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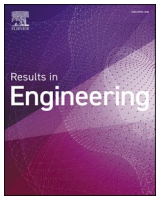

Stochasticity of the respiratory mechanics during mechanical ventilation treatment

Christopher Yew Shuen Ang [a], Yeong Shiong Chiew [a,*], Xin Wang [a], Mohd Basri Mat Nor [b], J. Geoffrey Chase [c]

[a] School of Engineering, Monash University Malaysia, Subang Jaya, 47500, Malaysia
[b] Kulliyah of Medicine, International Islamic University Malaysia, Kuantan, 25200, Malaysia
[c] Centre of Bioengineering, University of Canterbury, Christchurch, 8041, New Zealand

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ABSTRACT

Stochastic models have been used to predict dynamic intra-patient respiratory system elastance (E_{rs}) in mechanically ventilated (MV) patients. However, existing E_{rs} stochastic models were developed using small cohorts, potentially showing bias and overestimation during prediction. Thus, there is a need to improve the stochastic model's performance. This research investigates the effect of the kernel density estimator (KDE) parameter tuned with a constant, c on the performance of a 30-min interval E_{rs} stochastic model. Thirteen variations of a stochastic model were developed using varying KDE parameters. Model bias and overestimation were evaluated by the percentage of actual data captured within the 25th – 75th and 5th – 95th percentile lines (Pass50 and Pass90). The optimum range of c was chosen to tune the KDE parameter and minimise the temporal variations of model-predicted 25th – 75th and 5th – 95th percentile values of E_{rs} (ΔRange50 and ΔRange90) in an independent retrospective clinical cohort of 14 patients. In this cohort, the values of ΔRange50 and ΔRange90 exhibit a converging behaviour, resulting in a cohort-optimised value of $c = 0.4$. Compared to $c = 1.0$ (benchmark study model), $c = 0.4$ significantly reduces model overestimation by up to 25.08% in the 25th – 75th percentile values of E_{rs}. Overall, $c = 0.3$–1.0 presents as a generalised range of optimum c values, considering the trade-off between data overfitting and model overestimation. Optimisation of the KDE parameter enables more accurate and robust E_{rs} stochastic models in cases of limited training data availability.

1. Introduction

Respiratory system elastance (E_{rs}) describes the elastic properties of the respiratory system during mechanical ventilation (MV) treatment [1–4]. Studies show that E_{rs} can guide MV settings [5–8]. However, E_{rs} shows significant intra-patient temporal variability, along with patient-specific disease state and response to MV care [9,10]. This dynamic evolution of patient-specific condition makes it challenging to ensure consistent optimal care. Thus, the ability to capture and predict the temporal dynamics of patient-specific E_{rs} could pave the way for individualised MV treatment [11].

Several methods have been devised for predictive applications in various fields of research, particularly the use of statistical and machine learning models [12–15]. In healthcare, predictive data mining models have been employed for prediction applications related to Covid-19 [16]. Stochastic modelling presents as a statistical method that has been used in clinical settings where it has been used in glycaemic control protocols in critical care [17–22]. The use of stochastic forecasting in the protocol led to more precise glycaemic control in ~90% of ICU patients, leading to significant reductions in hypoglycaemia and clinical workload [22,23]. Thus, stochastic models have the capability to facilitate personalized medicine in environments such as the ICU, where heterogeneity may impact the performance of conventional deterministic modelling methods.

Stochastic models have also been used to describe the probabilistic behaviour of E_{rs} dynamics, where it can predict future values of patient specific E_{rs} in MV patients [24]. A stochastic model was developed and validated using retrospective E_{rs} obtained using model-based methods [25–27] and sorted into 10-min intervals to capture short-term intra--patient variation. Ang et al. extend the stochastic model using 54

* Corresponding author.
E-mail addresses: christopher.ang@monash.edu (C.Y.S. Ang), chiew.yeong.shiong@monash.edu (Y.S. Chiew), Wang.Xin@monash.edu (X. Wang), m.basri@iium.edu.my (M.B. Mat Nor), geoff.chase@canterbury.ac.nz (J.G. Chase).

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patients from 2 cohorts with a 30-min prediction interval [28]. This model provides significantly improved E_{rs} prediction ranges and added clinical practicality, thus making it feasible for synchronising to help guide clinical interventions. Despite significant improvements, the extended stochastic model still demonstrates model bias and over-estimation. Similar limitation was also raised for the stochastic model of Lee et al. [24].

In a study by Dias et al. applies a non-parametric stochastic model based on kernel density estimator (KDE) for the analysis of hydrological time series [29]. The study states the importance of the selection of the kernel bandwidths as a large bandwidth may lead to overly smooth distributions while too small a bandwidth will result in noisy distributions. Optimisation of the kernel bandwidths have been investigated where methods such as the minimisation of the mean integrated squared error (MISE) have been devised [30]. However, this presents a complex mathematical optimisation problem where the computational complexity [31] may not be best suited for real-time bedside applications in clinical settings.

This manuscript presents a tighter, more accurate probability distribution for the respiratory elastance stochastic model via optimisation of the KDE parameter. While shown to be feasible for glycaemic control stochastic models [19], the optimised KDE parameter is only specific to the patient cohort and application of blood glucose data used in that study. Therefore, further investigation of the KDE parameter in respiratory elastance stochastic models is warranted, where this research is the first of its kind for respiratory elastance stochastic models. Tuning of the KDE parameter would result in much tighter E_{rs} prediction intervals, and hence increased prediction confidence, further adding to the clinical utility of the stochastic models with potential application in stochastic-integrated MV setting guidance protocols. In addition, this significant improvement in prediction performance can be achieved using existing data sets, thus alleviating the need for additional patient recruitment via resource intensive clinical trials, presenting a cost- and resource-effective approach towards personalising MV patient care.

2. Methodology

2.1. Patient cohorts

The respiratory system elastance, E_{rs} from 68 retrospective patients across clinical data from 3 cohorts receiving invasive MV for respiratory failure are used in this study [28,32,33]. The three cohorts (ethics approval) are denoted: **1**) $CARE_{01}$ (Ref: IIUM/504/14/11/2/IREC 666); **2**) $CARE_{SG}$ (DSRB Ref:2018/00042); and **3**) $CARE_{02}$ (Ref: IIUM/504/14/11/2/IREC 2020–100). The details are shown in Table 1 [28]. The respiratory elastance, E_{rs} and respiratory resistance, R_{rs} of the 3 patient cohorts are found to be significantly different from one another ($P < 0.05$).

2.2. Stochastic model development

The 30-min transition of E_{rs} can be described using a stochastic model based on a two-dimensional kernel density estimation method.

Table 1
Patient cohorts and the respiratory mechanics of each cohort. E_{rs} and R_{rs} values are presented as median [interquartile range, IQR].

