Available online at www.sciencedirect.com

ScienceDirect

IFAC Papers Online CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 54-15 (2021) 186–191

Identification of Asynchronous Effect via Pressure-Volume Loop Reconstruction in Mechanically Ventilated Breathing Waveforms

Cong Zhou[1,2], J. Geoffrey Chase[2], Qianhui Sun[2], Jennifer Knopp[2], Merryn H. Tawhai[3], Thomas Desaive[4], Knut Möller[5], Geoffrey M. Shaw[6], Yeong Shiong Chiew[7], Balazs Benyo[8]

[1]*School of Civil Aviation, Taicang Yangzte River Delta Research Institute, Northwestern Polytechnical University, China (e-mail: cong.zhou@nwpu.edu.cn)*

[2]*Dept of Mechanical Engineering; Dept of Mechanical Eng, Centre for Bio-Engineering, University of Canterbury, Christchurch, New Zealand (e-mail: cong.zhou@canterbury.ac.nz; geoff.chase@canterbury.ac.nz; qianhui.sun@pg.canterbury.ac.nz;jennifer.knopp@canterbury.ac.nz)*

[3]*Auckland Bioengineering Institute, The University of Auckland, Auckland, New Zealand (e-mail: m.tawhai@auckland.ac.nz)*

[4]*GIGA-In Silico Medicine, Institute of Physics, University of Liege, Liege, Belgium(e-mail: tdesaive@uliege.be)*

[5]*Institute for Technical Medicine, Furtwangen University, Villingen-Schwenningen, Germany (e-mail: knut.moeller@hs-furtwangen.de)*

[6]*Dept of Intensive Care, Christchurch Hospital, Christchurch, New Zealand (e-mail: geoff.shaw@cdhb.health.nz)*

[7]*School of Engineering, Monash University, Subang Jaya, Malaysia(e-mail: yeong.shiong@monash.edu)*

[8]*Dept of Control Engineering and Information Technology, Budapest University of Technology and Economics, Budapest, Hungary, bbenyo@iit.bme.hu*

Abstract: Patient-specific lung-mechanics during mechanical ventilation (MV) can be modelled via using fully ventilated/controlled waveforms. However, patient asynchrony due to spontaneous breathing (SB) effort commonly exists in patients on full MV support, leading to variability in breathing waveforms and reducing the accuracy of identified, model-based, and patient-specific lung mechanics. This study aims to extract ventilated breathing waveforms from affected asynchronous breathing cycles using an automated virtual patient model-based approach. In particular, change of lung elastance over a pressure-volume (PV) loop is identified using hysteresis loop analysis (HLA) to detect the occurrence of asynchrony, as well as its type and pattern. The identified HLA parameters are then combined with a nonlinear mechanics hysteresis loop model (HLM) to extract and replicate the ventilated waveforms from the coupled asynchronous breaths. The magnitude of asynchrony can then be quantified using an energy dissipation metric, E_{asyn}, comparing the area difference of PV loops between model-reconstructed and original breathing cycles. A proof-of-concept study is conducted using clinical data from 2700 breathing cycles of two patients exhibiting asynchrony during MV. The reconstruction root mean square errors are within 5-10% of the clinical data for 90% of the cycles , indicating good and robust reconstruction accuracy. Estimation of E_{asyn} shows significant asynchrony magnitude for Patient 1 with E_{asyn} greater than 10% for over 50% breaths, while asynchrony occurrence for Patient 2 is lower with 90% breaths at $E_{asyn} < 10\%$, which is a minimal asynchrony magnitude. These results match direct observation, thus validating the ability of the virtual patient model and methods presented to be used for a real-time monitoring of asynchrony with different types and magnitudes, which in turn would justify prospective clinical tests.

Keywords: Asynchrony; Mechanical ventilation; Hysteretic lung mechanics; Hysteresis loop model; Virtual patient.

1. INTRODUCTION

Mechanical ventilation (MV) is a core therapy for respiratory failure patients in the intensive care unit (ICU) (Major et al., 2018), and is particularly important for managing Covid-19 patients. Model-based methods have proven their potential and accuracy (Chiew et al., 2011, Morton et al., 2019a, Morton et al., 2020a, Zhou et al., 2021) for guiding and optimizing MV care to avoid ventilator induced lung injury (VILI) and reduce length of stay, mortality, and cost (Ricard et al., 2003). However, significant inter- and intra- patient variability in lung mechanics and condition can make model identification difficult reducing the accuracy of lung mechanics identified. This issue is compounded when patient exhibit spontaneous breathing (SB) efforts, or any mismatch with the ventilator delivery, more generally referred to asynchrony.

