurring for an extended period, or intermittent and limited breath data due to technical difficulties. Furthermore, data collection for Patients 9 to 13 was intermittent due to a technical difficulty with the CURESoft system, and Patient 6 has a lower number of breath data available due to discontinuation of the trial by staff for clinical reasons. However, the overall data set is relatively large for this type of analysis.

The collected $E_{rs,N}$ pairs are shown in Fig. 5a and are the main foundation of the stochastic model shown in Fig. 5c. The resulting stochastic model in Fig. 5c is very dependent on the data from which it is generated. If given data with lower local data density, the distance between percentile lines (Fig. 5e) would potentially increase to compensate for any greater spread between data, indicating greater variability or lack of data to

FIGURE 5. Stochastic model results. (a) Spread of $E_{rs,N}$ data pairs, (b) conditional probability density $P(E_{rs,N+1}|E_{rs,N})$, (c) stochastic model percentiles and (d) stochastic model probability intervals. (e) Cascade plot of $E_{rs,N}$ probability density functions.

create a more detailed distribution. However, overall data density appears good in Fig. 5 and the resulting stochastic model in Fig. 5c has no discontinuities or inexplicable values.

Figure 5e shows a cascade plot of conditional density functions across the $E_{rs,N}$ range. From this figure, the conditional probability density functions are largely uni-modal and symmetric except for exceptionally low and high values of $E_{rs,N+1}$ where data is more scarce. For example, for $E_{rs,N} = 70$ cmH$_2$O/L and higher, the conditional density functions appear to have more variation in shape, which could indicate the stochastic model of $E_{rs,N}$ is absorbing an underlying physiology or dynamic not captured by Eq. 1. However, given it only occurs at extremely high values of $E_{rs,N}$, it is more likely the uneven conditional density function is caused by the data scarcity at these higher values. For this reason, the axis limits of the stochastic model have been limited the 10–100 cmH$_2$O/L range.
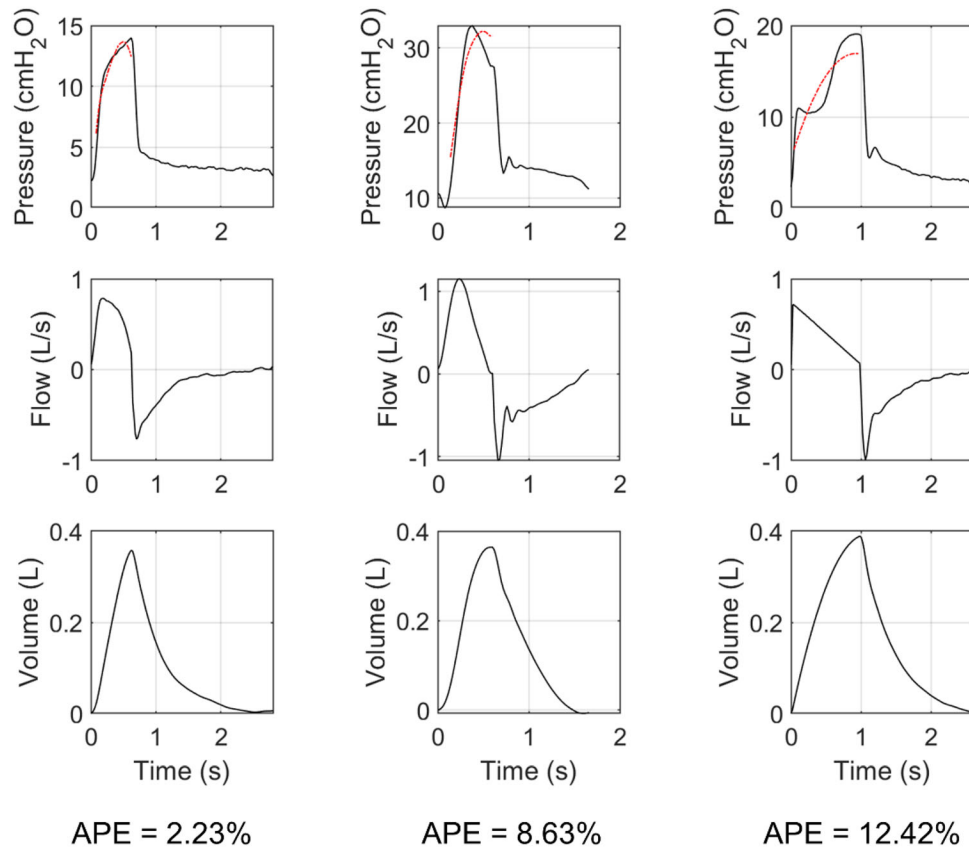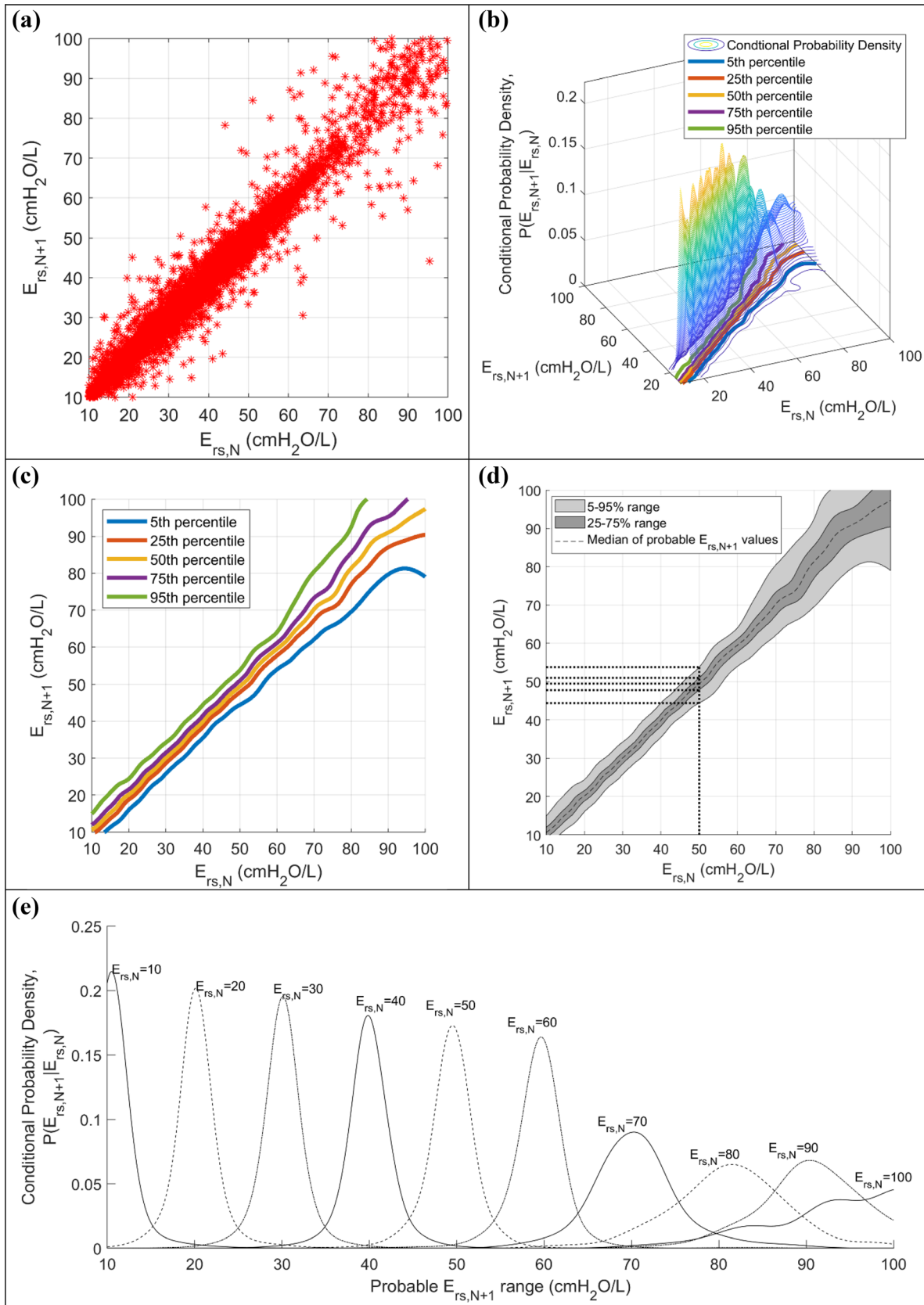