Patient cohort	No. of patients	Days of data	No. of breaths	E_{rs} (cmH_2O/L)	R_{rs} ($cmH_2O.s/L$)
$CARE_{01}$	24	127	2,120,834	36.95 [27.51–47.40]	7.93 [5.55–12.51]
$CARE_{02}$	30	200	4,783,264	36.51 [26.31–48.66]	8.82 [6.29–11.68]
$CARE_{SG}$	14	35	742,493	33.11 [23.59–50.21]	10.70 [9.55–12.34]

The kernel density estimation method results in a bi-variate probability density function (PDF) of the E_{rs} dataset by combining the PDFs of each datapoint [19]. The distribution of $E_{rs,N+1}$ varies with $E_{rs,N}$, and cannot be described using a single standard statistical distribution, where $E_{rs,N}$ and $E_{rs,N+1}$ are two consecutive mean E_{rs} values over the current (N) and subsequent ($N + 1$) 30-min interval [18,24]. As the conditional PDFs of future $E_{rs,N}$ values depend only on the current $E_{rs,N}$ value, the variations in $E_{rs,N}$ can be treated as a Markov process. The conditional probability density of $E_{rs,N+1} = y$ given the value of $E_{rs,N} = x$ is described as:

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

where β represents the term $P(E_{rs,N} = x)$. A 2-dimensional kernel density estimated joint probability density function across the x-y plane $P(x, y)$ is defined by the fitted values of E_{rs} data pairs with coordinates x_i and y_i [31]:

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

$$p_{x_i}=\int_0^{\infty}\varnothing\left(x;x_i,\sigma_{x_i}^2\right) \tag{3}$$

$$p_{y_i}=\int_0^{\infty}\varnothing\left(y;y_i,\sigma_{y_i}^2\right) \tag{4}$$

The terms $\varnothing(x;x_i,\sigma_{x_i}^2)$ and $\varnothing(y;y_i,\sigma_{y_i}^2)$ represent the normal PDFs centred at individual data points of x_i and y_i, with $\sigma_{x_i}^2$ and $\sigma_{y_i}^2$ being the variances. The variance describes the local data density within a centred and orthonormalised space of x and y [19]. The normalised summation of terms $\varnothing(x;x_i,\sigma_{x_i}^2)$ and $\varnothing(y;y_i,\sigma_{y_i}^2)$ in **(3)** and **(4)**, effectively results in probability distributions that are normalised in the positive domain, and enforces physiological validity with positive-only E_{rs} values. This is necessary as physiologically, a patient's breath-specific E_{rs} must be a positive-only value [26]. β can be calculated by integrating **(2)** with respect to y:

$$\beta=\int P(x,y)dy=\frac{1}{N}\sum_{i=1}^{N}\frac{\varnothing\left(x;x_i,\sigma_{x_i}^2\right)}{p_{x_i}}\int\frac{\varnothing\left(y;y_i,\sigma_{y_i}^2\right)}{p_{y_i}}dy=\frac{1}{N}\sum_{i=1}^{N}\frac{\varnothing\left(x;x_i,\sigma_{x_i}^2\right)}{p_{x_i}}$$

- 1

(5)

Thus, **(1)** can be expressed:

$$P\left(E_{rs,N+1}=y\middle|E_{rs,N}=x\right)=\frac{\sum_{i=1}^{N}\frac{\varnothing\left(x;x_i,\sigma_{x_i}^2\right)}{p_{x_i}}\frac{\varnothing\left(y;y_i,\sigma_{y_i}^2\right)}{p_{y_i}}}{\sum_{i=1}^{N}\frac{\varnothing\left(x;x_i,\sigma_{x_i}^2\right)}{p_{x_i}}} \tag{6}$$

where **(6)** defines the two-dimensional kernel density estimation for the conditional variation of E_{rs}, where E_{rs} depends on its prior state.

Knowing $E_{rs,N} = x$ at the time point N, this approach allows the probability of $E_{rs,N+1} = y$ at the time point $N + 1$ to be calculated. The result is a 2-dimensional stochastic model capturing the variability of E_{rs}. The probability interval of future $E_{rs,N+1}$ values is described by the model's percentile lines. Each stochastic model is trained with data from the $CARE_{01}$, and $CARE_{02}$ patient cohorts, consisting of 54 patients with 7,146 E_{rs} pairs.

2.3. Kernel density estimator (KDE) parameter

To optimise the KDE parameter of the stochastic model, the KDE parameter is tuned by modifying the variance estimators ($\sigma_{x_i}^2$ and $\sigma_{y_i}^2$) with a constant c in **(7)**.

$$P\left(E_{rs,N+1}=y\middle|E_{rs,N}=x\right)=\frac{\sum_{i=1}^{N}\frac{\varnothing\left(x;x_i,(c\sigma)_{x_i}^2\right)}{p_{x_i}}\frac{\varnothing\left(y;y_i,(c\sigma)_{y_i}^2\right)}{p_{y_i}}}{\sum_{i=1}^{N}\frac{\varnothing\left(x;x_i,(c\sigma)_{x_i}^2\right)}{p_{x_i}}} \quad (7)$$

where $(c\sigma)^2$ is the modified KDE parameter. The added constant c allows the adjustments of the kernel bandwidth and the degree of data smoothness of the stochastic model [19]. In this study, the effect of c ranging from 0.05 to 2.0 is investigated ($c = 0.05$, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5 and 2.0). Specifically, one stochastic model is developed for each value of c.

2.4. Model validation and analysis

2.4.1. Model self- and cross-validation

Over the range of $E_{rs,N}$ values, each of the developed stochastic models is used to generate the 25th – 75th and 5th – 95th percentile intervals of predicted E_{rs} values ($E_{rs,N+1}$). These predicted intervals are then compared to the actual $E_{rs,N+1}$ measurements and are quantified by.

- Pass50 (%): The percentage of actual data falling within the 25th – 75th percentile intervals of predicted E_{rs} values.
- Pass90 (%): The percentage of actual data falling within the 5th – 95th percentile intervals of predicted E_{rs} values.

This set of definitions is illustrated in Fig. 1. The ideal values for Pass50 and Pass90 are 50% and 90%, respectively. Thus, these metrics provide a form of model self-validation, where the same data is used for training and testing, and thus to assess model fitness.

Further, a 5-fold cross-validation is also performed on each of the developed stochastic models in a training-validation dataset split ratio of 80:20. In each validation-fold, unique and non-repeating E_{rs} from the test dataset is used to predict the 25th – 75th and 5th – 95th percentile intervals of $E_{rs,N+1}$, where the Pass50 and Pass90 are evaluated. Good model prediction performance is indicated by a smaller deviation of the results from the ideal 50% and 90% values. Minimal discrepancy between self- and cross-validation results would suggest a robust model and sufficient training data [21,24].