Patient SB effort is common as completed paralysis and heavy sedation of MV support may lead to ventilator induced diaphragmatic dysfunction (Epstein, 2011). Thus, patient-ventilator interaction is frequent in long-term MV treatment with respiratory work done by both the ventilator and patients. However, clinical data demonstrates patient SB effort can cause up to 43% asynchrony rate, associated with failure of MV weaning (Gholami et al., 2018). Therefore, it is important to extract the true ventilated lung mechanics response from the asynchrony waveforms to estimate the asynchrony effect so as to adjust the ventilator settings for asynchrony reduction.

Asynchrony reconstruction based on a single compartment linear lung model has been well-studied (Chiew et al., 2018, Damanhuri et al., 2016, Kannangara et al., 2016, Major et al., 2016, Redmond et al., 2019), mainly based on the single dimension information of airway pressure. However, these

10.1016/j.ifacol.2021.10.253

methods require a multistep analysis or iteration of the pressure waveform with accuracy and robustness depending on the convergence of the algorithm. Their main advantage was their model-based enabling of automated monitoring and analysis of both asynchrony and lung mechanics, where clinical methods typically rely on observation and manual assessment.

In contrast, a recently developed virtual patient model based on hysteretic pressure-volume (PV) loop analysis and hysteresis loop model (HLM) offers more complete respiratory information from both pressure and volume/flow measurements, improving the utility and robustness for model identification, focusing on the identification and prediction of non-asynchrony breathing cycles in prior work (Zhou et al., 2021). This paper extends the developed HLM model to identify additional nonlinearities due to asynchrony to extract the missing lung mechanics from the asynchronous PV loop. The major goal is to provide a breath-to-breath direct estimation of asynchrony incidence and magnitude using only ventilated breath waveform data and the virtual patient model framework for real-time bedside monitoring.

2. METHODS

2.1 Hysteretic modelling of ventilated PV loop

The mathematic equations developed for the HLM lung mechanics model is described (Zhou et al., 2021):

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

where V is the volume of air delivered to the lungs widely used in respiratory mechanics models (Morton et al., 2020a), and K_e represents the alveolar recruitment elastance. V_{h1} and V_{h2} are hysteretic volume response during inspiration and expiration, respectively, representing the key characteristics of nonlinear stress-strain or force-deformation relation, thus critical for determining the two nonlinear hysteretic springs, K_{h1} and K_{h2}, for alveolar hysteresis elastance during inspiration and expiration, respectively. R is the airway resistance, PEEP is the positive end-expiratory pressure, and $f_V(t)$ is the steady-state input force.

Given the availability of pressure and volume (or flow) data, the clinical hysteretic PV loop can be constructed, as seen in the blue cycle in Fig. 1. To model the clinical PV loop using the proposed HLM in Equation (1), hysteresis loop analysis (HLA) is implemented as a first key step to identify the stiffness (k_1-k_4) and breakpoints (V_{m1}, V_{m2}, V_{max}) of each nonlinear phase for a complete breath (Zhou et al., 2015, Zhou et al., 2017). This second step is shown as the purple dashed-line in Fig. 1. Model parameters for the HLM model can then derived and calculated based on HLA results to simulate and replicate the clinical PV loop, shown as the red solid line in Fig. 1. A detailed derivation of the model parameters based on HLA segmentation in the HLM lung mechanics model can be found in (Zhou et al., 2021), which is based in part on the prior basis function methods and models of (Morton et al., 2019b, Morton et al., 2019a, Morton et al., 2020b).

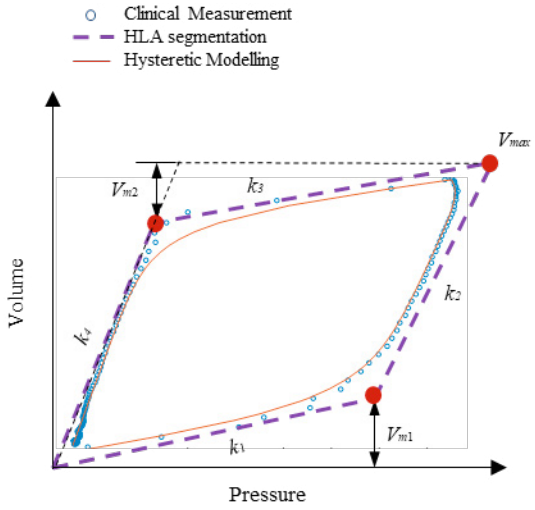

Fig. 1. Example of HLM modelling of a fully controlled clinical PV loop.