APE = 2.23%   APE = 8.63%   APE = 12.42%

FIGURE 4. Examples of breaths that meet APE criteria < 15%, with dotted dash line being the model-fitted pressure.
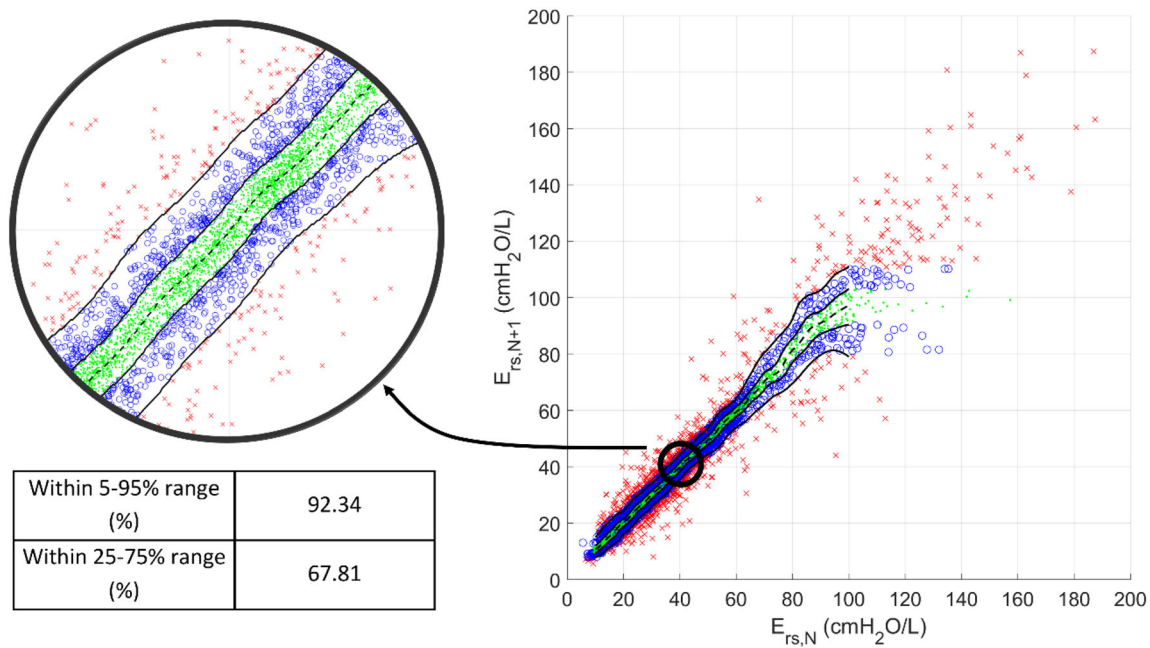
FIGURE 6. Stochastic $E_{rs,N}$ model self-validation graphical results, with zoomed-in section solely for clarity. Black solid lines are the percentile lines, dash dotted line is the median percentile, dots are data points within the 25–75% range, circles are within the 5–95% range and *x*'s are outside the prediction range.

TABLE 2. Stochastic $E_{rs,N}$ model cross validation results.