2.4.2. Clinical validation of stochastic model

Each stochastic model is also used to analyse retrospective patient data from the $CARE_{SG}$ cohort, ensuring clinical validity of the models. Model validation was performed using similar methods from previous studies [19,21]. The stochastic models are used to predict the future

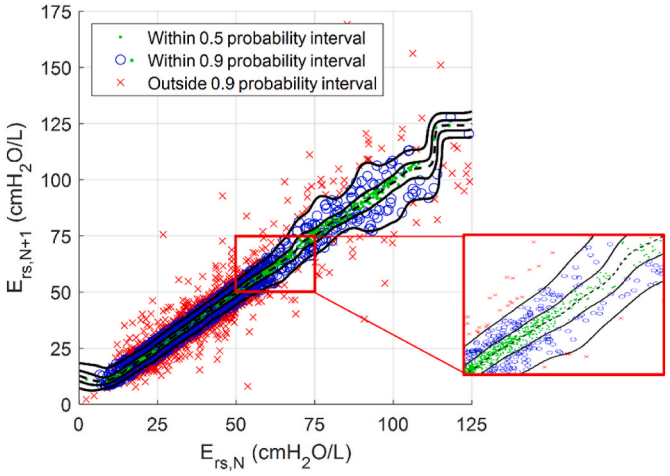

Fig. 1. Pass50 and Pass90 of the stochastic model for $c = 1.0$. The 0.9 probability interval represents the 5th – 95th percentiles and hence includes the 0.5 probability interval (25th – 75th percentiles).

25th – 75th and 5th – 95th percentile intervals of $E_{rs,N+1}$, which are then compared to the actual patient $E_{rs,N+1}$ values. Patient data are processed and sorted into 30-min time intervals. The first 12 h of data are analysed to ensure intra-cohort consistency of the analysed metrics (Δ Range50 and Δ Range90) as the amount of available MV data varies between patients.

Using different values of c ultimately affects the smoothness and tightness of the stochastic model percentile lines. Selection of the optimum value of c is based on Δ Range50 and Δ Range90:

$$\Delta Range50=\frac{1}{N}\sum_{i=1}^{N}\left|Range50_i-Range50_{i+1}\right| \quad (10)$$

$$\Delta Range90=\frac{1}{N}\sum_{i=1}^{N}\left|Range90_i-Range90_{i+1}\right| \quad (11)$$

$$\text{where } Range50=\frac{E_{rs,75}-E_{rs,25}}{E_{rs,patient}} \quad (12)$$

$$Range90=\frac{E_{rs,95}-E_{rs,5}}{E_{rs,patient}} \quad (13)$$

where the subscripts i and $i + 1$ denote two subsequent 30-min intervals. $E_{rs,5}$, $E_{rs,25}$, $E_{rs,75}$, and $E_{rs,95}$ are the stochastic model-predicted 5th, 25th, 75th, and 95th percentile values of E_{rs}, respectively. $E_{rs,patient}$ is the retrospective patient mean E_{rs} value of that time interval. This is illustrated in Fig. 2. Δ Range50 and Δ Range90 effectively describe the temporal variations of the model-predicted 25th – 75th and 5th – 95th percentile values of E_{rs}, respectively. A smaller value of Δ Range50 and Δ Range90 indicates a more consistent width of Range50 and Range90 over time, suggesting a more consistent stochastic model. This would be beneficial in terms of patient care as it ensures that the risk and consistency of MV treatment do not fluctuate. Thus, the c value resulting in the minimum Δ Range50 and Δ Range90 ($\Delta Range50_{min}$ and $\Delta Range90_{min}$) is defined as the cohort-optimised value of c.

For each increment of c, the absolute percentage difference of the median ΔRange50 ($\delta_{\Delta Range50}$) and ΔRange90 ($\delta_{\Delta Range90}$) with respect to its previous value is also calculated:

$$\delta_{\Delta Range50}(\%)=\left|\frac{\Delta Range50_{c,i+1}-\Delta Range50_{c,i}}{\Delta Range50_{c,i}}\right|\times 100\% \quad (14)$$

$$\delta_{\Delta Range90}(\%)=\left|\frac{\Delta Range90_{c,i+1}-\Delta Range90_{c,i}}{\Delta Range90_{c,i}}\right|\times 100\% \quad (15)$$

where i ranges from 1 to 13. Therefore, c_1 to c_{13} is 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5 and 2.0 respectively. A lower value of $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ indicates smaller differences between the median ΔRange50 and ΔRange90 values. A maximum threshold of 20% of $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ values is used to define a general range of optimum c values, allowing generalisation to other patient cohorts.

Subsequently, we also perform testing of the whole $CARE_{SG}$ data cohort of 29,520 min (492 h). The stochastic model developed with the optimised c value is used to predict future elastance values, $E_{rs,N+1}$ which are then compared to the retrospective patient data. The number of retrospective patient $E_{rs,N+1}$ falling into the model predicted 25th – 75th (Pass50) and 5th – 95th (Pass90) percentile ranges are also determined.

3. Results

3.1. Stochastic models

Four variations of the developed stochastic model and their percentile lines are presented graphically in Fig. 3. Self-validation results of the stochastic models are shown in Table 2, where the Pass50 and Pass90 values of each model are presented. The maximum absolute percentage difference of Pass50 and Pass90 with their ideal values are

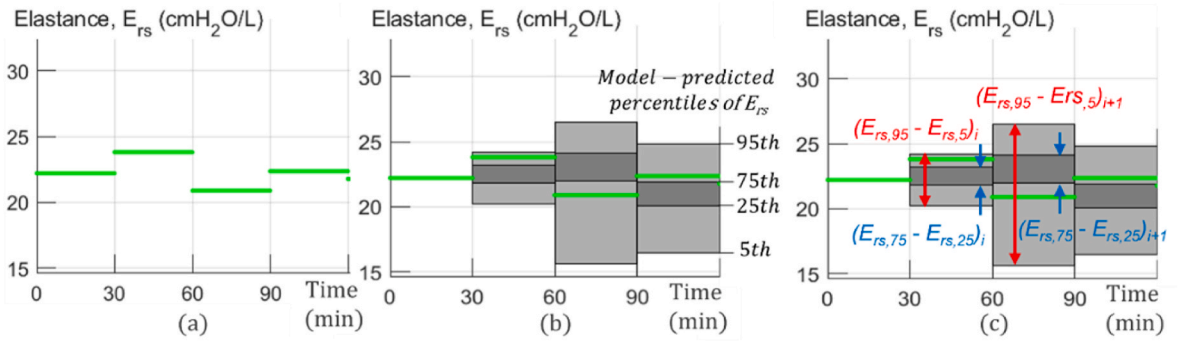

Fig. 2. (a) The retrospective patient E_{rs} values are shown as horizontal green lines. (b) shows the stochastic model-predicted 5th, 25th, 75th, and 95th percentile values of E_{rs} (bottom to top). (c) $E_{rs,75}$ - $E_{rs,25}$ (vertical blue arrows) and $E_{rs,95}$ - $E_{rs,5}$ (vertical red arrows) of the first two model-predicted E_{rs} intervals are shown. These values are normalised by $E_{rs,patient}$ to yield Range50 and Range90 respectively.