2.2 HLA identification of asynchronous PV loop

Patient SB effort changes airway pressure and flow curves at any phase in a breath, resulting different types of asynchrony. Reverse triggering is a common type of asynchrony due to a reflexive neural response triggered by the ventilator applied pressure and flow (Baedorf Kassis et al., 2021, Major et al., 2016), yielding an "M" shaped pressure curve in Fig. 2(a), further causing the change of nonlinear hysteretic mechanics in the measured PV loop shown in Fig 2(c).

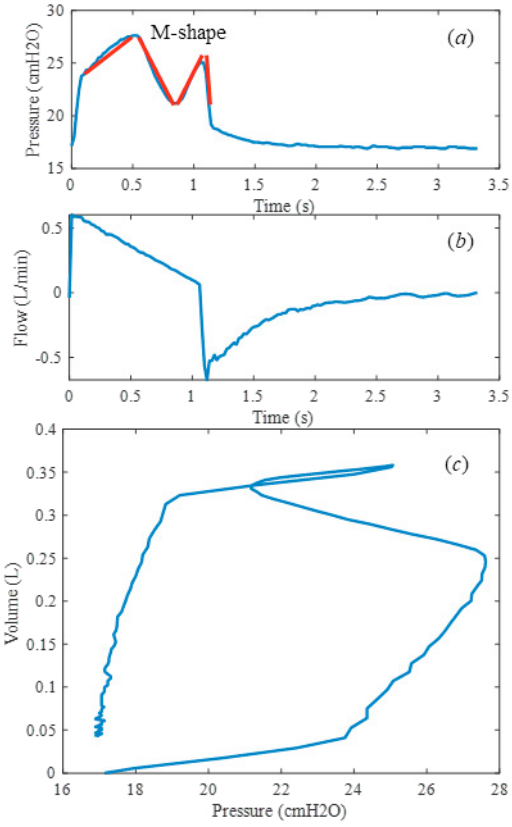

Fig. 2. Reverse triggering asynchronous breath with M-shaped curve in the pressure waveforms, while flow waveforms stays largely the same.

However, a major advantage of HLM over the prior single compartment linear lung model for modelling a breathing cycle is the ability to provide a more comprehensive estimate and better observations of nonlinear features over both inspiration and expiration. In this study, HLA identifies the presence, and thus incidence, of asynchrony. The identified model can then be used to assess the magnitude of asynchrony.

In particular, HLA is applied to the constructed asynchronous PV loop to identify the stiffness k_{a1}-k_{a6} and breakpoints V_{m1}-V_{m2}, as shown in Fig. 3. The breakpoint V_{max} for fixing the tidal volume can then be calculated based on the intersection point of k_{a2} segment and k_{a5} segment, while the stiffness parameters, k_1, k_2, k_3 and k_4, for HLM are readily obtained from the identified k_{a1}, k_{a2}, k_{a5} and k_{a6}, respectively. Therefore, the reconstruction of the ventilated response can be obtained using the HLM model with the HLA identification results (k_1-k_4, V_{m1}, V_{m2}, V_{max}) as presented in (Zhou et al., 2021).

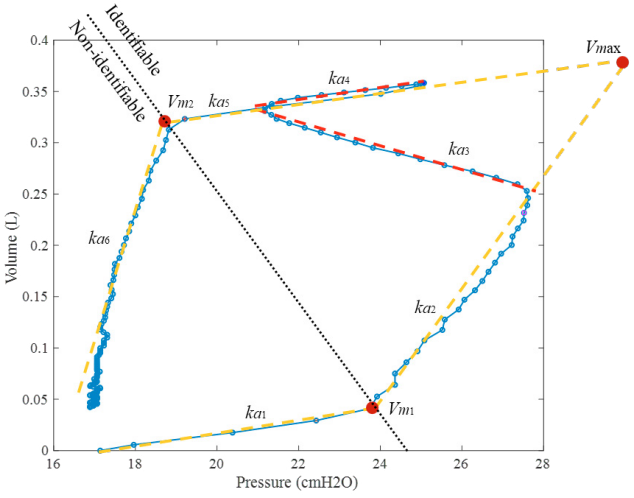

Fig. 3. HLA identification of HLM stiffness and breakpoints for reverse triggering asynchronous PV loop.