Group	Groups used in creating stochastic model	Percentage of actual $E_{rs,N+1}$ within 5–95% range (%)	Percentage of actual $E_{rs,N+1}$ within 25–75% range (%)
A	[–, B, C, D, E]	92.60	69.17
B	[A, –, C, D, E]	91.71	68.49
C	[A, B, –, D, E]	92.35	67.33
D	[A, B, C, –, E]	94.45	71.15
E	[A, B, C, D, –]	91.81	66.68
Average ± standard deviation		**92.59 ± 1.12**	**68.56 ± 1.74**

[a]A hyphen (–) indicates that the group in place was not used as a training set to create the stochastic model.

Further data and larger data sets would enable expansion using the same methodology.

Overall, this model can be used as a look-up table in real-time to predict the next most probable range and distribution of future elastance over the next $N+1$ interval given the current elastance value at interval N, as illustrated in Fig. 5d. Knowing the future distribution and range enables MV settings to be optimised using the model in Eq. 1 to minimise risk of extreme values in this range increasing the risk of VILI.

From self-validation results, 92.34% and 67.81% of $E_{rs,N+1}$ fall within the model-predicted 5–95% and 25–75% range, as shown in Fig. 6. Ideally, 90 and 50% of the data should lie within these ranges to demonstrate the model perfectly represents the cohort. However, self-validation produces overly optimistic, best case

results, as model performance has been evaluated on using the same data to build the model.[38] Equally, this over estimation is likely due to the assumed normal distributions used in the stochastic model not fully capturing the distributions seen, where a tightening coefficient could be used to improve these results.[39] However, clinically, such over estimation, which is modest at the clinically more relevant 5–95% range, would represent a conservative choice as slightly more results lie within this range, thus offering an ~ 93% likelihood of elastance in the range.

Table 2 indicates a very similar overall cross-validation performance of 92.59% and 68.56% of $E_{rs,N+1}$ within the 5–95% and 25–75% ranges respectively. This performance is encouraging as it is near the ideal values, albeit slightly conservative in over-estimating
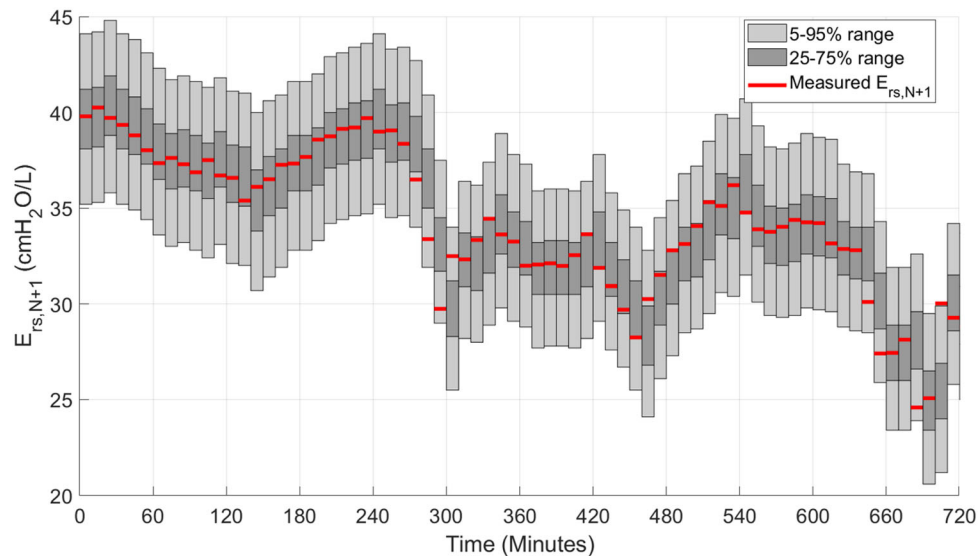
FIGURE 7. Time-step prediction of $E_{rs,N+1}$ for first 12 hours of Patient 5, Session 2.

slightly the 5–95th percentile range. The very consistent results for both self- and cross-validation, particularly for the clinically relevant 5–95th percentile range, suggest the model contains sufficient data to account for the range of dynamics observed in this cohort.