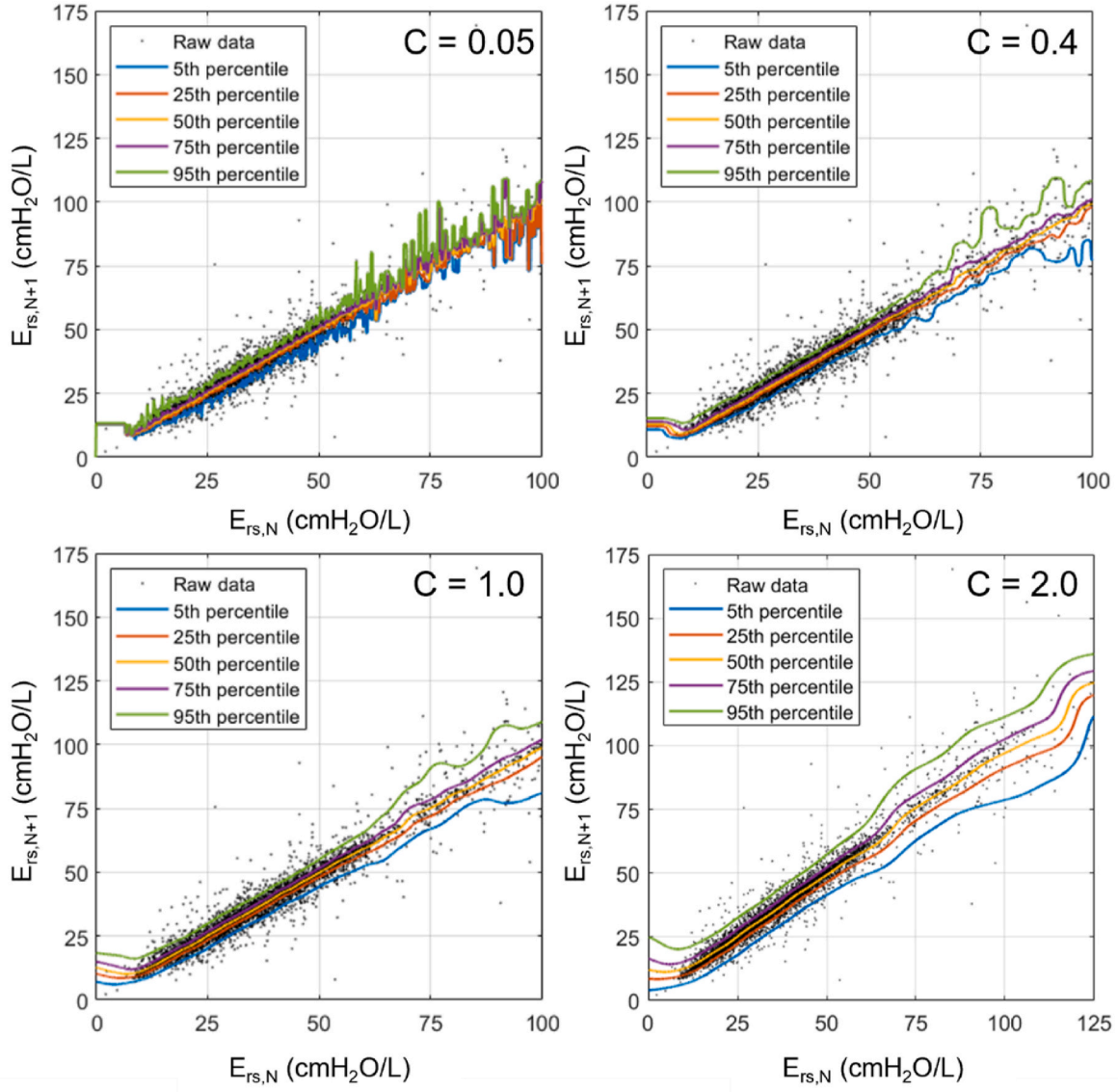

Fig. 3. Developed stochastic models and their percentile lines for $c = 0.05$ (top left), $c = 0.4$ (top right), $c = 1.0$ (bottom left) and $c = 2.0$ (bottom right).

61.29% and 7.18% respectively, when $c = 2.0$. The minimum absolute difference occurs at $c = 0.05$, where the difference between Pass50 and Pass90 with their ideal values are 0.81% and 0.25%. Results of the 5-fold cross-validation are also presented in Table 2, where the self- and cross-validation results differ only by a maximum of ~5%.

Table 2
Self- and cross-validation results for stochastic models developed with different values of *c*.

	Self-validation		5-fold cross-validation			
	Pass50, % (% Diff)	*Pass90, % (% Diff)*	Pass50, %	Pass90, %	% Diff SV (Pass50)	% Diff SV (Pass90)
0.05	*50.41 (0.81)*	*89.77 (0.25)*	*49.59 [48.50 - 50.88]*	*86.75 [86.50 - 88.79]*	*2.96 [1.62 - 3.79]*	*3.36 [1.10 - 3.65]*
0.1	*50.41 (0.81)*	*89.43 (0.63)*	*49.52 [49.30 - 50.95]*	*88.46 [87.64 - 88.80]*	*2.19 [1.77 - 4.35]*	*1.31 [1.09 – 2.00]*
0.2	*51.23 (2.46)*	*88.97 (1.14)*	*52.37 [50.76 - 52.48]*	*88.87 [88.83 - 89.11]*	*2.22 [2.00 - 2.43]*	*0.16 [0.16 - 2.08]*
0.3	*52.84 (5.68)*	*89.22 (0.86)*	*53.98 [52.46 - 54.60]*	*89.29 [89.23 - 89.65]*	*2.15 [0.93 - 3.32]*	*0.48 [0.08 - 2.18]*
0.4	*54.73 (9.46)*	*89.66 (0.38)*	*54.61 [54.02 - 55.96]*	*90.24 [90.08 - 91.26]*	*2.24 [1.31 - 3.04]*	*0.65 [0.47 - 1.78]*
0.5	*57.00 (13.99)*	*89.81 (0.21)*	*58.31 [57.58 - 59.51]*	*90.48 [89.97 - 90.84]*	*2.30 [1.03 - 4.41]*	*1.14 [0.75 - 1.88]*
0.6	*59.17 (18.33)*	*90.26 (0.29)*	*60.74 [60.10 - 61.63]*	*91.00 [90.60 - 91.67]*	*2.66 [1.58 - 4.17]*	*1.56 [0.82 - 1.76]*
0.7	*61.10 (22.19)*	*90.72 (0.80)*	*63.89 [62.16 - 64.08]*	*91.40 [90.93 - 92.15]*	*4.57 [1.73 - 4.88]*	*1.45 [0.75 - 1.57]*
0.8	*63.03 (26.06)*	*91.23 (1.36)*	*66.27 [64.58 - 67.02]*	*91.69 [91.61 - 92.86]*	*5.14 [2.46 - 6.33]*	*1.27 [0.51 - 1.79]*
0.9	*65.32 (30.65)*	*91.87 (2.08)*	*68.47 [66.70 - 68.82]*	*92.43 [92.24 - 93.58]*	*4.82 [2.11 - 5.36]*	*1.23 [0.61 - 1.86]*
1.0	*67.27 (34.54)*	*92.44 (2.71)*	*70.38 [68.45 - 70.73]*	*92.88 [92.81 - 94.11]*	*4.63 [1.75 - 5.15]*	*1.29 [0.47 - 1.80]*
1.5	*75.23 (50.46)*	*94.85 (5.39)*	*78.00 [76.92 - 78.52]*	*95.36 [95.20 - 96.19]*	*3.68 [2.24 - 4.38]*	*0.67 [0.54 - 1.42]*
2.0	*80.65 (61.29)*	*96.46 (7.18)*	*82.33 [81.85 - 83.28]*	*96.95 [96.75 - 97.20]*	*2.09 [1.49 - 3.27]*	*0.51 [0.31 - 0.77]*