It is worth noting the observability of V_{m1}-V_{m2} points in the measured data are critical for the identifiability or reconstruction of the ventilated PV loop. They provide the minimum information needed to identify stiffnesses k_{a2} and k_{a5} via HLA, as shown in the black dots line in Fig. 3. However, patient asynchrony over the entire breathing cycle or for a long duration within a breathing cycle is rare. They would also indicate the existence of very significant SB efforts, suggesting weaning from MV without the need for special monitoring or methods. Thus, the identifiability and reconstruction of ventilated PV loop with the proposed HLM and HLA are considered feasible for more common, relatively smaller asynchrony durations.

2.3 Estimation of asynchrony effect

Energy dissipation refers to the work done by the ventilator in the airway for a ventilated patient, and can be directly calculated from the enclosed area of a measured PV loop. It is a critical measure of energy required for ventilating a patient and thus represents the essential patient recruitablity (Barnes et al., 2019), where a high energy or work of breathing would indicate a stiff lung and a less recruitable patient. While patient asynchrony produces negative work against the work of breathing done by ventilator, reducing its total value, the difference of area between the asynchronous PV loop and the reconstructed ventilated PV loop indicates the magnitude of asynchrony in a value relative to the ventilated energy required to support breathing. Thus, a metric to quantify asynchrony can be defined:

$$E_{asyn} = \frac{A_{ventilated} - A_{asyn}}{A_{ventilated}} \times 100\% \qquad (2)$$

where E_{asyn} is the quantified measure of the asynchrony effect in a breathing cycle, $A_{ventilated}$ is the area of reconstructed ventilated PV loop without asynchrony, and A_{asyn} is the area of the asynchronous PV loop.

3. CLINICAL DATA

Clinical data from two MV patients from the pilot CURE trial conducted in the Christchurch Hospital ICU in 2016 are used to interpret and provide a proof-of-concept validation of the proposed reconstruction method based on the HLM virtual patient model. Airway pressure and flow data were collected with sampling size of 50Hz using a bedside monitoring device CURESoft (Szlavecz et al., 2014). The New Zealand Southern Regional Ethics Committee granted ethics approval for this pilot trial (Davidson et al., 2014). Pressure and flow data were recorded at a sampling rate of 50Hz from a Puritan Bennett 840 ventilator (Covidien Boulder, CO, USA). Patient demographics for this proof of concept analysis of the methods presented are given in Table 1.

Table 1. Patient demographics.

Patient	Sex	Age	Clinical Diagnostic
1	Female	53	Fecal Peritonitis - surgery
2	Male	60	Pneumonia

Asynchrony phenomenon with different types and magnitude was observed using manual inspection for each ventilated patient in Table 1. In addition, each patient was given muscle relaxants to suppress SB effort before a stepwise recruitment manoeuvre (RM). Therefore, fully ventilated/controlled breaching cycles with SB effort eliminated by sedation and paralysis should be observed near the RM, enabling a comparison to the reconstructed waveforms for validation of the reconstruction and models.

Specifically, reconstruction using these models is applied to 350 breathing cycles. Reconstruction accuracy is validated by comparing the pressure waveform to the observed breathing cycles using root mean squared error, defined:

$$RMS = \frac{\sqrt{\frac{1}{n}\sum_{i=1}^{n}(P_i - \hat{P}_i)^2}}{\frac{1}{n}\sum_{i=1}^{n} P_i} \times 100\% \qquad (3)$$

where P_i is the clinical pressure data, $\hat{P}_i$ is the reconstructed pressure data, and n is the number of points for a breathing cycle. A low RMS error indicates an accurate reconstruction, ensuring an accurate estimation of the asynchrony using the metric E_{asyn} in Equation (2).