As shown in Fig. 7, the potential application of the stochastic model in a clinical setting presents the possibility of better optimising patient-specific ventilator settings. Provided the current patient-specific $E_{rs,N}$, the stochastic model can predict the likely range of patient-specific $E_{rs,N+1}$ values over the next 10 min. By utilising the developed stochastic model in a clinical setting, a decision support system can be developed to assist recommending optimal patient-specific MV settings based on the produced patient-specific $E_{rs,N}$ predictions. The stochastic model can also be utilised together with the single compartment model to predict other parameters, such as pressure and flow which could serve as guides to limit driving pressure and tidal volume settings. However, model-based respiratory mechanics are required as patient specific elastance cannot be directly obtained without an additional real-time computational platform to allow model analysis and identification, breath-to-breath if required. In practice, this potential application would require a computational device to be provided or installed within the ICU or as part of the ventilators themselves (e.g. Refs. [48,59]).

More specifically, understanding possible variation in elastance can provide clinicians an approximate forecast of other important parameters, such as monitoring plateau pressure when in volume control ventilation or monitoring tidal volumes when in pressure

control ventilation. An illustrative example for volume control ventilation is presented in Fig. 8. The potential process begins with using the stochastic model to predict future E_{rs}. Together with pre-set MV settings, the volume and flow waveform from the ventilator can be used as input to a single compartment model, with airway pressure waveform as the output. By using the 5th and 95th percentiles of predicted E_{rs}, a forecast of plateau pressure can be created. If the forecast value exceeds recommended plateau pressure safety limits of 30 cmH_2O,[31,42] clinicians could pre-emptively adjust other MV settings to avoid potential lung injury. This approach can potentially be used in pressure-controlled ventilation as well to provide a forecast of outcome tidal volume to avoid VILI.

More generally, in pressure controlled MV, the low end of the range would capture risk of volutrauma and the high end the potential risk of under ventilation and atelectasis for any given setting.[52] These limits can be tested in the same model to pick a best PEEP and other settings to best account for the risk of very high (95th percentile) or low (5th percentile) elastance due to evolution of patient condition over time. Figure 8 illustrates this potential process. This risk-based dosing approach is unique to a limited number of model-based methods and has been extensively proven clinically in glycemic control studies.[12,57,64]