* % Diff is the absolute percentage difference of the Pass50 and Pass90 values with the ideal values of 50% and 90%.
* % Diff SV is the absolute percentage difference of the cross- and self-validation values of Pass50 and Pass90. Results are presented in terms of median [IQR].
*Pass50 and Pass90 of the cross-validation refer to the median [IQR] values of all 5 validation folds.

3.2. Independent $CARE_{SG}$ patient cohort analysis

Stochastic models developed with different values of *c* are used to predict future E_{rs} values based on retrospective patient E_{rs} data. The Δ Range50 and Δ Range90 are calculated for all patients of the $CARE_{SG}$ cohort while varying the value of *c*. The median values are presented in Table 3 and illustrated in Fig. 4. It is shown that the median Δ Range50 and Δ Range90 values of the patient cohort are the lowest when $c = 0.4$, with a Δ $Range50_{min}$ of 11.26×10^{-3} [6.64×10^{-3} - 13.17×10^{-3}] and Δ $Range90_{min}$ of 31.54×10^{-3} [24.70×10^{-3} - 45.94×10^{-3}]. Therefore, using a *c* value of 0.4 is shown to be the optimum for this patient cohort. All further retrospective clinical studies are performed using this model. In addition, based on a threshold of 20% of $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ values, a generalised range *c* values between 0.3 and 1.0 is defined for the 30-min respiratory elastance stochastic model. Analysis of the $CARE_{SG}$ patient cohort using the cohort-optimised model ($c = 0.4$) shows >90% of actual patient E_{rs} falling within the model-predicted 5th – 95th E_{rs} range (Table 4).

Fig. 5 illustrates this analysis for Patients 1, 4 and 6 of the $CARE_{SG}$ cohort to showcase model prediction performance on different trends and ranges of patient E_{rs}. Patient 1 exhibits relative stable and small E_{rs} values (<12 cmH_2O/L), whereas Patient 4 and 6 exhibits more varying E_{rs} trends at relatively higher values (>15 cmH_2O/L). Long term E_{rs} prediction of up to 492 h of retrospective patient E_{rs} data was performed with the optimised stochastic model ($c = 0.4$), where patient E_{rs} trends for Patient 5, 6, 7 and 9 are presented in Fig. 6.

Table 3
Δ Range50 and Δ Range90 values of the patient cohort for different values of *c*.

c	Median ΔRange50 (10^{-3})	Median ΔRange90 (10^{-3})	$\delta_{\Delta Range50}$ (%)	$\delta_{\Delta Range90}$ (%)
0.05	22.15 [17.03–33.43]	83.18 [68.83–99.53]	–	–
0.1	16.52 [11.23–21.62]	58.69 [46.22–68.31]	29.44	25.43
0.2	13.04 [7.76–14.64]	40.78 [32.20–52.26]	30.52	21.04
0.3	11.30 [7.01–12.64]	33.12 [27.45–48.21]	18.77	13.33
0.4	11.26 [6.64–13.17]	31.54 [24.70–45.94]	4.77	0.37
0.5	11.30 [6.33–13.71]	32.66 [22.97–43.92]	3.54	0.36
0.6	11.79 [7.12–13.73]	34.19 [22.07–43.72]	4.71	4.34
0.7	13.04 [7.14–14.22]	35.58 [21.31–43.55]	4.06	10.56
0.8	13.19 [7.35–15.97]	37.01 [20.57–44.94]	4.00	1.14
0.9	13.67 [7.55–16.22]	38.92 [21.23–46.16]	5.17	3.64
1.0	14.80 [7.77–16.88]	41.02 [21.85–48.76]	5.40	8.30
1.5	19.06 [9.63–20.93]	49.08 [26.22–57.46]	19.64	28.76
2.0	23.10 [11.89–25.96]	58.43 [31.67–68.32]	19.06	21.20

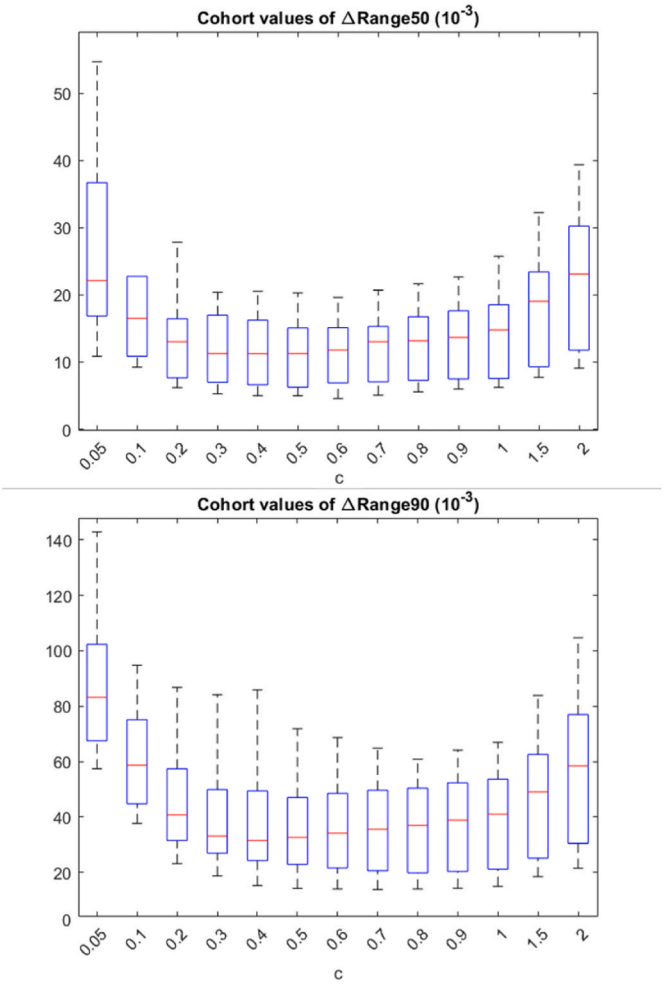

Fig. 4. Box and whisker plots presenting the cohort values of Δ Range50 (top) and Δ Range90 (bottom) with varying *c*.