4. RESULTS AND DISCUSSION

4.1 Reconstruction and Estimation of Asynchrony

Fig. 4 shows an example breath from Patient 1 with a clear M-shaped SB effort leading to patient asynchrony observed in both the PV loop and pressure waveform. HLA is applied to the asynchronous PV loop to identify the values k_1, k_2, k_3, k_4, V_{m1} and V_{m2} needed to calculate the HLM virtual patient model parameters. Reconstruction is performed using forward simulation of the identified HLM model, where differences are used to estimate asynchrony magnitude. The reconstructed breathing cycle is then compared to the non-asynchronous breaths near RM, as shown in Fig. 5. It can be seen the reconstructed loop and pressure waveform match very well with the non-asynchronous breath during paralysis with RMS error of 1.8%, thus indicating a successful reconstruction using the proposed method.

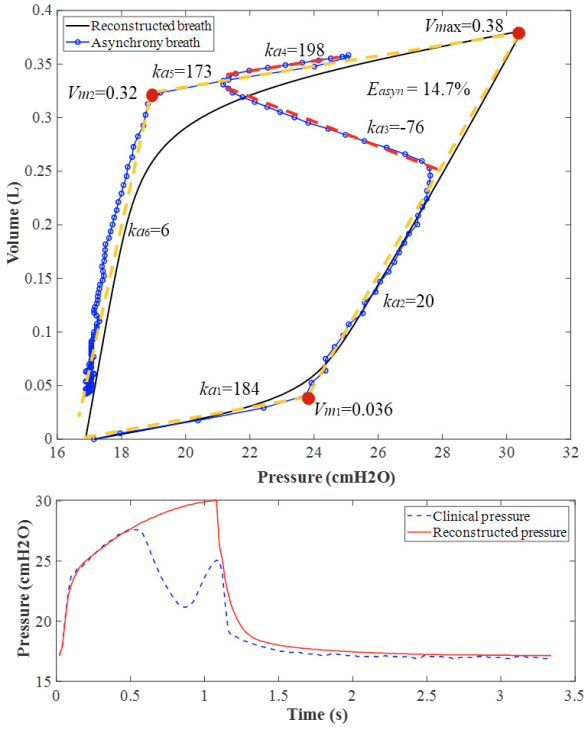

Fig. 4. Reconstruction of asynchrony breath cycle using HLM.

In addition, the calculated E_{asyn} for quantifying the asynchrony effect is 14.7% based on energy dissipation, indicating a significant asynchrony magnitude, matching the observation in Fig. 4. It should be noted the HLM virtual patient model and methods are a fully automated process (Zhou et al., 2021). Thus, the estimation of E_{asyn} can be readily conducted breath-to-breath automatically for a real-time assessment of asynchrony effect, and there is no need beyond validation to compare to paralysed breaths, as in Fig. 5.

4.2 Results summary for all breathing cycles

Fig. 6 summarizes the reconstruction RMS errors for all the breath cycles for both patients. RMS errors for both patients are within 10% for 90% breaths, indicating good and robust reconstruction accuracy. Larger errors are mainly due to the significant lack of necessary information for Vm_1 or Vm_2 or both, as shown in an example in Fig. 7, missing Vm_1 and thus failing to estimate k_1 and k_2 for the reconstruction.

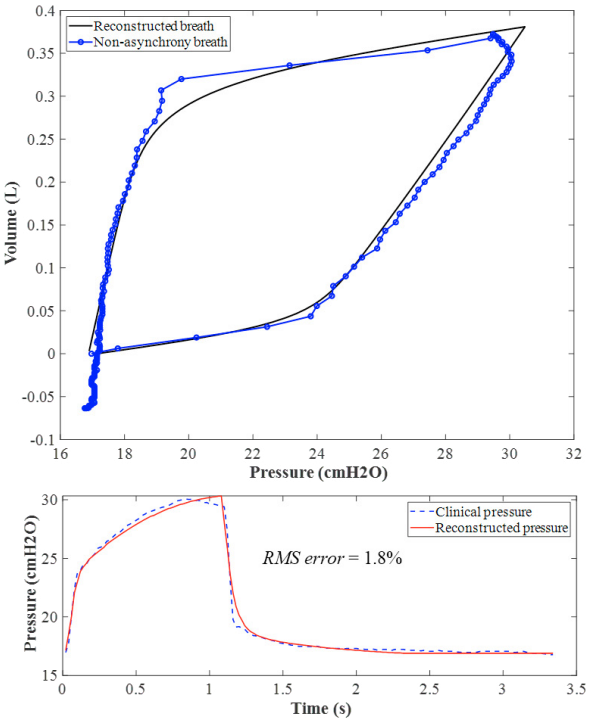

Fig. 5. Comparison of the reconstructed breath cycle to the observed non-asynchrony breath cycle.

