

Mechanical ventilatory parameters based on a mathematical model for diagnosis/treatment of older adults with ARDS

by

Ivan Dario Ruiz Hidalgo M.Sc

Directors:

Guillermo Andres Jaramillo Pizarro PhD.

Jose Isidro García Melo PhD.



**IMPETUS
INDOMITUS**

Research Team in energy conversion
& propulsion revolution



Escuela de Ingeniería Mecánica
Universidad del Valle
Santiago de Cali
2025

Abstract

This study introduces the development and evaluation of a novel mathematical model designed to estimate mechanical ventilatory parameters in older adults diagnosed with Acute Respiratory Distress Syndrome (ARDS). Expanding upon the traditional Single Compartment Model (SCM), the proposed model, called the Recruitment and Distention Elastance Analysis + Slice model (RDEA + Slice), incorporates new strategies for improved physiological representation. Validation with real patient data showed that the RDEA + Slice offers enhanced numerical accuracy compared to conventional methods, especially under conditions involving spontaneous breathing and patient ventilator asynchronies.

To further explore asynchrony detection, the pressure signal was interpreted as a combination of a synchronous baseline and noise introduced by asynchronous activity. This noise was considered to be random in nature and dependent on the type of asynchrony. A frequency-domain filtering approach was used to isolate these components, leading to the formulation of two indices: the Asynchrony Event Percentage (AE%) and the Asynchrony Index (AI%). These metrics were applied to three datasets, allowing for the identification of threshold-based criteria to distinguish between synchronous and asynchronous breathing patterns. While the method proved effective in detecting common asynchrony types such as flow mismatch and premature cycling, limitations were observed in cases involving ineffective effort and double triggering, which may not significantly alter the pressure waveform.

Additionally, image processing techniques were validated and employed to extract ventilatory data from video recordings of ventilator screens, addressing technological limitations in resource-constrained environments. The extracted data, validated through comparisons with sensor-derived measurements, demonstrated high fidelity, achieving high R^2 values and maintaining low Mean Squared Error. This approach provides a practical solution for data acquisition in low-resource settings, a common challenge in emerging economies.

The results suggest that the proposed model, detection indices, and image processing methodology could support clinical decision-making by providing insights into patient-specific respiratory mechanics. Future work should focus on integrating the approach into real-time systems, expanding patient datasets, and exploring predictive modeling for early identification of asynchrony events in intensive care settings.

Acknowledgements

I would like to express my sincere gratitude to Hospital San José de Buga for granting access to their facilities and allowing the development of this study within their institution. Their support and collaboration were essential to the completion of this work.

In Homer's words: 'Do it for her.'
In my heart: 'Do it for Nicolás.'

(Thank you, my son, for being my inspiration.)

Table of Contents

List of Tables	7
List of Figures	8
Nomenclature and Abbreviations	11
Nomenclature	11
1 Introduction	12
1.1 Problem Definition	14
1.2 Justification	16
1.3 Objectives	18
1.4 Methodology	18
1.5 Organization of this dissertation	21
2 State of the Art	22
2.1 Theoretical framework	22
2.1.1 Respiratory system: Anatomy and physiology	23
2.1.2 Pathologies	25
2.1.3 Mechanical Ventilation	27
2.1.4 Measurement of Pulmonary Data	28
2.1.5 Lung Mechanics	29
2.1.6 The Single Compartment Model	31
2.1.7 Spontaneous Breathing in Mechanical Ventilation	33
2.2 Pulmonary Dynamics Background	34
2.2.1 Exploring Pulmonary Dynamics through Computational Methods .	35
2.2.2 Reduced Order Models	36

TABLE OF CONTENTS

2.2.3	Patient-Specific models	37
2.2.4	Researches on SBs	38
2.2.5	Background Summary	39
2.3	Conclusions	41
3	Data acquisition process	43
3.1	Methods	44
3.1.1	Validation of Image Processing with a Ventilator Emulator	44
3.1.2	Clinical Data Acquisition	45
3.1.3	Evaluation of Image Processing Performance	45
3.1.4	Data Analysis	46
3.1.5	Replication of Results Using Image Processing	48
3.2	Results	48
3.3	Elastance analysis using Image Processing	51
3.4	Conclusions	51
4	Proposing a new Model	54
4.1	Methods	55
4.1.1	Shape functions approach	56
4.1.2	Recruitment Elastance Analysis Model (REA)	56
4.1.3	Distention Elastance Analysis Model (DEA)	58
4.1.4	Recruitment and Distention Elastance Analysis Model (RDEA)	58
4.1.5	RDEA + SLICE method	59
4.1.6	Model Analysis	60
4.1.7	Patients data	60
4.2	Results and Discussion	61
4.2.1	The REA Model	63
4.2.2	The DEA Model	64
4.2.3	The RDEA Model	64
4.2.4	Analysis and Summary of REA, DEA, and RDEA Model Results	65
4.2.5	Evaluating RDEA + Slice model	67
4.2.6	Model Identification	70
4.3	Conclusions	71

5	Obtaining an Asynchrony Index	73
5.1	Methods	74
5.1.1	Derivation of Asynchrony Event Percentage (AE%)	75
5.1.2	Derivation of the Asynchrony Index (AI%)	76
5.1.3	Patient Data	77
5.2	Results	80
5.2.1	Evaluating the AE% and AI%	80
5.2.2	Performance of the Asynchrony Index and Clinical Interpretation .	86
5.3	Discussion	87
5.4	Conclusions	91
6	Conclusions and Future Works	92
	References	95

List of Tables

2.1	Contribution of the present work	41
3.1	Dataset	48
3.2	R^2 for Reconstructed Ventilatory Curves	49
3.3	MSE for Reconstructed Curves Compared with Sensor Data	51
4.1	Dataset 1	61
4.2	Dataset 2	61
4.3	Shape functions proposal summary	66
4.4	R^2 for SCM, Morton and proposed models Dataset 1	67
4.5	R^2 for SCM, Morton, and proposed models – Dataset 2	69
4.6	Comparison of MRE for all evaluated models	70
4.7	Model Identifiability: Determinant and Rank	71
5.1	Patient Dataset 1	77
5.2	Patient Dataset 2	78
5.3	Patient Dataset 3	79
5.4	Asynchrony Index Values	87
5.5	Asynchrony Index Values Dataset 3	90

List of Figures

1.1	Problem Tree	15
1.2	Proposed Methodology	20
2.1	Respiratory mechanics parts	23
2.2	Lung Airways	24
2.3	Lung Airways	30
2.4	SCM: a) Lung structure b) Pneumatic analogy, c) Electric analogy	31
2.5	Application of the SCM in: a) Patient completely sedated b) Patient with partial Sedation	33
3.1	Data acquisition setup	44
3.2	Ventilator and patient emulator developed by Universidad del Valle	45
3.3	Emulator monitoring screen	46
3.4	Sensor-derived ventilatory data from the emulator	47
3.5	Image Processing Flowchart: a) Original Image (Pressure vs. Time), b) Binarized Image, c) Pixel-Based Reconstruction, d) Filtered Data	47
3.6	Pressure waveform: a) P1, b) P2, c) P3, d) P4, e) P5, f) P6, g) P7, h) P8	49
3.7	Comparison of Reconstructed Ventilatory Curves: a) Original Waveforms; b) Normalized Graphics	50
3.8	Performance Evaluation: MSE of Image Processing Methods Against Sensor-Derived Data	50
3.9	Bland-Altman Analysis of Agreement Between Sensor Data and Image-Derived Methods for Pressure (a and d), Volume (b and e), and Airflow (d and f)	52
3.10	Expiratory Elastance vs Inspiratory Elastance linear regression	52
4.1	Evolution from Base Models to Proposed Models	55
4.2	Morton Shape Functions. a) ϕ_1 , b) ϕ_2 , c) θ_1 , and d) θ_2	57

4.3	Shape function proposal for REA	57
4.4	Shape function proposal for DEA	58
4.5	RDEA+Slice model	59
4.6	Pressure (P) and airflow (Q) versus time for each patient. a) P1, b) P2, c) P3, d) P4, e) S1, f) S2, g) S3, h) S4	62
4.7	SCM and Morton Comparison. a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4	63
4.8	R^2 values for shape function $\phi_1 = 1 - N(V - 1)^2$. a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4	64
4.9	R^2 for shape function $\phi_2 = (P/60)^M$. a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4	65
4.10	R^2 for shape functions $\phi_1 = 1 - N(V - 1)^2$ and $\phi_2 = (P/60)^M$ combined. a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4	66
4.11	REA, DEA and RDEA comparison a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4	67
4.12	RDEA + Slice method, dataset 1. a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4	68
4.13	RDEA + Slice method, dataset 2. a) Patient S1, b) Patient S2, c) Patient S3, d) Patient S4	69
5.1	Pressure signal interpretation in the presence of RAs	75
5.2	E vs t example	75
5.3	AE% vs t example	76
5.4	P and Q vs t for Patient Dataset 1	77
5.5	P and Q vs t for Patient Dataset 2	78
5.6	P and Q vs t for Patient Dataset 3	79
5.7	Frequency analysis dataset 1: Patient a)P1, b)P2, c)P3 and d)P4	81
5.8	Frequency analysis dataset 2: Patient a)S1, b)S2, c)S3 and d)S4	81
5.9	Cutoff frequency (F_c) dataset 1: Patient a)P1, b)P2, c)P3 and d)P4	82
5.10	Cutoff frequency (F_c) dataset 2: Patient a)S1, b)S2, c)S3 and d)S4	82
5.11	Original and filtered signal dataset 1: Patient a)P1, b)P2, c)P3 and d)P4	83
5.12	Original and filtered signal dataset 2: Patient a)S1, b)S2, c)S3 and d)S4	83
5.13	Asynchrony events on dataset 1: Patient a)P1, b)P2, c)P3 and d)P4	84
5.14	Asynchrony events on dataset 2: Patient a)S1, b)S2, c)S3 and d)S4	84