Table 4
The percentage of actual patient E_{rs} values predicted by stochastic model percentile lines for $c = 0.4$. A total of 29,520 min (492 h) of MV data were analysed.

Patient	Minutes (Hours) of MV data	Within 25–75%	Within 5–95%	Outside 5–95%
1	1140 (19.0)	29.73	86.49	13.51
2	2640 (44.0)	52.87	85.06	14.94
3	1350 (22.5)	47.73	93.18	6.82
4	1650 (27.5)	61.11	96.30	3.70
5	3690 (61.5)	54.92	91.80	8.20
6	4260 (72.0)	65.73	99.30	0.70
7	2700 (45.0)	56.18	89.89	10.11
8	930 (15.5)	56.67	90.00	10.00
9	2550 (42.5)	64.29	95.24	4.76
10	1350 (22.5)	31.82	68.18	31.82
11	840 (14.0)	59.26	88.89	11.11
12	1140 (19.0)	86.49	100.00	0.00
13	3090 (51.5)	73.53	94.12	5.88
14	2070 (34.5)	67.65	95.59	4.41
Median [IQR]	1860 [1192.5–2685.0] (31.0 [19.9–44.8])	57.96 [53.38–65.37]	92.49 [89.14–95.50]	7.51 [4.50–10.86]

4. Discussion

In this study, the effects of c on a respiratory elastance stochastic model is investigated. While respiratory resistance, R_{rs} is part of a patient's respiratory mechanics, it remains largely unchanged during MV with only small variations which are mainly influenced by the ventilator circuit [1,34,35]. Significant changes to R_{rs} is normally a result of changes to the positive end-expiratory pressure (PEEP) which is not considered in the developed stochastic models [36]. The stochastic models in Fig. 3 show that for increasing values of c, there is an increase in percentile line width, particularly in the ranges of $E_{rs,N} > 60$ cmH_2O/L. There is also an increase in percentile line smoothness with increasing value of c. This outcome is expected, as a larger KDE parameter results in a wider kernel bandwidth, and thus, a greater degree of data smoothness of the stochastic model [19]. The 'jaggedness' of the model percentile lines for $E_{rs,N} > 60$ cmH_2O/L with small values of c suggests overfitting of the data, reducing the generalisation ability of the model.

Wider model percentile lines also capture a larger distribution of patients E_{rs} as seen in Table 2, where Pass50 and Pass90 values increase with c. The self- and cross-validation of Pass50 and Pass90 differ only by a maximum of ~5%, suggesting there is sufficient data for model training to account for E_{rs} heterogeneity within the patient cohorts. The Pass50 and Pass90 self-validation values for $c = 0.05$ are closest to the ideal values with an absolute percentage difference of 0.81% and 0.25%, respectively. However, the optimal selection of c also needs to be based on the trade-off between data overfitting and model overestimation.

In the calculations of Range50 and Range90, the model-predicted 25th – 75th and 5th – 95th E_{rs} intervals are normalised by the patient E_{rs}. Stochastic model percentile ranges increase in width with increasing E_{rs} due to data scarcity at these higher ranges of E_{rs} (Fig. 3). As patient-specific E_{rs} profiles exhibit large intra- and inter-patient heterogeneity, normalisation by patient E_{rs} allows for fair comparisons between patients.

Cohort values of Δ Range50 and Δ Range90 (Table 3) exhibit a converging behaviour, as seen in Fig. 4, with minimum median values of 11.26×10^{-3} [6.64–13.17] $\times 10^{-3}$ and 31.54×10^{-3} [24.70–45.94] $\times 10^{-3}$ respectively at $c = 0.4$. This value of $c = 0.4$ presents a cohort-optimised value of the KDE parameter. The $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ values are also presented in Table 3. These metrics are based on the median values of ΔRange50 and ΔRange90 of the entire patient cohort (Table 3). The $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ values are highly dependent on the ΔRange50 and ΔRange90 of the previous value of c, respectively ($\Delta Range50_{c,i}$ and $\Delta Range90_{c,i}$ respectively). This is important as the $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ values effectively describe the relative differences of model behaviour between consecutive values of c, where too large of a percentage difference could indicate deviation of model behaviour from an optimal range. On the other hand, a relatively small $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ suggests that the two consecutive c values in comparison result will yield stochastic models with relatively small differences in terms of their prediction behaviour which could then be used to define a general range of optimum c values. It is observed that $c = 0.4$ is the first value of c where there is a relatively small change in $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$, while also being the inflection point of c (Fig. 4). Thus, this further justifies the selection of $c = 0.4$ as the cohort-optimised value of c. The values of $c = 0.3$–1.0 result in $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ values that fall within the defined 20% threshold, suggesting relatively small differences in model behaviour and is thus defined as a general range of optimum c values, allowing generalisation to other patient cohorts.

Furthermore, Pass50 and Pass90 values (self-validation) of $c = 0.4$ are 54.73% and 89.66%, respectively (Table 2), which are close to the ideal values of 50% and 90%. Compared to $c = 1.0$, this set of results provides a reduction in % Diff (absolute percentage difference with respect to ideal values) of 25.08% and 2.33% for Pass50 and Pass90 respectively. This results in a significant reduction in model overestimation for the 25th – 75th percentile range, whereas this improvement is not significant for the 5th – 95th percentile range. The change of c values may not observe a big difference in % Diff in the 5th – 95th percentile range, as this range covers a wider data range which is more consistent.

Analysis of the independent $CARE_{SG}$ patient cohort using the optimised model ($c = 0.4$) shows that the model can accurately predict >90% (median) of actual patient E_{rs} values within the model-predicted 5–95th percentile range, demonstrating the clinical practicality of the model. The use of the 5–95th percentile ranges offers a more conservative prediction confidence interval as it takes into account the more extreme ranges of patient conditions. This prediction range has also been used for stochastic predictions in tight glycaemic control for ICU patients [18,19,22,23]. The relatively poor E_{rs} prediction performance of Patient 10 is due to sudden and large fluctuations E_{rs} values.

The E_{rs} prediction profiles of three different stochastic models are shown in Fig. 5. With $c = 0.05$, the E_{rs} prediction profiles show inconsistent widths of the predicted 5th – 95th percentile of E_{rs} (Range90), further demonstrating model prediction behaviour under conditions of data-overfitting. Overfitting of the model is also demonstrated by the overly jagged percentile lines of the stochastic model developed with $c = 0.05$ (Fig. 3). and the relatively large median ΔRange50 and ΔRange90 values of 22.15×10^{-3} [17.03–33.43] $\times 10^{-3}$ and 83.18×10^{-3} [68.83–99.53] $\times 10^{-3}$ respectively (Table 3). This also results in a large absolute percentage difference with $\Delta Range50_{min}$ and $\Delta Range90_{min}$ of ~97% and ~164% respectively. Patients with high E_{rs} have a more severe lung condition, warranting a more conservative prediction and potential treatment. Therefore, a more robust and consistent stochastic model is required, where the E_{rs} prediction percentile ranges (Range50 and Range90) should be consistent in size. A relatively more consistent Range90 width is achieved with $c = 1.0$. However, model-overestimation as a result of overly wide model percentile lines (Fig. 3) as well as $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ values (Table 3) greater than the defined 20% threshold results in overly conservative 5th – 95th percentile ranges of predicted E_{rs}.