However, the occurrence of inaccurate reconstruction is lower than 10%, merely affecting the trend analysis of patient asynchrony. Clinically, the presence of asynchrony might vary for each single breath, while patient condition may not vary for a short-period such as 30 secs or 60 secs equivalent to 10-20 breath cycles. Thus, a moving average of reconstruction could be implemented across every 10-20 breaths (~1 min on average at typical breathing rates for ventilated ICU patients of 15-20 breaths per minute), enabling a steady and accurate reconstruction of ventilated response or fundamental mechanics, as well as the estimation of asynchrony severity.

In addition, the proposed method provides a breath-to-breath real-time reconstruction of asynchrony as HLA and HLM identification and simulation are direct calculation suffering no convergence issues or high complexity. Therefore, the steady and accurate reconstruction can be readily available in real-time via moving average of the current breath and previous setting breaths, which would be critical for practical clinical use.

Finally, asynchrony magnitude is assessed using E_{asyn}, as shown in Fig. 8. Patient 1 shows significant asynchrony with over 50% breaths having $E_{asyn} > 50\%$, which matches direct manual observations over these analysed breathing cycles. In contrast, the asynchrony magnitude and incidence for Patient 2 is much lower with $E_{asyn} < 10\%$ for over 90% of breaths likely because a SIMV ventilation mode was applied to Patient 2 producing a better adjustment of ventilator delivery. Therefore, accurate reconstruction of asynchrony offers automated, high quality assessment of asynchrony incidence and magnitude based on the energy dissipation metric E_{asyn} presented.

Clinically, controlling energy dissipation is considered an efficient tool to adjust MV settings to minimise ventilator induced lung injury (Barnes et al., 2019). Hence, the overall results show the potential of the virtual patient model from clinical condition monitoring perspective. As noted in prior work it is also effective at predicting response to changes in care to provide guidance for a wide range of MV scenarios.

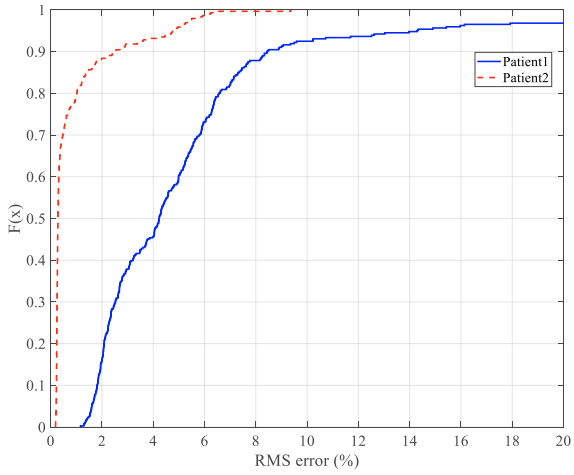

Fig. 6. Empirical cumulative distribution (CDF) of reconstruction RMS error for Patient 1 and Patient 2.

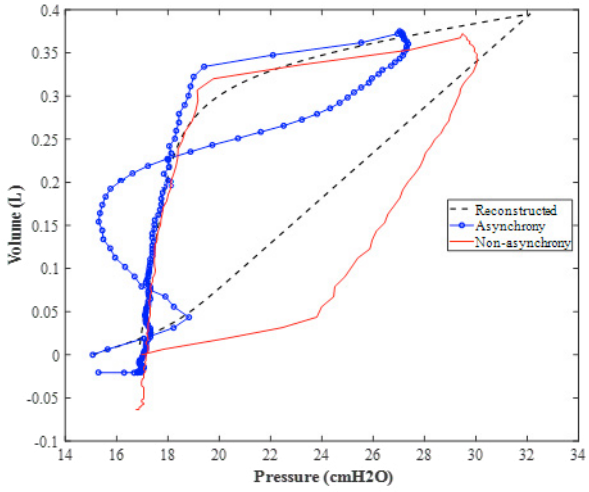

Fig. 7. Example of inaccurate reconstruction due to missing V_{m1} for Patient 1.