LIST OF FIGURES

5.15	Sensitivity analysis showing the AI% as a function of the selected AE% Tolerance range for synchronous (P1-P4, blue) and asynchronous (S1-S4, orange) patients.	85
5.16	a) AUC of the AI% classifier as a function of the selected Tolerance Band, b) Final ROC Curve for the best AI% classifier (AUC = 0.87).	86
5.17	Frequency analysis dataset 3: Patient a)T1, b)T2, c)T3 and d)T4	88
5.18	Cutoff frequency (F_c) dataset 3: Patient a)T1, b)T2, c)T3 and d)T4	88
5.19	Original and filtered signal dataset 3: Patient a)T1, b)T2, c)T3 and d)T4	89
5.20	Asynchrony events on dataset 3: Patient a)T1, b)T2, c)T3 and d)T4	89

Nomenclature and Abbreviations

Nomenclature

E	Elastance
P_{aw}	Airways Pressure
P_{ip}	Intrapulmonary Pressure
P_{pl}	Pleural Pressure
Q	Airflow
R	Resistance
V_t	Lung tidal volume
V	Volume

Abbreviations

ALI	Acute Lung Injury
AT	Auto Triggering
ARDS	Acute Respiratory Distress Syndrome
COPD	Chronic Obstructive Pulmonary Disease
DC	Delayed Cycling
DT	Double Triggering
FA	Flow Asynchrony
$F_I O_2$	Fraction Inspired Oxygen
FRC	Functional Residual Capacity
ICU	Intensive Care Unit
IE	Ineffective Effort
MV	Mechanical Ventilation
PEEP	Positive End Expiratory Pressure
PIP	Peak Inspiratory Pressure
PC	Premature Cycling
PV	Pulmonary Ventilation
PVA	Patient-Ventilator Asynchrony
$P_a O_2$	Partial Pressure of Oxygen
$P_a CO_2$	Partial Pressure of Carbon Dioxide
RA	Respiratory Asynchrony
RT	Reverse Triggering
SB	Spontaneous Breathing
VILI	Ventilator Induced Lung Injury
WOB	Work of Breathing

Chapter 1

Introduction

Mechanical ventilation (MV) is a critical intervention for patients with severe clinical conditions [1, 2] and serves as vital support for individuals experiencing respiratory failure in an Intensive Care Unit (ICU) [3]. Despite substantial advancements in MV, a persistent gap remains in the clinical information required to optimize patient recovery [4]. In response, researchers have widely employed model-based methods [5–7] to analyze lung mechanics and develop tools that offer crucial insights without necessitating additional invasive monitoring devices. These methodologies enable a deeper understanding of pulmonary dynamics, which is essential for advancing personalized therapeutic strategies. As highlighted by Chase et al.[8], simplified models have significantly contributed to shifting care in ICUs from a 'one-size-fits-all' approach toward more adaptive and patient-specific strategies.

While MV significantly contributes to air delivery toward alveolar surfaces, it may also lead to Patient-Ventilator Asynchronies (PVAs), which are events characterized by a mismatch between patient respiratory demand and ventilator assistance [9]. These PVAs can result in an increased respiratory workload, prolonged weaning periods, and extended stays in ICUs. Asynchronies may occur during any ventilation mode, whether fully controlled or partially assisted; however, they are more frequent during non-invasive ventilation or partially assisted modes, in which spontaneous patient breathing triggers ventilator support [10].

Selecting appropriate ventilatory parameters is essential for minimizing Ventilator-Induced Lung Injuries (VILIs) [11, 12] and plays a critical role in patient recovery, as these settings must be continuously adjusted through recruitment maneuvers [13]. Although general guidelines currently guide ventilator parameter selection using a conventional 'one-size-fits-all' approach [14, 15], there is a growing emphasis on developing patient-specific models to enable personalized treatment strategies [16–18]. In this context, accurate detection of Respiratory Asynchronies (RAs) becomes crucial, as these events significantly influence patient outcomes by increasing respiratory effort, extending the duration of ventilatory support, and prolonging ICU stays [19, 20]. Timely and precise detection of asynchronies can thus support clinical decisions, allowing clinicians to optimize ventilator settings and personalize therapeutic interventions. Additionally, effective identification of these events

could facilitate the indirect, non-invasive estimation of clinical parameters such as the Work of Breathing (WOB), providing further insights into respiratory mechanics and muscle status without resorting to invasive techniques.

However, the presence of Spontaneous Breathing (SB) complicates the identification and characterization of RAs. While respiratory cycles in fully sedated patients are entirely driven by the ventilator, patients under partial sedation exhibit breathing efforts partially assisted or synchronized with the device, making it challenging to clearly distinguish patient-driven versus ventilator-driven dynamics. As noted by Kim et al. (2021) [21], the complexity of SB is further highlighted by observing elastance-time curves, which can display negative elastance values in the presence of SBs or RAs. This underscores the necessity of developing robust and reliable tools specifically aimed at detecting and characterizing RAs, ultimately enabling clinicians to better tailor respiratory support to individual patient needs.

Monitoring ventilatory mechanics is essential for assisting healthcare professionals in optimizing ventilatory maneuvers using simplified mathematical models [2, 17, 22]. Nevertheless, these models often have significant limitations, as they typically do not consider RAs and SBs [3]. These phenomena frequently go undetected and unquantified in clinical settings [23], primarily because conventional models are unable to adequately capture the complexities inherent in ventilatory waveforms under such conditions. As a result, the assessment of patient respiratory dynamics remains incomplete, which compromises both comprehensive monitoring and effective treatment [1].

Currently, SBs and RAs have been analyzed by measuring variables not routinely monitored in ICUs, such as esophageal and gastric pressures. While studies have attempted to analyze spontaneous respiratory behaviors and quantify their clinical impact, recent research, such as that by Knopp et al. (2024) [24], emphasizes that there remains a critical need for more adaptable and comprehensive models. These models should be capable of accurately capturing and quantifying the effects of these additional respiratory efforts resulting from asynchronies. Thus, pressure reconstruction methods [3, 23] have been developed to produce respiratory curves that closely reflect respiratory dynamics, thereby minimizing the variability caused by RAs [25].

Considering the clinical relevance of promptly identifying RAs, it is critical to develop tools capable of real-time detection and quantification of these events [10, 24]. For instance, Poole et al. (2014) [10] introduced parameters such as the Asynchrony Index, which quantifies the percentage of asynchrony events relative to total breaths in real time. This further underscores the potential of real-time monitoring systems to enhance clinical decision-making and improve patient outcomes by enabling personalized respiratory management strategies.

Damanhuri et al. (2016) [26] developed a method to quantify the additional efforts associated with respiratory asynchronies by reconstructing pressure-time (P vs. t) curves. This technique was applied primarily to respiratory cycles visibly affected by pressure variations resulting from patient efforts during asynchronies. The analysis of these reconstructed waveforms enabled the authors to propose a tool for real-time detection of RAs. Subsequently, Chiew et al. (2018) [23] introduced the Iterative Pressure Reconstruction

(IPR) method to evaluate asynchrony during MV. This method reconstructs asynchronous airway pressure waveforms by iteratively adjusting them to closely resemble passive breathing. The authors suggested that future applications of this method could facilitate real-time monitoring of asynchrony magnitude, thereby contributing to the optimization of MV therapy. More recently, Arunachalam et al. (2020) [27] proposed the Gaussian Effort Model, derived from the Single Compartment Model, to capture patient effort pressures.

Conventional respiratory models, such as the widely used Single Compartment Model (SCM), have demonstrated significant limitations when attempting to replicate or detect RAs and SB events during MV, highlighting the need for more sophisticated modeling approaches [3, 25, 28]. The objective of this research is to propose a tool for detecting RAs by first developing a mathematical model capable of accurately reproducing patient-ventilator interactions in the presence of SB efforts. It is anticipated that the analysis of ventilatory parameters derived from a model that closely matches clinical ventilatory curves (particularly the pressure-time waveform) can provide valuable insights and establish a foundation for defining parameters that could enable real-time detection of RAs. The following section presents the problem statement and its justification. Subsequently, the proposed objectives and the general methodology adopted to achieve them are outlined. Finally, this chapter concludes with an explanation of how the present document is organized.

1.1 Problem Definition

In current clinical practice, it is common for patients diagnosed with Acute Respiratory Distress Syndrome (ARDS) to receive treatment through MV, with ventilatory parameters typically configured based on the clinical judgment of the attending physician [8]. This approach presents considerable challenges in establishing standardized protocols, particularly regarding ventilatory maneuvers, due to patient variability, as each individual responds differently to both the underlying condition and the applied treatment. Consequently, this variability complicates the creation of consistent recovery strategies and contributes to persistently high hospital mortality rates [4].

Within this context, the analysis of respiratory mechanics, particularly through simplified mathematical models, becomes crucial for assisting healthcare providers in clinical decision-making processes [5, 8]. Although widely-used models, such as the Single Compartment Model (SCM), have shown utility in describing general respiratory mechanics, they exhibit significant limitations when faced with SBs and RAs, failing to accurately represent the complexities of patient-ventilator interactions under these conditions [3, 28]. As a result, critical respiratory events like PVAs often remain undetected and unquantified, impairing optimal clinical management and patient outcomes [1].

The RAs are particularly relevant from a clinical perspective, as they increase patient discomfort, respiratory effort, lengthen the weaning process, and prolong ICU stays [10]. Thus, timely and accurate detection of these events is clinically significant. Nonetheless, detecting RAs currently depends on invasive and specialized monitoring methods that are not routinely available or practical in many ICU settings.

Despite substantial research efforts aimed at quantifying RAs through techniques such as Gaussian effort modeling [27], iterative airway pressure reconstruction (IPR) [23], and pressure-time curve reconstruction methods [26], a significant gap remains. Current mathematical models still lack the capacity to robustly capture the complexities of SB efforts and RA. Consequently, clinicians face considerable difficulties in standardizing patient monitoring protocols, which limits their ability to implement reliable real-time detection tools in everyday clinical practice. Moreover, given the heterogeneity of patients and the inherent complexity of pulmonary dynamics, existing models can only approximate the natural behavior of SB, underscoring the necessity for improved modeling approaches and leaving considerable scope for clinically meaningful contributions.