The clinical E_{rs} prediction results of the stochastic model developed with $c = 0.4$ shown in Table 4. Results show a median [IQR] Pass50 and Pass90 of 57.96% [53.38–65.37]% and 92.49% [89.14–95.50]%, respectively. These values are expected and show relatively little deviation from the self-validation results, with a percentage difference in Pass50 and Pass90 of only 5.9% and 3.2%, respectively. A long term longitudinal study was also performed using the model with the optimised KDE parameter ($c = 0.4$) where a total of 492 h of retrospective

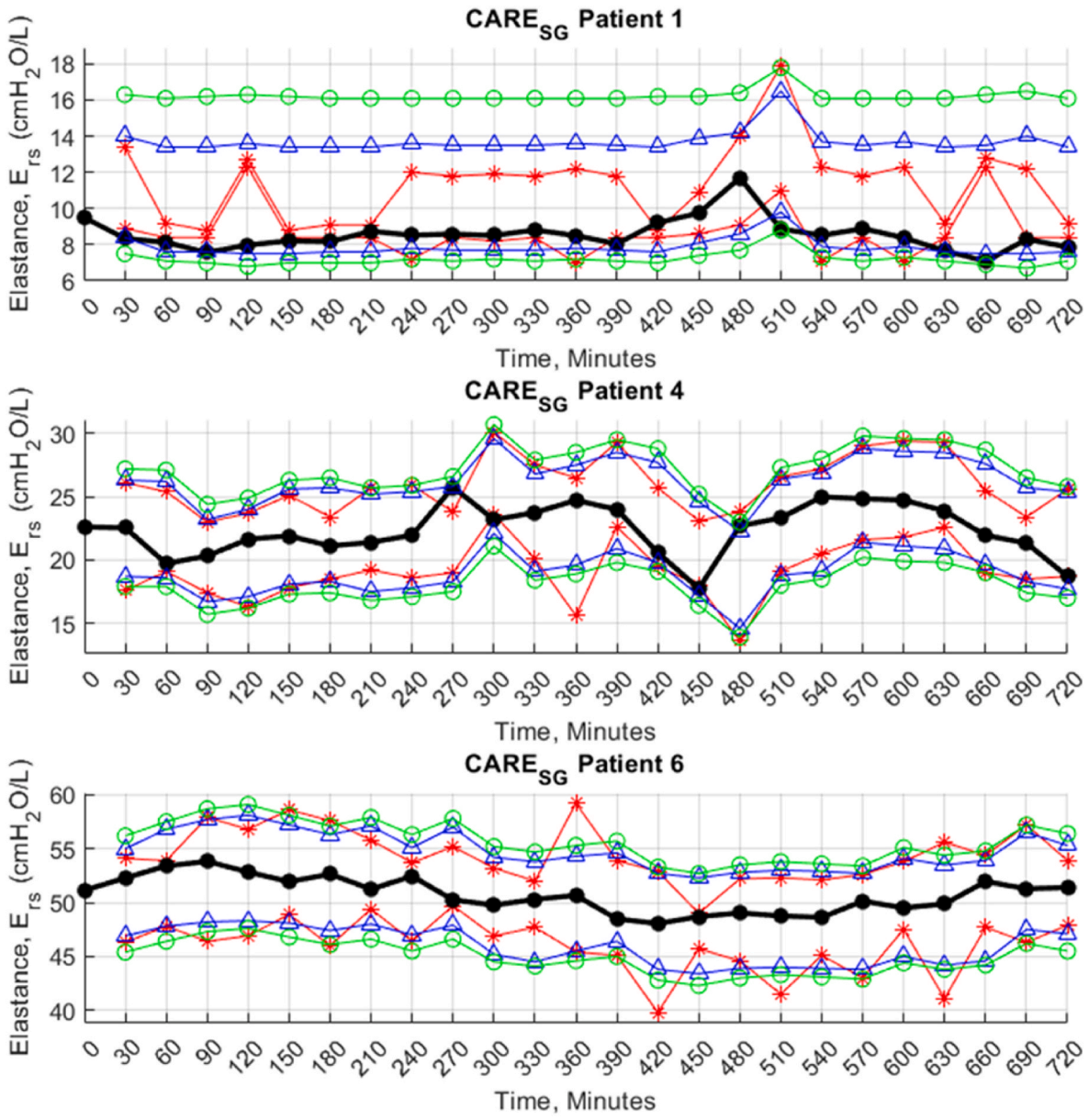

Fig. 5. Stochastic models developed with $c = 0.05$ (red star), $c = 0.4$ (blue triangle) and $c = 1.0$ (green circle) are used to predict the 5th – 95th percentile range of future E_{rs} values based on the retrospective patient E_{rs} data (black solid circle). The figure shows predictions made for Patients 1, 4 and 6 (top to bottom).

patient E_{rs} data were analysed. The E_{rs} plots in Fig. 6 demonstrate the ability of the stochastic model to adapt the abrupt changes in patient E_{rs} and produce accurate $E_{rs,N+1}$ predictions at elevated levels of E_{rs} in a clinical setting, while alleviating the issue of model overestimation as observed with models developed with larger values of c.

Optimisation of stochastic model performance and behaviour have been investigated where methods such as the minimisation of the mean integrated squared error (MISE) have been devised [30]. Other methods include using different univariate kernel types, using different classes of bandwidth selectors (such as Rule-of-thumb selector, least squares cross validation selector and smoothed cross validation selector) and even Fast Fourier Transform (FFT) based algorithms for bandwidth selection [31]. However, the proposed method of optimising the KDE parameter using c presents a simple, computationally efficient method for adjusting the effective kernel bandwidth and the degree of data smoothness of the stochastic model while facilitating direct comparisons of model behaviour and performance.

Overall, a c value optimised based on a cohort-wide dataset of $c = 0.4$ would produce a robust and consistent stochastic model, providing a balance between overfitting and overestimation. Using the value of $c = 1.0$ demonstrates model overestimation and hence would not be optimal for clinical use. Therefore, any value of c greater than 1.0 would also be unsuitable for the same reasons as the resulting model percentile lines will be even wider as seen in Fig. 3. In this study, the results of $c = 1.5$ and 2.0 are presented to demonstrate two examples of more extreme cases of overestimation. The optimised KDE parameters result in tighter stochastic model prediction percentiles, thus increasing prediction confidence and accuracy. This further adds to the clinical utility of the models where cohort-specific prediction performance can be improved in cases where only a limited amount of training data is available, where this data may be difficult to obtain in a high-cost clinical setting.