The prediction interval of the stochastic model was chosen to have prediction limits of 10 to 100 cmH_2O/L. While a majority of elastance values usually fall within this range,[3] it could be useful to be able to extend the predictive capabilities of the stochastic model beyond these limits. With more patient data, the stochastic model can be extended to much lower and
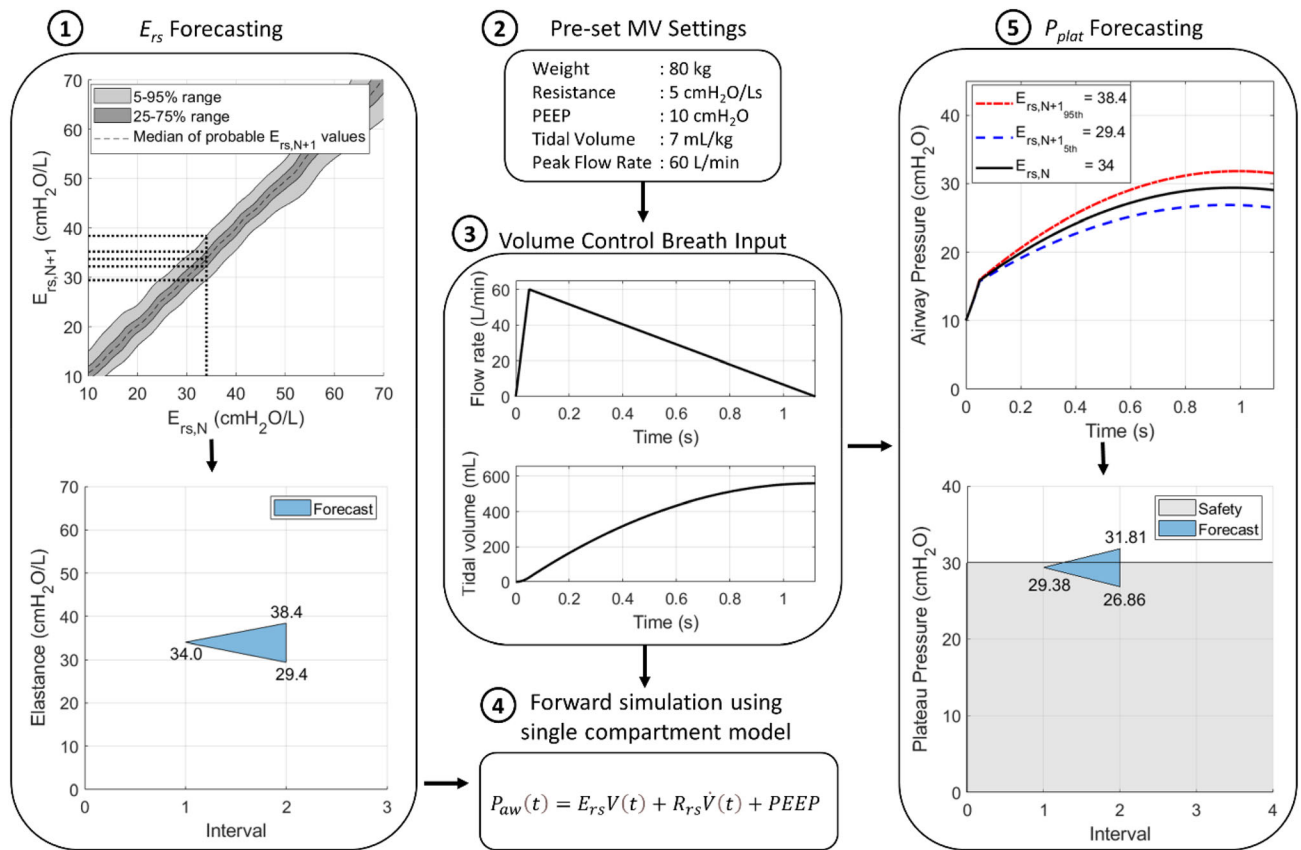
FIGURE 8. Potential application of using E_{rs} prediction together with pre-set settings to forward simulate possible plateau pressure predictions using the single compartment model. Step 1 uses current patient E_{rs} to produce a forecast of E_{rs} at the next interval. In Step 2, pre-set MV settings such can produce the volume and flow breath waveform shown in Step 3. All the information in Step 1, 2 and 3 can then be used as input for a single compartment model in Step 4. The potential output airway pressure waveform is shown in Step 5, and a graph of potential plateau pressures can be forecasted. *Flow, volume, and pressure graphs in this figure only show the inspiratory phase of a single breath. **Plateau pressure safety limit of 30 cmH$_2$O follows recommendations based on literature.[31,42].

higher values, as was the case in the glycemic control application.[41,63] Further studies could include assessing interval to interval variability in sub-cohorts, where similar analyses in glycemic control and MV have found differences between sexes that can impact care.[24,36,62]

Furthermore, the interval size N of 10 min was arbitrarily chosen as a proof of concept in this work. To link the gap between simulation and practical application to ICU patients, intervention intervals need to be clinically and physiologically relevant to ensure unnecessarily increase of workload, and to capture changes in care in a timely manner. Hence, future work should check the validity of producing stochastic models to predict average future elastance values of longer intervals, such as 30 min or 1 h, where the 10 min range is a likely lower limit for physiological evolution of lung mechanics in critical illness. However, a larger interval size would require a greater amount of data, which can be collected readily using