In view of these limitations, the central research question emerges: "What clinically relevant mechanical ventilatory parameters can be obtained from mathematical modeling approaches to assist in the diagnosis and/or treatment of older adults with ARDS?" Chronic respiratory diseases account for approximately 4 million deaths annually [29], with older adults (over 60 years) representing one of the most vulnerable populations [30]. Among respiratory conditions, ARDS—clinically defined by the Berlin definition—is especially critical, as it can rapidly deteriorate and lead to chronic complications or high mortality rates [31–33]. Addressing the aforementioned research question could therefore significantly impact clinical outcomes for this vulnerable demographic, reducing dependence solely on clinician expertise, promoting the standardization of ventilatory protocols, and potentially lowering ICU mortality rates associated with ARDS management [8]. Consequently, this research seeks to advance mathematical modeling techniques enriched with actual clinical data, enabling a more accurate representation of respiratory mechanics and providing reliable parameters to detect RAs.

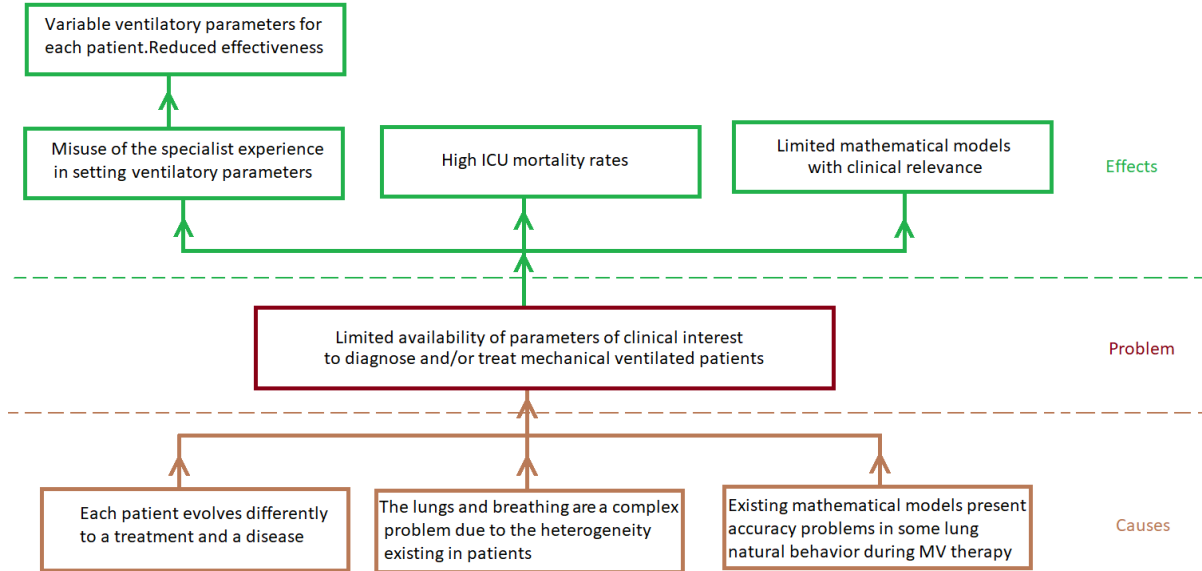


Figure 1.1: Problem Tree

The previously discussed limitations and challenges associated with MV in the context of RAs and SBs can be systematically illustrated through the problem tree depicted

in Figure 1.1. This diagram summarizes the core issue—the limited availability of clinically relevant parameters for diagnosing and treating mechanically ventilated patients—as well as its primary causes and the subsequent clinical consequences. Specifically, it highlights that the heterogeneity of patient responses, the inherent complexity of pulmonary dynamics, and the shortcomings of existing mathematical models collectively result in insufficient clinical information. Consequently, this lack of reliable parameters translates into variable and potentially ineffective ventilatory settings, misuse of specialist expertise, limited application of mathematical modeling tools, and ultimately, high ICU mortality rates. Therefore, addressing this central problem through the development of more robust mathematical tools for detecting RAs could significantly enhance clinical decision-making and patient outcomes.

Therefore, the present research aims to address this gap by proposing a novel mathematical model, derived from clinical patient data, that effectively incorporates SB dynamics. Analysis of the ventilatory parameters derived from this model seeks to identify key indicators for detecting RAs. Ultimately, this tool has the potential to support clinical decision-making, improve therapeutic strategies, and enhance patient recovery outcomes in ICU settings. Although validated using real patient data, further clinical studies and integration into real-time monitoring systems would be necessary before its direct clinical implementation.

1.2 Justification

Currently, MV remains an essential therapy in critical care, where individualizing treatment has become increasingly important to enhance therapeutic outcomes, reduce ICU mortality, and minimize ventilator-associated complications, such as overstretching or lung injury due to inappropriate ventilator settings [8]. Despite ongoing technological advancements, MV management practices have not significantly evolved over the past three decades, leaving ample opportunity for research and clinical improvements [8]. Prolonged use of MV considerably increases patient care costs, placing a heavy financial burden on hospitals by occupying critical ICU resources that could be utilized for other patients [34].

Predictive models have been proposed to support clinicians in ventilatory maneuvers [35, 36]. However, there remains a significant gap in developing effective tools for capturing and quantifying respiratory efforts associated with SBs and RAs [37]. Although monitoring techniques such as electromyography of the diaphragm or esophageal pressure measurements can assist clinicians in visualizing RAs, these methods are invasive and therefore not routinely implemented in ICU settings [9]. The occurrence of SBs is known to increase respiratory effort, producing distinct alterations in ventilatory curves, thereby complicating the accurate estimation of essential ventilatory parameters such as resistance and elastance. Consequently, valuable clinical information may be lost, affecting the quality of patient care [26]. In this context, Kallet et al. (2018) [38] have demonstrated that SB trials and daily sedation interruptions—strategies that periodically test a patient’s readiness for spontaneous ventilation and momentarily reduce sedation to assess ventilatory

autonomy—can effectively reduce MV duration and ICU length of stay, highlighting the importance of appropriately detecting and managing SB efforts.

Patients undergoing invasive MV with an endotracheal tube have a mortality rate four times higher than that of non-ventilated patients [4]. Despite the risks associated with intubating a patient in an ICU, MV remains one of the most effective methods for treating patients with ARDS [2]. However, there is limited relevant clinical information available to establish the correct diagnosis and possible treatments for ventilated patients. This becomes even more pronounced in the presence of SB, where asynchronies prevent conventional models from accurately reproducing the ventilatory curves of a patient with SB, leading to the loss of valuable information regarding the additional effort exerted during the inspiratory phase, which could compromise the recovery process.

Ventilatory parameters are predominantly adjusted based on clinicians’ experience, leading to significant variability in treatment protocols and potentially increasing patient injuries and mortality rates among intubated patients [4, 39]. Inaccurate ventilator settings chosen by clinicians can result in barotrauma, volutrauma, atelectasis, and other forms of lung damage collectively known as VILI [4, 40]. Therefore, developing patient-specific protocols becomes crucial, as individualized ventilatory strategies can enhance lung recruitment and improve blood oxygenation while minimizing VILI risks.

To address these challenges, various studies have focused on identifying and quantifying RAs, which can exacerbate lung damage if left undetected. For instance, Major et al. (2016) [25] investigated a specific type of RA known as “reverse-trigger,” which occurs primarily during the inspiratory phase and significantly increases the associated respiratory effort. These authors quantified this additional effort by comparing reconstructed respiratory waveforms with normal waveforms. Similarly, waveform reconstruction techniques have been utilized by other researchers to develop methods for real-time detection of RAs, contributing to the advancement of personalized ventilatory management [3, 23, 41].

Hence, emerging model-based methods are critically important for improving the accuracy of ventilator settings to enhance alveolar recruitment and reduce the risk of VILIs [2–4]. The motivation behind this research is to develop and analyze a mathematical model capable of more precisely replicating respiratory mechanics in mechanically ventilated older adults diagnosed with ARDS experiencing SB. Current conventional models struggle to accurately reproduce ventilatory waveforms under SB conditions, limiting their clinical utility. Therefore, by proposing a more robust mathematical representation that better captures spontaneous respiratory behavior, this work aims to identify clinically relevant ventilatory parameters that could serve as a foundation for creating effective tools for detecting RAs. Previous authors have contributed to this field by attempting to quantify RAs and the associated WOB, underscoring the persistent limitations of conventional models [1, 3]. Thus, this research seeks to advance this area by developing a mathematical framework applicable to real-time monitoring and decision-making in ICU settings.

1.3 Objectives

General Objective

Obtain mechanical ventilatory parameters based on a mathematical model as an insight supply for diagnosis and/or treatment of older adults with Acute Respiratory Distress Syndrome (ARDS)

Specific Objectives

- Propose a mathematical model based on a statistical analysis of the Single Compartment Model (SCM).
- Improve numerical accuracy of the proposed mathematical model with respect to the SCM in a specified study target group: older adults with ARDS.
- Evaluate the respiratory state of the patient based on the analysis of the proposed mathematical model.

1.4 Methodology

This study was conducted in strict compliance with applicable ethical guidelines. Approval was obtained from the Ethics Committee of the Universidad del Valle (Approval No. 047-020), with the submission made on August 24, 2020 and final approval granted on September 14, 2020. Furthermore, the study underwent additional review and was approved by the Research Ethics Committee of Fundación San José de Buga (Valle del Cauca, Colombia), with formal approval granted on December 11, 2023. To ensure the protection of patient privacy, all data were anonymized. Consequently, the project was structured into three distinct phases to safeguard data integrity and ethical compliance throughout the study.

To achieve the general objective, the research methodology was structured into three sequential phases, each designed to systematically address the specific objectives of this dissertation. Phase 1 (Chapter 3) focuses on validating the data acquisition process to ensure reliability for subsequent analyses. Phase 2 (Chapter 4) addresses Objectives 1 and 2 through a quantitative and statistical evaluation of the Single Compartment Model (SCM). Based on this analysis, a new mathematical model is proposed and shown to outperform the SCM in terms of numerical accuracy. Phase 3 (Chapter 5) addresses Objective 3 by applying the proposed model to develop an index aimed at evaluating the respiratory condition of the patient.