A more general range of c between 0.3 and 1.0 could allow generalisation for application in other patient cohorts. An optimum c value of 0.5 was suggested in the works of Le Compte et al., thus falling into the above range of $c = 0.3$–1.0 [19]. However, the values of c from the two analyses should be treated independently due to the inherent difference

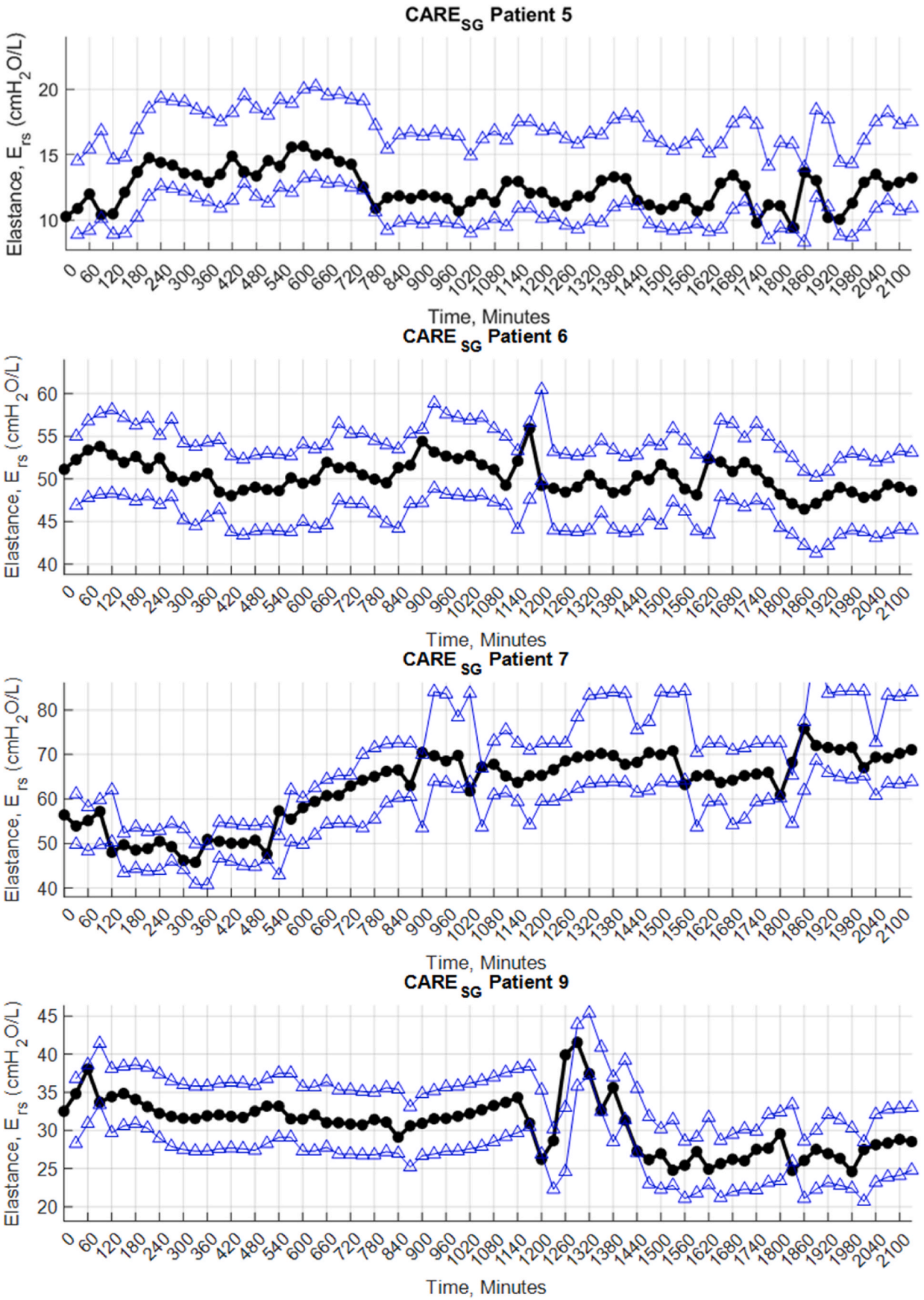

Fig. 6. Retrospective patient E_{rs} data for Patients 5, 6, 7, and 9 (black solid circles) were analysed using the stochastic model ($c = 0.4$). The 5th and 95th percentiles of the model-predicted E_{rs} interval are plotted as blue triangles. The first 36 h of patient data are presented in the plots above.

in distributions between blood glucose and E_{rs} data. While the range of $c = 0.3–1.0$ is that of a general patient cohort, with clinical utility in mind, it is also important to conduct these analyses to obtain a cohort-specific value of c. Therefore, this study not only establishes a generalisable range of c values, but also introduces a method to obtain the cohort-optimised value of c via the ΔRange50, ΔRange90, $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ metrics.

It is also important to note that the optimisation of the parameter c is performed on a per cohort-basis, similar to the works of Le Compte et al. [19]. The model predicted E_{rs} probability ranges based on the optimised value of $c = 0.4$ would usually be more conservative than necessary for patients with less dynamic E_{rs}. This choice accounts for patients exhibiting more dynamic E_{rs} profiles within the patient population. While individualised stochastic models can be developed, a significant amount of patient-specific data will be required to achieve sufficient model prediction accuracy, and this level of data may not be feasible or clinically practical to obtain for this use.

5. Conclusion

In this study, several variations of a 30-min respiratory elastance stochastic model were developed using KDE parameters modified with a constant, c ranging from 0.05 to 2.0. A generalised range of optimum values of c is found to be between $c = 0.3–1.0$ based on $\delta_{\Delta Range50}$ and $\delta_{\Delta Range90}$ analyses on a separate independent patient cohort. This range of c values could allow generalisation for further application in other patient cohorts. Compared to a model from a benchmark study ($c = 1.0$), a cohort-specific value of $c = 0.4$ enabled tighter and more consistent E_{rs} percentile lines. The $c = 0.4$ model also demonstrates robust, long-term prediction ability, where the model can accurately predict >90% (median) of actual patient E_{rs}. Optimisation of the KDE parameter provides an optimum balance between data overfitting and model overestimation, enabling more accurate and robust E_{rs} stochastic models.

Credit author statement

CYS Ang: Conceptualisation, Methodology, Data curation, Formal analysis, Writing – original draft. YS Chiew: Conceptualisation, Writing – review & editing. X Wang: Conceptualisation, Writing – review & editing. MB Mat Nor: Conceptualisation, Resources, Writing – review & editing. JG Chase: Conceptualisation, Writing – review & editing.

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 data that has been used is confidential.

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