In terms of limitations, this work only provides a proof-of-concept validation using clinical data from two patients, although the two patients represent two very different typical asynchrony types and magnitudes. Thus, the performance of this method should be further validated with more clinical data, particularly for its robustness and generalisability to different patient conditions and lung mechanics. In addition, a further improvement might be achieved by predefining typical asynchrony patterns for different MV modes, thus enabling a more efficient and accurate reconstruction with additional constraints. However, the results in this work show validate its feasibility and potential for clinical use.

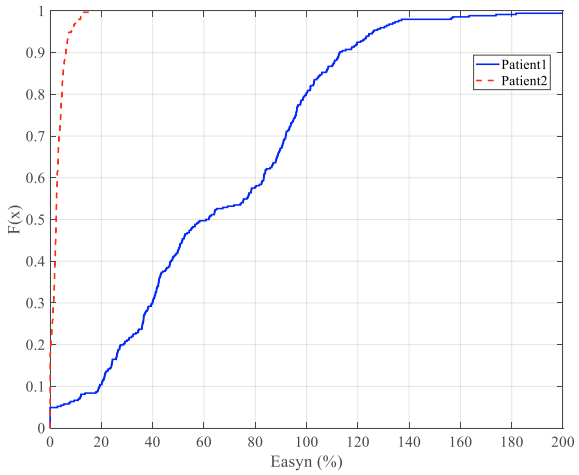

Fig. 8. Empirical cumulative distribution (CDF) of asynchrony effect metric E_{asyn} for Patient 1 and Patient 2.

5. CONCLUSIONS

This work extends a validated virtual patient model from fully ventilated respiratory response to asynchrony breathing cycles without undermining its automatous ability and calculation efficiency. Results show a high accuracy of reconstruction with the observability of the two breakpoints in the PV loop. More importantly, the modelling and reconstruction can be implemented in breath-to-breath in real-time, critical for practical clinical use. In addition, the asynchrony effect can be readily estimated via comparison of the energy dissipation of the reconstructed and measured breathing cycles. Finally, this work validates the versatility of the proposed virtual patient model for current typical MV cases, with a key feature to be implemented automatically in a breath-to-breath fashion for bedside monitoring and guidance of MV care.

6. ACKNOWLEDGEMENTS

The authors acknowledge support from the NZ Tertiary Education Commission (TEC) fund MedTech CoRE (Centre of Research Excellence; #3705718) and the NZ National Science Challenge 7, Science for Technology and Innovation (2019-S3-CRS). The authors also acknowledge support from the EU H2020 R&I programme (MSCA-RISE-2019 call) under grant agreement #872488 — DCPM. The support from the Taicang Yangtze River Delta Research Institute of Northwestern Polytechnical University is also acknowledged.

REFERENCES

Baedorf Kassis, E., Su, H. K., Graham, A. R., Novack, V., Loring, S. H. and Talmor, D. S. 2021. Reverse trigger phenotypes in acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine,* 203**,** 67-77.

Barnes, T. and Enk, D. 2019. Ventilation for low dissipated energy achieved using flow control during both inspiration and expiration. *Trends in Anaesthesia and Critical Care,* 24**,** 5-12.

Chiew, Y. S., Chase, J. G., Shaw, G. M., Sundaresan, A. and Desaive, T. 2011. Model-based PEEP optimisation in mechanical ventilation. *Biomedical engineering online,* 10**,** 1-16.

Chiew, Y. S., Tan, C. P., Chase, J. G., Chiew, Y. W., Desaive, T., Ralib, A. M. and Nor, M. B. M. 2018. Assessing mechanical ventilation asynchrony through iterative airway pressure reconstruction. *Computer methods and programs in biomedicine,* 157**,** 217-224.

Damanhuri, N. S., Chiew, Y. S., Othman, N. A., Docherty, P. D., Pretty, C. G., Shaw, G. M., Desaive, T. and Chase, J. G. 2016. Assessing respiratory mechanics using pressure reconstruction method in mechanically ventilated spontaneous breathing patient. *Computer methods and programs in biomedicine,* 130**,** 175-185.

Davidson, S. M., Redmond, D. P., Laing, H., White, R., Radzi, F., Chiew, Y. S., Poole, S. F., Damanhuri, N. S., Desaive, T. and Shaw, G. M. 2014. Clinical Utilisation of Respiratory Elastance (CURE): Pilot trials for the optimisation of mechanical ventilation settings for the critically Ill. *IFAC Proceedings Volumes,* 47**,** 8403-8408.

Epstein, S. K. 2011. How often does patient-ventilator asynchrony occur and what are the consequences? *Respiratory care,* 56**,** 25-38.