Phase 1 – Obtaining Data through Image Processing

In this initial phase, ventilatory waveform data are acquired from 10 sedated patients, each contributing one minute of recorded ventilatory therapy, using an image-processing approach at Hospital San José de Buga. The goal is to validate image processing as a reliable method for extracting ventilatory data, especially in resource-limited environments common to emerging economies such as Colombia. Inspired by the approach of Leros et al. (2023) [42], who utilized image-processing techniques to capture ventilatory curves from graphical data, and benchmarking against the analysis performed by Howe et al. (2020) [17], we demonstrate that inspiratory and expiratory waveforms obtained through image processing are statistically indistinguishable from those directly measured by ventilator sensors. This validation underscores the feasibility of a cost-effective and clinically relevant solution, filling a notable gap in the field of respiratory mechanics by providing a robust alternative for settings where advanced monitoring resources may be limited. The verification of image processing as a tool for obtaining patient ventilatory curves was addressed in Chapter 3.

Phase 2 – Model Development

After confirming the reliability of the image-based data acquisition in Phase 1, this second phase is dedicated to the core model development of this dissertation. The methodology begins with a quantitative analysis of the Single Compartment Model (SCM) to establish its performance limitations when fitting the pressure-time (P vs. t) curves of patients exhibiting SB. This initial evaluation, using statistical metrics like the coefficient of determination (R^2) and Mean Relative Error (MRE), provides the necessary foundation to then propose an improved model with superior numerical accuracy, a process detailed in Chapter 4. This effort was inspired by the shape-function approach proposed by Morton et al. (2019) [43], who accounted for factors such as pulmonary distensibility, alveolar recruitment, and higher-order airway resistance, thereby improving curve-fitting performance for sedated patients. Building on these principles, the present work seeks to extend the method by proposing additional shape functions capable of capturing the RAs that commonly arise in SB cases.

To achieve this, data from eight patients presenting SB events were subdivided into two independent datasets, each recording 6 minutes of therapy and comprising four patients (see Figure 1.2). The first dataset was used to propose and calibrate the new mathematical model, while the second dataset served for testing and validation, thereby mitigating the risk of circular reasoning. Initially, families of shape functions were proposed, tested, and analyzed to explore a broad range of possible representations and identify those offering the best fit for the ventilatory curves. Although these new shape functions improved the model behavior, they were insufficient to fully capture the complexity of the waveforms. Consequently, the approach was refined by incorporating a modification of the Slice method proposed by Guttmann et al. (1994) [44], resulting in a more robust model capable of detecting and quantifying RAs effectively. The details of this procedure are discussed in Chapter 4.

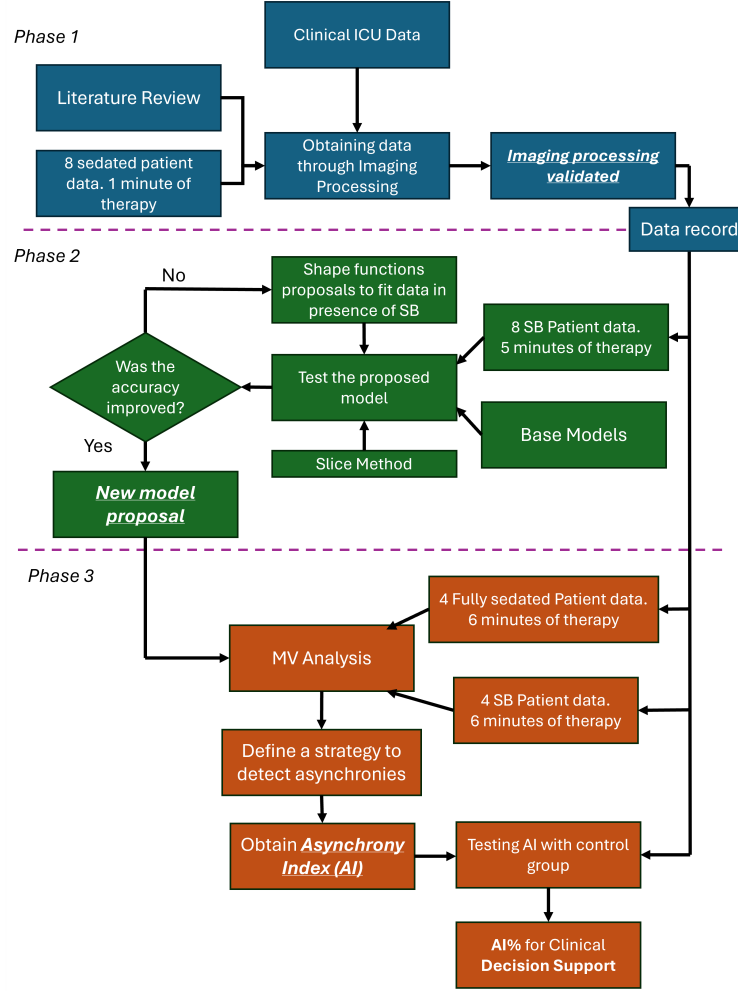


Figure 1.2: Proposed Methodology

Phase 3 – Proposing an Asynchrony Index

After obtaining the new mathematical model, the next step was to derive clinically relevant parameters that could support the diagnosis and treatment of ventilated patients. The ultimate aim was to quantify and detect RAs. The model developed in Phase 2 was employed to analyze ventilatory data from 8 additional patients (4 under controlled ventilation and 4 exhibiting SB, each contributing six minutes of recorded therapy). To validate the performance of the proposed asynchrony index, a third group of patients was used as a control group, allowing for a comparative evaluation of the accuracy and robustness of the index in detecting asynchronies. By examining the pressure-time (P vs. t) curves, this approach enabled the formulation of an asynchrony index that potentially complements the information provided by conventional MV therapy and enriches the clinical perspective on patient recovery status.

This final phase not only confirms the usefulness of the refined mathematical model in capturing patient-specific respiratory mechanics but also establishes a foundation for

future clinical tools. By providing healthcare professionals with parameters and reference values that describe asynchronies and the associated extra effort in SB, this phase opens avenues for more personalized MV maneuvers, guiding specialists in optimizing patient care, recovery, and weaning processes. Chapter 5 presents the study of ventilatory mechanics in these patients and explains how it integrates with a tool for detecting RAs. In this context, Figure 1.2 shows a summary of the proposed methodology.

1.5 Organization of this dissertation

This dissertation is organized as follows: Chapter 2 presents the state of the art, including relevant definitions and equations necessary for this research. Chapter 3 proposes and validates an image-processing methodology for acquiring patient ventilatory waveforms. Although this image-based approach has not been previously explored by other authors in the field, its implementation constitutes a significant contribution to respiratory mechanics research. Chapter 4 introduces a novel mathematical model designed to accurately capture and replicate RAs, accompanied by performance validation. Chapter 5 employs the proposed mathematical model to analyze MV patients experiencing RAs and SBs, subsequently proposing an asynchrony index aimed at detecting these events during MV. Finally, Chapter 6 summarizes the main conclusions of this study, discusses identified limitations, and highlights potential directions for future research.

Chapter 2

State of the Art

This chapter provides an overview of the theoretical and conceptual foundations underlying the study of human respiration, followed by a review of relevant research conducted in this field. The first section (Theoretical Framework) introduces the fundamental concepts essential for understanding respiratory mechanics, including the anatomy and physiology of the respiratory system, common pathologies, and the principles of MV. It also examines methodologies for measuring pulmonary data, explores lung mechanics, and presents the Single Compartment Model (SCM), which serves as a basis for the models discussed later. Additionally, a brief overview of the definitions of SBs and RAs, along with their role in influencing patient-ventilator interaction, is provided.

The second section (Background) reviews the key contributions made by the scientific community in modeling pulmonary dynamics. This includes an exploration of computational methods used to analyse respiratory processes, the development of reduced-order models (also known as bedside models) aimed at predicting patient-specific respiratory mechanics, and research focusing on SBs and RAs. A synthesis of previous studies is also provided to contextualize the significance of the approaches adopted in this work. Finally, the chapter concludes with a summary that highlights the most relevant findings and establishes the conceptual framework upon which the subsequent chapters are built.

2.1 Theoretical framework

This section introduces the essential concepts and principles necessary to analyze the human respiratory dynamics and its interaction with MV. This section begins by describing the anatomy and physiology of the respiratory system, followed by an overview of common pathologies that may alter pulmonary mechanics and affect MV performance. Next, it explores the fundamental aspects of MV and conventional techniques used to measure pulmonary data, which are crucial for assessing respiratory function. A discussion of lung mechanics is then provided, emphasizing the importance of understanding compliance and resistance in the context of MV. The section also introduces the SCM, a simplified representation of the respiratory system frequently used to estimate ventilatory parameters.

Finally, attention is given to the role of SBs during MV, highlighting their impact on patient-ventilator synchronization and overall respiratory outcomes.

2.1.1 Respiratory system: Anatomy and physiology

Respiration is the mechanism by which all living beings exchange gases with their environment. In humans, respiration consists of two fundamental processes: ventilation and perfusion. Ventilation involves inhalation (inspiration), where air enters the lungs, and exhalation (expiration), where air leaves the lungs. On the other hand, perfusion is primarily responsible for gas exchange ($O_2 - CO_2$) through a diffusion process that occurs at the alveolar surfaces, facilitating the transfer of gases between the circulating air and the bloodstream [45, 46]. Both processes are governed by fluid mechanics, where mass transfer plays a central role, though they operate based on different physical principles. Nevertheless, ventilation and perfusion must work synergistically to ensure effective respiration.

In this context, Figure 2.1a illustrates the main components involved in respiration. This process is regulated by the central nervous system, which coordinates the interaction of various structures, including the intercostal muscles, rib cage, diaphragm, and other anatomical elements, to facilitate natural breathing.