the software used in this study, noting the number of data pairs in this research was more than adequate given the consistency of results in cross-validation. Such data could arise from clinical trials such as in the work of Kim et al.[37] Stochastic models with different N values could thus be created to match clinical needs or specific cohorts. With more data, patients can be further broken down into more distinct categories, based on gender, age or probable illnesses. In this study, a broad, diverse range of patients is used to ensure good coverage of patient types and provide enough data to create a valid stochastic model.[39,41] This model and data level was validated as acceptable in the 5-fold cross validation presented. Overall, it would be valuable to generate unique stochastic models for each sub-cohort to further increase patient-specificity and further improve personalised care, but it will require a level of data not yet available to the study authors.

While there exist more descriptive lung mechanics models,[47,60,69] the single compartment linear lung

model was selected as it forms the basis for all other models, and is readily identifiable using linear and nonlinear basis functions while providing very good predictive accuracy.[16,47,65] Furthermore, the respiratory elastance and resistance identified using the model has shown to be clinically relevant and similar to those identified from other models.[51] Finally, more descriptive nonlinear models risk issues, even when identifiable, with model mismatch to dynamics in the observed and measured data, which can lead to inaccurate parameter identification[54,71] and thus poor prediction and bedside decision support. It is important to note the single compartment linear lung model is also easily identifiable, which is of singular importance so it can be used with available clinical data. While many FEA model studies do a remarkable job of providing thorough descriptions of the physiology of the lung,[6,45,50,60] many are simply not identifiable, or at least require invasive procedures to assist in identifying specific parameters. This data is often not clinically feasible or available,[11] and can interrupt patient care and increase clinical workload. Validating the concept of a stochastic model using a relatively simple model will eventually pave the way towards incorporating more descriptive models using the distributions and likelihoods defined in the results of this analysis.

Finally, as noted, the percentages within the 5–95% and 25–75% range are higher than the ideal values of 50 and 90% in both self-validation and cross validation results. This over estimation could indicate over smoothening of the produced stochastic model. Having prediction ranges that are too wide may not help in deducing optimal MV settings. To alleviate this problem, a constant could be introduced to adjust the variance estimators used to produce $P(E_{\text{rs},N+1}|E_{\text{rs},N})$, as done by Le Compte *et al.*[39] By adjusting this introduced constant, the produced stochastic model could possess tighter percentile lines which could consequently yield performance results closer towards the ideal 50 and 90%. However, equally, the relatively slight over estimation at the 5–95th percentile interval could be considered a conservative choice and thus useful in clinical implementation.[29]

To surmise, the key potential limitations of this work include the smaller sample size and the relatively simple lung mechanics model used, where these issues trade-off with computational issues of identifiability and the cross validation used. With regards to future work, an increase in available data will not only allow larger interval sizes, but also allow further distinction between patients and patient sub-groups, allowing an even greater level of personalisation via sub-cohort specific stochastic models based on distinctive characteristics, such as gender, age, and diagnoses. Based on the results in this study, it would be interesting to observe the effect on the stochastic model produced if a different lung mechanics model was used, as well to ensure adequacy of the underlying modelling methods in addition to their already demonstrated clinical utility. A more descriptive model could potentially more accurately a stochastic model better reflecting a cohort.

CONCLUSION

A stochastic model of mechanically ventilated patient-specific respiratory elastance was developed. Cross validation shows promising results with 92.59% and 68.56% of actual $E_{\text{rs},N+1}$ values within the 5–95% and 25–75% range respectively. Thus, the model can predict future $E_{\text{rs},N}$ values well, particularly in the clinically more relevant 5–95th percentile range. The overall outcomes justify prospective validation of the clinical utility of this model in helping personalise and more optimally guide mechanical ventilation. Limitations include a smaller sample size, restricting analysis to the full cohort, and relatively simple model used, where these limitations are offset by its identifiability and cross-validation results. Future works point towards increasing the sample size to further categorize patients by age, gender, and diagnosis to create more patient-specific models with greater clinical utility.

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