Gholami, B., Phan, T. S., Haddad, W. M., Cason, A., Mullis, J., Price, L. and Bailey, J. M. 2018. Replicating human expertise of mechanical ventilation waveform analysis in detecting patient-ventilator cycling asynchrony using machine learning. *Computers in biology and medicine,* 97**,** 137-144.

Kannangara, D. O., Newberry, F., Howe, S., Major, V., Redmond, D., Szlavecs, A., Chiew, Y. S., Pretty, C., Benyó, B. and Shaw, G. M. 2016. Estimating the true respiratory mechanics during asynchronous pressure controlled ventilation. *Biomedical Signal Processing and Control,* 30**,** 70-78.

Major, V., Corbett, S., Redmond, D., Beatson, A., Glassenbury, D., Chiew, Y. S., Pretty, C., Desaive, T., Szlávecz, Á. and Benyó, B. 2016. Respiratory mechanics assessment for reverse-triggered breathing cycles using pressure reconstruction. *Biomedical Signal Processing and Control,* 23**,** 1-9.

Major, V. J., Chiew, Y. S., Shaw, G. M. and Chase, J. G. 2018. Biomedical engineer's guide to the clinical aspects of intensive care mechanical ventilation. *Biomed Eng Online,* 17**,** 169.

Morton, S. E., Knopp, J. L., Chase, J. G., Möller, K., Docherty, P., Shaw, G. M. and Tawhai, M. 2019a. Predictive virtual patient modelling of mechanical ventilation: impact of recruitment function. *Annals of biomedical engineering,* 47**,** 1626-1641.

Morton, S. E., Knopp, J. L., Chase, J. G., Docherty, P., Howe, S. L., Möller, K., Shaw, G. M. and Tawhai, M. 2019b. Optimising mechanical ventilation through model-based methods and automation. *Annual Reviews in Control*.

Morton, S. E., Knopp, J. L., Tawhai, M. H., Docherty, P., Heines, S. J., Bergmans, D. C., Möller, K. and Chase, J. G. 2020a. Prediction of lung mechanics throughout recruitment maneuvers in pressure-controlled ventilation. *Computer Methods and Programs in Biomedicine,* 197**,** 105696.

Morton, S. E., Knopp, J. L., Tawhai, M. H., Docherty, P., Heines, S. J., Bergmans, D. C., Möller, K. and Chase, J. G. 2020b. Prediction of Lung Mechanics Throughout Recruitment Maneuvers in Pressure-Controlled Ventilation. *Computer Methods and Programs in Biomedicine***,** 105696.

Redmond, D. P., Chiew, Y. S., Major, V. and Chase, J. G. 2019. Evaluation of model-based methods in estimating respiratory mechanics in the presence of variable patient effort. *Comput Methods Programs Biomed,* 171**,** 67-79.

Ricard, J. D., Dreyfuss, D. and Saumon, G. 2003. Ventilator-induced lung injury. *Eur Respir J,* 22**,** 2s-9.

Szlavecz, A., Chiew, Y. S., Redmond, D., Beatson, A., Glassenbury, D., Corbett, S., Major, V., Pretty, C., Shaw, G. M. and Benyo, B. 2014. The Clinical Utilisation of Respiratory Elastance Software (CURE Soft): a bedside software for real-time respiratory mechanics monitoring and mechanical ventilation management. *Biomedical engineering online,* 13**,** 1-14.

Zhou, C., Chase, J. G., Rodgers, G. W., Tomlinson, H. and Xu, C. 2015. Physical Parameter Identification of Structural Systems with Hysteretic Pinching. *Computer-Aided Civil and Infrastructure Engineering,* 30**,** 247-262.

Zhou, C., Chase, J. G., Rodgers, G. W. and Iihoshi, C. 2017. Damage assessment by stiffness identification for a full-scale three-story steel moment resisting frame building subjected to a sequence of earthquake excitations. *Bulletin of Earthquake Engineering,* 15**,** 5393-5412.

Zhou, C., Chase, J. G., Sun, J. K. Q., Tawhai, M., Möller, K., Heines, S. J., Bergmans, D. C., Shaw, G. M. and Desaive, T. 2021. Virtual Patients for Mechanical Ventilation in the Intensive Care Unit. *Computer Methods and Programs in Biomedicine,* 199**,** 105912.