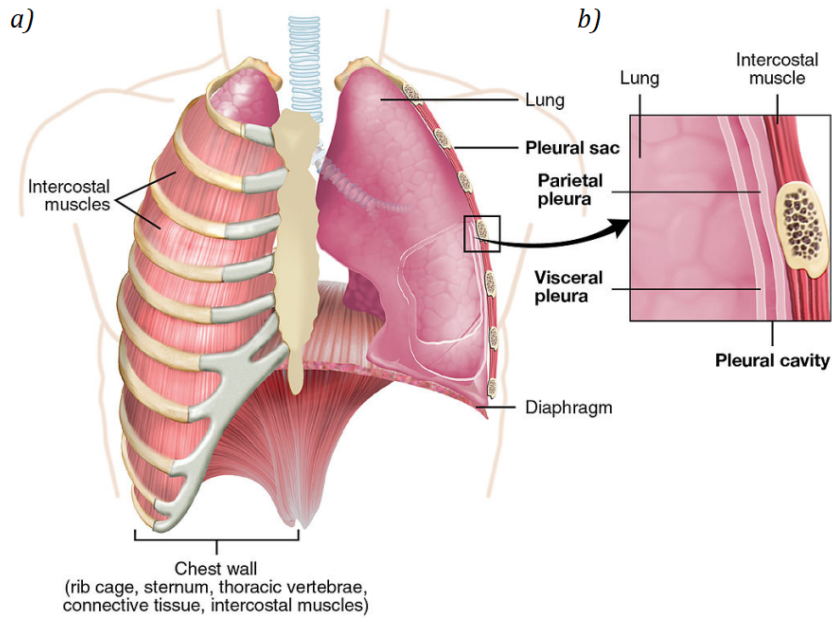


Figure 2.1: Respiratory mechanics parts

Source: Based on Howe et al. (2020)[47]

Each lung is surrounded by a membrane called the pleura, which consists of two membranes and the space between them: the visceral pleura, parietal pleura, and the pleural cavity (filled with pleural fluid) respectively (see Figure 2.1b) and act as a lubricant layer enabling the intercostal muscles and the diaphragm to move with minimal friction [47].

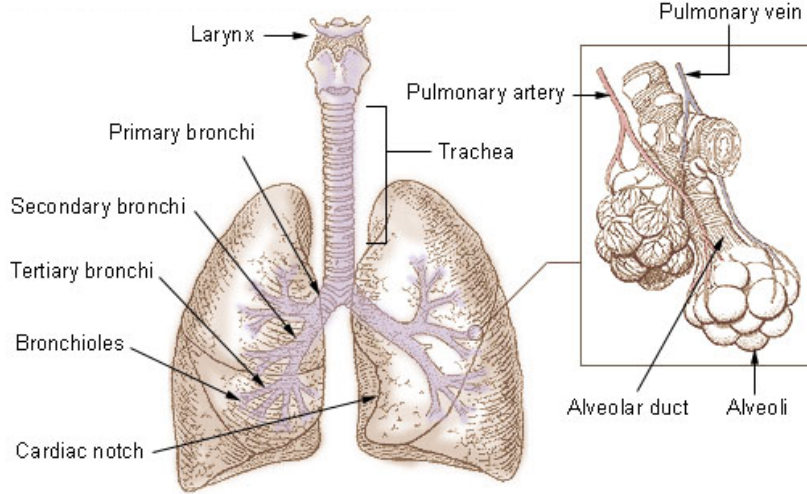


Figure 2.2: Lung Airways

Source: Based on [48]

In ventilation, the air passes through the trachea, which divides into two primary bronchi (one for each lung). Further divisions of the bronchi occur, reaching up to 23 levels (see Figure 2.2). The initial 16 branches are important for air humidification, warming, and filtering, while the subsequent branches are primarily responsible for gas exchange. At the final level, an alveolar sac is present where pulmonary veins and arteries connect with the cardiovascular system [47]. Here, perfusion takes place by diffusion across the alveolar surfaces (see Figure 2.2) [49, 50].

When a person breathes, there must be a pressure difference between the alveoli and the external atmospheric environment. Inspiration occurs when the alveolar pressure is lower than the outer environmental pressure. This happens when the diaphragm and external intercostal muscles contract, causing the thoracic cavity to expand. On the other hand, expiration is the result of an alveolar pressure higher than the outer environmental pressure. During expiration, the diaphragm and intercostal muscles relax, causing the thoracic cavity to contract. These concepts are consistent with Boyle’s Law (Equation 2.1), which is commonly used to describe respiration because it relates pressure (P) and volume (V) in two different states as follows [2, 47, 51]:

$$P_1 V_1 = P_2 V_2. \quad (2.1)$$

In this equation, P_1 and V_1 represent the initial pressure and volume of the gas, corresponding to the state before any respiratory change, such as the beginning of inspiration or expiration. Similarly, P_2 and V_2 denote the final pressure and volume, representing the conditions after the change has occurred, such as after lung expansion or compression.

During inspiration, the lung volume increases while the pressure decreases below atmospheric pressure, driven by the expansion of the thoracic cavity and the contraction of the intercostal muscles and diaphragm. Conversely, during expiration, the volume decreases as the pressure increases. This is caused by the relaxation of these muscles and the resulting

contraction of the thoracic cavity. Overall, these changes in volume and pressure during inspiration and expiration allow for the movement of air in and out of the respiratory system [17].

2.1.2 Pathologies

Pathology is the branch of medical science that investigates the causes and nature of diseases by studying and describing the conditions they produce in the body. In respiratory health, pathologies are commonly classified as either Obstructive or Restrictive [2, 47]. Indeed, while there are clear differences between obstructive and restrictive pathologies, both conditions are often present in diseases that compromise lung function.

Obstructive lung pathologies mainly affect the expiration phase due to airway obstructions caused by inflammation, bronchoconstriction, or phlegm. This type of pathology results in inadequate exhalation, causing air to become trapped in the lungs. This, in turn, reduces lung capacity and leads to shortness of breath, a persistent cough, and wheezing. The most common examples are asthma and Chronic Obstructive Pulmonary Disease (COPD), both characterized by airway obstruction. A typical feature of COPD is emphysema, which involves the progressive destruction of lung tissue at a microstructural level. In severe cases, this condition is usually treated with supplemental oxygen [2]. Generally, obstructive pathologies are managed with medications such as inhalers and steroids, which help reduce airway inflammation and improve airflow [47].

Restrictive lung pathologies are characterized by a decrease in the maximum amount of air that can be inhaled, limiting the expansion of the thoracic cage. This produces a reduction in tidal volume (see section 2.1.3) caused by an increase in lung elastance, meaning a decrease in lung compliance (see section 2.1.5), a condition commonly known as pulmonary fibrosis [2, 47]. In addition, other conditions such as neuromuscular disorders and obesity can also contribute to a reduced inspired volume because they weaken the muscles responsible for respiration, thus limiting the amount of air that can be inhaled.

Respiratory diseases are one of the leading causes of morbidity and mortality worldwide, highlighting the importance of respiratory health for general well-being [52]. The recent emergence of threats such as the SARS-CoV-2 virus, responsible for the COVID-19 pandemic, has compounded the global health challenge posed by respiratory disease. The virus causes severe respiratory complications and decreased pulmonary ventilation, necessitating continued exploration of respiratory mechanics with a particular emphasis on advancing research to address the urgent challenges associated with MV [53].

Therefore, personalized respiratory care has emerged as a priority in mitigating the mortality and morbidity associated with MV. Predictive mathematical models of lung mechanics have proven instrumental in customizing patient-specific therapies to optimize clinical outcomes [8]. Model-based methods facilitate the analysis of airflow and the prediction of respiratory dynamics, offering invaluable insights into the treatment of respiratory conditions such as asthma [54] and COPD [42], as well as other pathologies that impact respiratory mechanics and require tailored interventions [23, 26]. By integrating patient data, these models enhance diagnostic accuracy and therapeutic interventions, and their

application in refining ventilatory strategies has been linked to reductions in mortality rates [55, 56].

Respiratory failure

Respiratory failure is a term used to describe inadequate gas exchange, resulting in hypoxemia (low oxygen levels) or hypercapnia (high carbon dioxide levels) in the bloodstream. This condition can manifest in two ways. The first is associated with poor ventilation, where inhaled air fails to reach the alveolar surfaces. The second is attributed to poor perfusion, meaning the blood flow is insufficient to adequately perfuse the lungs (often as a consequence of cardiovascular issues) [3].

The human body requires an appropriate partial pressure of oxygen (P_aO_2) and must effectively remove carbon dioxide (CO_2) to maintain suitable partial pressure of carbon dioxide (P_aCO_2) levels in the bloodstream [3]. In clinical terms, respiratory failure occurs when the lungs are unable to perform adequate gas exchange, resulting in two types of failure (Type 1 and Type 2) depending on the concentrations of oxygen and carbon dioxide in the blood [16].

Type 1 respiratory failure refers to low levels of oxygen without a significant increase in carbon dioxide. This type is commonly caused by conditions such as embolism, pneumonia, pulmonary edema, and acute respiratory distress syndrome (ARDS) [16, 47]. This disorder often results in a condition known as a shunt, where the alveoli are not adequately reached by the ventilation process. As a result, there is impaired oxygen-carbon dioxide exchange, leading to low blood oxygen levels (hypoxemia) [3].

On the other hand, Type 2 respiratory failure is characterized by insufficient elimination of carbon dioxide (hypercapnia). This is often caused by high airway resistance associated with COPD or asthma. Other less common causes of hypercapnia include muscle weakness and severe obesity [47].

Respiratory failure can also be classified into two general groups: chronic and acute conditions. Chronic conditions require long-term treatment, including medication and multiple sessions of pulmonary rehabilitation. In contrast, acute conditions are emergencies that often necessitate MV for immediate patient support [16]. Acute conditions will be discussed in the following section.

Acute Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome (ARDS) is a potentially life-threatening lung condition characterized by the inability of the lungs to receive sufficient air and oxygen. There are various direct and indirect causes that can lead to the development of ARDS in a person. Examples of direct causes include pneumonia and smoke inhalation, where the damage directly affects the lungs. Indirect causes are associated with severe trauma, lung transplantation, and septic shock, among others [4].

The first standardized definition of ARDS was established in 1994 by the American-European Consensus Conference. It used the ratio of arterial oxygen tension (P_aO_2) to the fraction of inspired oxygen (F_IO_2) to classify and diagnose the condition. A P_aO_2/F_IO_2 ratio of less than 300mmHg was defined as Acute Lung Injury (ALI), while a ratio of less than 200mmHg indicated ARDS. However, due to confusion among clinicians, a refined definition was introduced in 2011 known as the Berlin definition which eliminated the ALI category and classified ARDS into three severity levels: mild ($200mmHg < P_aO_2/F_IO_2 < 300mmHg$), moderate ($100mmHg < P_aO_2/F_IO_2 < 200mmHg$), and severe ($P_aO_2/F_IO_2 < 100mmHg$) [3, 4, 33].

2.1.3 Mechanical Ventilation

Currently, there is no specific treatment for ARDS. As a result, MV remains the most important and effective form of support for ARDS patients, as it reduces the WOB and improves lung recruitment and blood oxygenation. However, ventilation settings must be carefully adjusted to minimize the risk of VILI, which can occur if parameters are not properly selected. MV settings represent a balance between providing adequate respiratory support and avoiding additional VILIs [4]. To better understand MV and its settings, two key ventilator parameters must be taken into account: Positive End-Expiratory Pressure (PEEP) and Tidal Volume (V_t).

Positive End-Expiratory Pressure (PEEP)

PEEP, as the name implies, refers to a positive pressure applied at the end of the expiratory phase during MV. It is primarily used to recruit collapsed alveoli in ARDS patients. Higher PEEP values are often adjusted to promote alveolar recruitment and enhance blood oxygenation. However, studies have shown that excessively high PEEP levels may lead to adverse effects such as increased lung stiffness, alveolar overstretch, and potential injury [4].

Therefore, selecting an appropriate PEEP level during therapy is essential. However, in clinical practice, this decision is often based on the experience of the medical specialist [3]. If PEEP is set too high, it can result in a VILI caused by excessive pressure—commonly referred to as barotrauma. On the other hand, if PEEP is set too low, sufficient alveolar recruitment may not be achieved. Nevertheless, some studies have shown that limiting inspiratory volume and pressure while applying higher PEEP levels is associated with a reduced risk of VILI and shorter ICU stays [57].

Tidal Volume (V_t)

Tidal Volume (V_t) refers to the volume of air delivered to the lungs with each breath. Selecting an appropriate V_t is critical to optimizing gas exchange while minimizing the patient's breathing effort. Setting an optimal V_t is essential because if it is set too high,

it may cause a VILI known as volutrauma. Conversely, if V_t is set too low, it can lead to inadequate oxygenation and potential alveolar collapse or injury [58].

2.1.4 Measurement of Pulmonary Data

During MV, various physical variables must be measured and monitored over time to provide clinicians with relevant information regarding the patient’s respiratory condition. The three fundamental variables in pulmonary monitoring are pressure, volume, and airflow (also referred to as flow rate). These variables are recorded continuously as time series and are typically visualized as waveforms, commonly referred to as ventilatory curves, which serve as the basis for evaluating lung mechanics and patient–ventilator interaction.

Each of these signals provides unique insights into the respiratory process. Pressure, typically measured in centimeters of water (cmH_2O), indicates the force exerted by the ventilator or the patient’s respiratory muscles on the airways. Flow rate describes the speed at which air moves into or out of the lungs and is most commonly reported in liters per second (L/s), although liters per minute (L/min) are also used in some clinical devices. Volume refers to the amount of air inhaled or exhaled and is generally expressed in liters (L) or milliliters (mL), depending on the context and precision required. These three variables are inherently interconnected: the flow signal corresponds to the derivative of volume with respect to time, while volume is obtained by integrating the flow rate over time.

These relationships are essential for deriving clinically relevant parameters such as tidal volume (V_t), which corresponds to the total volume of air moved in or out of the lungs during a single respiratory cycle. The tidal volume is typically extracted from the volume–time curve and is a key indicator of lung strain, often evaluated as the ratio of V_t to the functional residual capacity (FRC). FRC refers to the amount of air remaining in the lungs at the end of a normal expiration and is challenging to measure noninvasively in clinical practice [2, 47].

The following subsections describe how each of these variables is measured in practice.

Pressure

Pressure in the respiratory system is typically measured using piezoresistive pressure transducers. These sensors detect pressure based on the mechanical deformation of an elastic material, which generates a voltage difference as a function of the deformation [2, 47]. Transducers commonly used in respiratory applications measure the pressure difference between the target pressure and a reference—usually atmospheric pressure.

Several types of pressures are present within the thoracic cavity and are essential for studying lung mechanics and estimating the work of breathing (WOB). Although measuring pleural pressure can provide valuable information, direct measurement within the pleural cavity is invasive and presents additional risks [17, 47].

Volume Airflow Rate

One of the most widely used devices for measuring airflow in respiratory applications is the pneumotachograph. This device consists of a calibrated flow resistance, typically a mesh or screen, placed in the airflow path. As air moves through the resistance, a pressure drop (ΔP) is generated, which is proportional to the flow rate. By drawing an analogy to Ohm's law—where ΔP is analogous to voltage and Q (flow rate) to current, the relationship between pressure drop and flow rate is described as follows:

$$\Delta P = RQ, \tag{2.2}$$

where, R represents the internal resistance of the pneumotachograph.

Volume

As mentioned previously, volume is computed by integrating the flow signal over time. In clinical settings, volume is usually referenced to a zero baseline, corresponding to the start of inspiration. The resulting volume-time curve enables the estimation of tidal volume (V_t), which quantifies the air exchanged in each respiratory cycle. V_t is a critical parameter in assessing ventilation strategies and must be carefully monitored to avoid volutrauma or under-ventilation.

2.1.5 Lung Mechanics

The process of breathing involves several mechanical properties that govern the behaviour of the lungs and airways. One of these properties is elastance (E), which quantifies the lung's ability to resist deformation under pressure [47]. Elastance is defined as the ratio of pressure in the lung (P_l) to the change in volume (V), and it is expressed by the following equation (Equation 2.3):

$$E = \frac{P_l}{V}. \tag{2.3}$$

It is important to note that the inverse of elastance is known as compliance, which describes how the lung volume changes in response to a given change in pressure. Compliance is also defined as a measure of the lung's ability to stretch and expand [59]. A low compliance value (indicating high elastance) suggests a stiff lung, commonly observed in conditions such as fibrosis, where greater effort is required to achieve a normal tidal volume during inspiration [47].

In addition to elastance and compliance, another critical component of lung mechanics is airway resistance (R), which reflects the opposition encountered by airflow as it moves through the respiratory tract. Airway resistance accounts for the energy lost due to friction between the moving air and the airway walls, and its value significantly influences the

work required by the respiratory muscles during both inspiration and expiration [2, 47]. Increased resistance can be observed in conditions such as chronic obstructive pulmonary diseases (COPD), where narrowed or obstructed airways impede normal airflow, leading to an increased workload for the respiratory system.

Consequently, the respiratory muscles must perform mechanical work to facilitate the process of breathing, and this effort depends on both lung elastance and airway resistance. These two factors interact to determine the overall effort required to ventilate the lungs effectively.

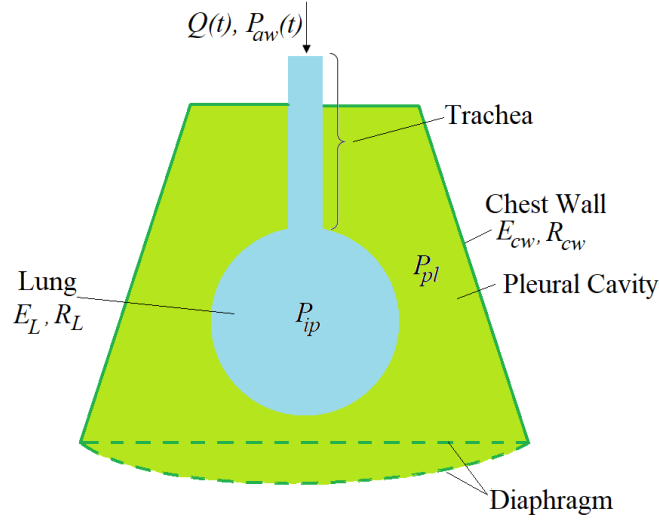


Figure 2.3: Lung Airways
Source: Based on Bates (2009)[2]

The concepts of mechanical ventilation (MV) and pulmonary ventilation (PV) have been studied extensively over the years. As early as the 1950s, Otis et al. [60] investigated the dynamics of the lungs and their interaction with a ventilator. One of the simplest approaches to modeling the lungs is to consider them as a balloon connected to a pipe. In this analogy, the balloon represents the lung, while the pipe represents the airways [2]. This approach, known as the SCM, simplifies the respiratory system, as depicted in Figure 2.3, which is itself a simplification of the respiratory system shown in Figure 2.1.

In Figure 2.3, several pressures within the thoracic cage are defined: P_{ip} represents the intrapulmonary pressure, P_{pl} denotes the pleural pressure, and P_{aw} signifies the airway pressure. Both the chest wall and the lungs have their own elastance (E_{cw} and E_L , respectively) and resistance (R_{cw} and R_L , respectively). An airflow Q enters the lung during inspiration and leaves during expiration, causing changes in both lung volume and pressure. Understanding the interplay between elastance and resistance is essential for accurately modeling the behavior of the respiratory system and optimizing ventilatory support in clinical settings.

2.1.6 The Single Compartment Model

In previous section there was shown that one of the first attempts to model the respiratory system (Figure 2.4a) is by understanding the lungs as a balloon that inflates and deflates during the processes of inspiration and expiration (Fig. 2.3). However, it is much easier to conceptualize the lung capacity as a compartment with a movable wall that depends on the elasticity of a spring, as shown in Fig. 2.4b. These simplifications are known as pneumatic analogies that aim to replicate the most important components of respiration.

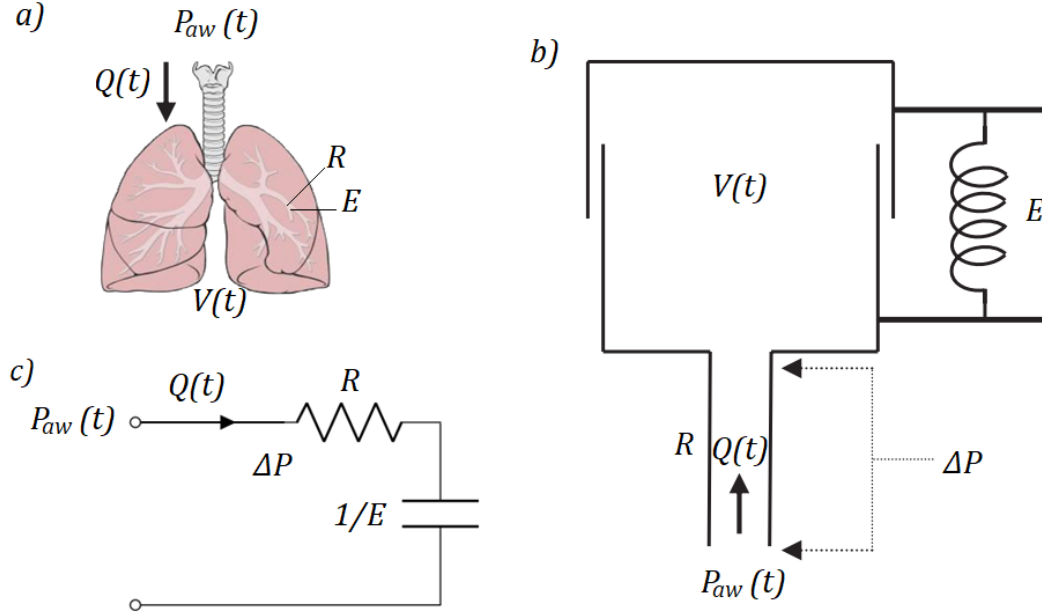


Figure 2.4: SCM: a) Lung structure b) Pneumatic analogy, c) Electric analogy

Source: Based on [61], [2] and [31]

Based on these models, authors like Bates [2] have found an interaction between airflow $Q(t)$, volume $V(t)$, and pressure at the mouth $P_{aw}(t)$ through the equation of motion (Equation 2.4) of the Single Compartment Model (SCM) where E_{rs} and R_{rs} represent the elastance and resistance of the respiratory system, respectively. These parameters are a combination of the elastance and resistance of the lung, airways, and chest wall. Additionally, it is important to highlight that P_0 denotes a reference pressure that largely corresponds to PEEP in terms of physiological significance.

$$P_{aw}(t) = E_{rs}V(t) + R_{rs}Q(t) + P_0. \quad (2.4)$$

Despite the importance of pneumatic models, also is crucial to understand the respiratory process through electrical analogies, as depicted in Figure 2.4c. Such simplifications aid in the application and derivation of Equation 2.4 using Kirchhoff's laws of voltage, where the sum around the loop must be zero. By analyzing the respiration process as an Resistor-Capacitor circuit, the equation of motion can be derived by considering that pres-

sure is analogous to voltage, airflow to current, and volume to the charge on a capacitor with a capacitance of $1/E$.

Both models are equally valid and widely used to describe respiratory mechanics due to their simplicity. However, more complex models can also be employed, incorporating elements such as the diaphragm, intercostal muscles, chest wall, among others. Several authors as Redmond (2017) [31] have proposed improvements to the electrical model (Fig. 2.4c) to achieve a more precise coupling of the equation of motion with experimental data from real patients.

The SCM has been widely used in MV due to its simplicity and clinical practicality [2, 62, 63]. While the model has limitations, it effectively describes pulmonary mechanics by linking key parameters: tidal volume (V), airflow (Q), and airway pressure (P), as shown in equation 2.4. Despite being a first-order approximation, it captures the essential dynamics of ventilation without requiring additional invasive data, making it highly applicable in clinical environments.

Researchers like Bates [2, 63], have applied the SCM in conjunction with inverse modeling techniques to estimate ventilatory parameters: Elastance (E), Resistance (R), and the reference pressure (P_0), which represents the pressure in the lungs at the end of expiration ($PEEP$). Equation 2.4 can be reformulated in matrix notation, as shown in equation 2.5.

$$\begin{pmatrix} P_1 \\ P_2 \\ \vdots \\ P_n \end{pmatrix} = \begin{pmatrix} V_1 & Q_1 & 1 \\ V_2 & Q_2 & 1 \\ \vdots & \vdots & \vdots \\ V_n & Q_n & 1 \end{pmatrix} \begin{pmatrix} E \\ R \\ P_0 \end{pmatrix}. \quad (2.5)$$

This formulation may alternatively be expressed in a compact form, as outlined in equation 2.6:

$$\underline{P} = \underline{A} \underline{x}. \quad (2.6)$$

Here, $\underline{P}$ represents a vector of pressure data, and $\underline{A}$ denotes the matrix constructed from the volume (V) and airflow (Q) data. The vector $\underline{x}$, which contains the ventilatory parameters (E , R , and P_0), can be determined by solving equation 2.4, as shown in equation (4).

$$\underline{x} = [\underline{A}^T \underline{A}]^{-1} \underline{A}^T \underline{P}, \quad (2.7)$$

where the term $\underline{A}^T$ denotes the transpose of matrix $\underline{A}$, and the expression $[\underline{A}^T \underline{A}]^{-1}$ represents the inverse of the product $\underline{A}^T \underline{A}$. This multiplication results in a square matrix, which is invertible under the condition that $\underline{A}$ has full column rank.

2.1.7 Spontaneous Breathing in Mechanical Ventilation

In a MV process, if the patient is fully sedated, a curve similar to the one shown in Figure 2.5a is obtained. However, it is possible that even in sedated patients, certain asynchronies may lead to changes in the ventilatory curves. This becomes more evident when spontaneous breaths occur due to low sedation levels or depending on the ventilation mode selected by the healthcare specialist [23].

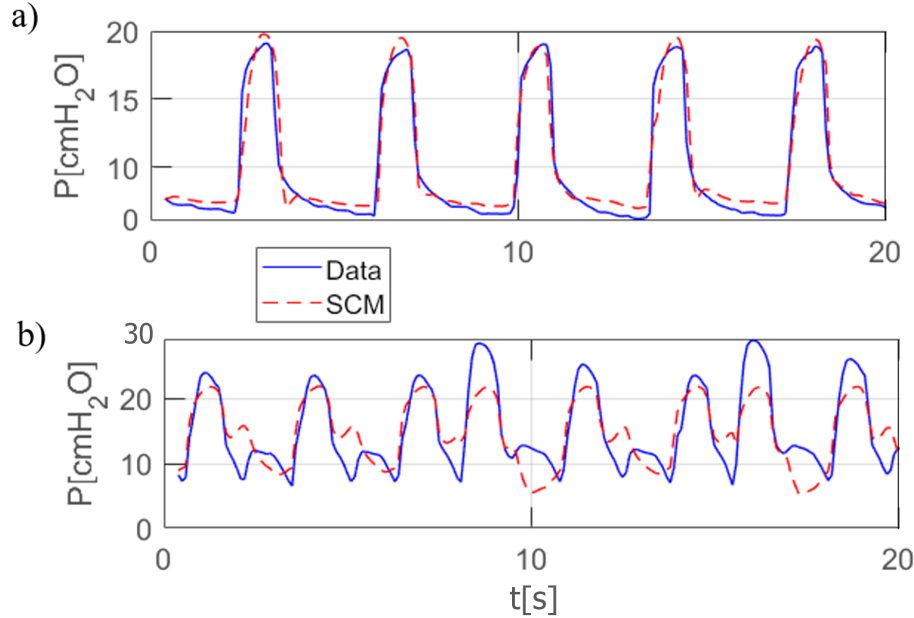


Figure 2.5: Application of the SCM in: a) Patient completely sedated b) Patient with partial Sedation

The challenge arises from the presence of asynchronies in the respiratory curves (see Figure 2.5b), which conventional models such as the SCM are unable to accurately describe. As shown in Figure 2.5, the pressure vs. time curve of a fully sedated patient can be modelled effectively using Equation 2.4. However, in the case of a partially sedated patient, the fit is significantly poorer, suggesting that modifications to Equation 2.4 are required to account for the variations observed in ventilatory curves under different patient conditions. SBs and RAs introduces additional patient efforts, resulting in irregular ventilation curves and leading to inaccurate parameter estimation. This is primarily because SB and other disturbances that occur in ventilated patients vary considerably depending on factors such as the patient's condition, sedation level, ventilation mode, and the initial ventilatory parameters configured [3, 23]. Given this variability, it becomes essential to classify and analyse the different types of PVAs that may arise during mechanical ventilation to refine the models and improve the accuracy of ventilatory curve predictions.

PVAs have been extensively defined by authors such as Souza et al. [64] and Ang et al. [65], highlighting their impact on mechanical ventilation efficiency, particularly in the presence of spontaneous breathing efforts. Ineffective Effort (IE) occurs when the respiratory effort of the patient fails to trigger the ventilator, often due to insufficient

sensitivity settings or increased airway resistance during expiration. This is common in patients attempting spontaneous breaths that are not fully supported by the ventilator. Double Triggering (DT) refers to two consecutive breaths delivered as a result of persistent inspiratory effort by the patient, typically caused by insufficient inspiratory time or volume delivered, often seen in scenarios where the ventilator is unable to accommodate spontaneous efforts. Auto Triggering (AT) arises when the ventilator is triggered without an actual respiratory effort from the patient, frequently due to external noise or circuit leaks that mimic spontaneous breaths.

Premature Cycling (PC) describes the ventilator switching from inspiration to expiration before the inspiratory effort of the patient is completed, which can occur when spontaneous breaths require prolonged inspiratory times. Conversely, Delayed Cycling (DC) occurs when the ventilator prolongs inspiration beyond the effort of the patient, leading to air trapping, particularly in patients with irregular spontaneous efforts. Reverse Triggering (RT) involves the activation of respiratory muscles in response to a ventilator-initiated breath, resulting in uncoordinated effort, and is more likely when spontaneous breathing patterns are inconsistent. Lastly, Flow Asynchrony (FA) is identified when the ventilator flow fails to meet the inspiratory demand of the patient, increasing work of breathing and discomfort, particularly during spontaneous efforts. The presence of SB can both exacerbate and reveal asynchronies, making its management crucial for optimizing patient-ventilator interaction.

One of the key factors influencing patient ventilator interaction is the presence of SB, which is closely related to RAs. Both SBs and RAs arise from the intrinsic respiratory drive of the patient, but while spontaneous breathing represents the natural effort to regulate ventilation, asynchronies occur when this effort is not properly coordinated with the ventilator assistance. Many asynchronies, such as IE, DT, and FA, are a direct result of spontaneous breaths that are either not detected, insufficiently supported, or mistimed by the ventilator. Additionally, cycling asynchronies, including PC and DC, often emerge when the ventilator inspiratory and expiratory transitions do not align with the spontaneous effort of the patient. Understanding this relationship is essential for optimizing ventilator settings and improving patient comfort, particularly in modes that allow or encourage spontaneous breathing.

2.2 Pulmonary Dynamics Background

The Background section presents a comprehensive review of the methodologies and approaches developed by the scientific community to analyse pulmonary dynamics and improve MV strategies. It begins by exploring the application of computational methods and numerical solutions to model respiratory processes, followed by a discussion on reduced-order models, commonly referred to as bedside models, which estimate patient-specific respiratory mechanics using limited data—an approach frequently used in ICUs. Additionally, this section reviews studies focused on patient-specific models that aim to refine MV strategies by adapting to individual patient characteristics. It also examines relevant research on SBs and RAs, which can significantly impact ventilatory performance.

Finally, a synthesis of previous studies is provided, highlighting the key contributions that have shaped the current understanding of pulmonary mechanics.

2.2.1 Exploring Pulmonary Dynamics through Computational Methods

Studying breathing behavior has been of great importance, and several authors have made contributions by employing specified physiological information and complex computational methods to investigate various problems related to pulmonary mechanics and its interaction with MV. For example, Aghasafari and Ridaparti (2018) [49] used Computational Fluid Dynamics (CFD) and Fluid-Solid Interactions (FSI) approaches to study the behavior of lungs affected by acute respiratory distress syndrome (ARDS) by modeling an alveolar sac with a 3D computational domain. They found that emphysema reduces airflow and lung elasticity, requiring more energy to breathe.

Furthermore, Tsega (2018) [66] conducted a study using CFD to analyze airflow in the tracheobronchial airways, specifically examining variations across different age groups. They concluded that the age range influences the type of flow, and both velocity and pressure decrease with age. The airways have been the subject of extensive research, with investigations primarily focusing on studying geometric parameters, velocity, pressure, and flow characteristics. Clinically, respiratory system obstructions can lead to severe complications and even death, underscoring the importance of accurate diagnosis and effective treatment for such pathologies [67].

An analysis of the impact of bronchodilator usage on a group of asthma patients with varying levels of severity, ranging from mild to moderately chronic, was presented in de Backer et al. (2008) [68]. Through this study, the authors determined that, after using a bronchodilator, patients improved airflow resistance without changing the tidal volume. For its part, Zhang et al. (2020) [54] investigated the airways of 4-year-old children with asthma, comparing the behavior of affected lungs with healthy ones. They found that the deposition of smog particles in children with asthma is significantly higher than in healthy children, which was expected from a clinical standpoint. Additionally, Chen and Zhao (2019) [59] examined conditions such as pulmonary fibrosis, utilizing CFD and FSI techniques to compare their behavior with that of a healthy lung. In their study, the authors concluded that analyzing changes in the lungs is crucial for both early diagnosis and disease classification.

The analysis of airways using CFD in a 3D domain was conducted by Yang et al. (2006) [69], focusing on individuals with COPD and examining the velocity profile in obstructed airways and its impact on patients. They concluded that the inlet velocity pattern leads to significant changes in the flow distribution in the bronchial tree. Similarly, Farghadan et al. (2019) [70] investigated flow dynamics in a patient-specific lung model using CFD, specifically studying transitional flow conditions and particle tracking to enhance understanding of particle transport and deposition in the respiratory tract, which can inform future research on drug delivery in the lungs.

Xi et al. (2015) [71] presented a case study of a bronchial tumor, utilizing CFD models to visualize air distribution in the lungs and assess its impact on the affected area, proposing a potential new respiratory mechanics test for diagnosing obstructive pathologies. Gu et al. (2019) [72] conducted a similar study on a patient with lung cancer, examining flow behavior in terms of velocity and pressure profiles in the lungs following surgical intervention. Because the surgical procedure caused morphological changes in the analyzed lungs, significant differences were found in flow behavior as a result of modifications in the bronchial tree. These studies exemplify the significance of CFD in analyzing various conditions and contribute to a better understanding of pulmonary mechanics.

The aforementioned studies are examples of how respiration has been investigated using different tools. However, these approaches typically require substantial physiological information about the patient, which may not be routinely measured in a clinical setting or could demand additional invasive procedures. While such methods help to illuminate the complexity of respiration, their direct application in an intensive care unit (ICU) can be limited by their complexity, potentially hindering proper implementation during patient recovery.

2.2.2 Reduced Order Models

Although computational models have been utilized to study various aspects of human breathing and lung performance, their complexity often limits their implementation in clinical environments. One of the main goals of this study is to develop a tool with direct potential application for a ventilated patient in an ICU are defined by some authors as 'bedside models' [8], which have the particularity of providing information about a patient ventilatory process using available data without additional invasive procedures. These kinds of approaches are commonly known as models with clinical relevance. Therefore, it becomes essential to understand reduced order models of lung behavior that can be effectively applied in hospital and in an ICU setting.

Authors such as Tomlinson et al. (1994) [6] have proposed analytical models of simplified lungs, drawing analogies with linear actuators incorporating spring and viscous resistance effects. They have also explored analogies between the lung system and other applications, such as RC circuits, to derive equations that relate pressure, volume, and flow.

Similarly, authors like Zin and Gomes (1999) [73] have emphasized the need to simplify the breathing problem while accurately capturing the mechanical behavior, considering physiological and pathological conditions. They have approached this by establishing analogies between anatomical and electrical representations. A similar perspective has also been discussed by Flores (2006) [74].

Moreover, authors like Ben-Tal (2006) [75] have presented a hierarchy of models focusing on blood oxygen transport. In some breathing problems, where rib cage expansion plays a crucial role, a rigid container model proves to be effective. To account chest expansion, a model with a moving wall was studied, subsequently, gas exchange and gas transport were incorporated into the model to achieve more complex and accurate respiratory equations.

In terms of gas exchange, Shekerdemian and Bhon (2005) [76] explore the interaction between the respiratory and cardiovascular systems, highlighting the impact of mechanical ventilation on blood circulation. They also emphasize the influence of pharmacology on the cardiovascular system. These studies shed light on the intricate relationship between the respiratory and cardiovascular systems and underscore the importance of considering both aspects in the context of mechanical ventilation.

Chiari et al. (1997) [77] present a comprehensive model of the human respiratory system that incorporates gas exchange, transport, and storage in adults. Their study aims to validate this model, which encompasses ventilation, circulation, and chemical aspects involved in the breathing process.

Jbaily et al. (2020) [78] have developed a novel mathematical framework that considers gas mixtures in alveoli. They simplify the bronchial tree as a tube, allowing for a more detailed model of gas exchange between the alveoli and the external environment.

The study of alveoli has been extensively explored by researchers such as Anderson et al. (2003) [53], who propose a mathematical model for soluble gas exchange in the lungs. They conceptualize the lung as a combination of airways and alveoli and validate their model using patient data. Archie (1997) [79] develops a mathematical approach based on mass and energy conservation, as well as the second law of thermodynamics, to represent the contribution of alveolar surface tension in the respiration process.

These studies demonstrate how respiration can be understood using reduced-order models that work with limited physiological information of the patient. These models aim to serve as a basis for understanding respiratory mechanics and providing additional information to the patient recovery processes.

2.2.3 Patient-Specific models

Given the significant heterogeneity among patients, it is inappropriate to assume that the same ventilatory parameters will be effective for all individuals, despite their anatomical and physiological similarities. To address this challenge, there has been a growing trend towards personalised therapies, which involve tailoring recovery protocols to each patient. This approach has motivated researchers to develop patient-specific models that refine the governing equations of pulmonary mechanics, such as the equation of motion used in the Single Compartment Model (SCM) (Equation 2.4), by incorporating real-time patient data and statistical analyses to improve model accuracy.

Several studies have contributed to enhancing conventional models by introducing patient-specific modifications. Damanhuri et al. (2015 and 2017) [4, 58] developed models that utilise real-time clinical data to personalise ventilatory parameters, providing complementary metrics for guiding MV decisions. Similarly, Redmond et al. (2017 and 2019) [3, 31] investigated the influence of patient effort on respiratory mechanics, aiming to improve clinical decisions regarding MV management by adapting ventilatory strategies to individual patient responses.

Building on these advancements, Howe et al. (2020) [17] introduced a model that leverages expiratory data to estimate inspiratory mechanics in partially sedated patients or those exhibiting spontaneous breathing. Their findings established a correlation between inspiratory and expiratory elastance, offering a new approach to account for variability in ventilatory parameters. However, they identified a critical gap in the estimation of airway resistance, highlighting the need for further refinement in patient-specific models—a gap that the present study aims to address.

Recent research has also explored the application of machine learning (ML) to develop predictive models that enhance patient-specific care. For instance, Douville et al. (2021) [80] demonstrated the potential of ML algorithms to predict the need for MV in COVID-19 patients, emphasising the importance of incorporating additional clinical parameters to improve prediction accuracy. Similarly, Morton et al. (2019) [16] applied predictive models to optimise ventilator settings, such as positive end-expiratory pressure (PEEP) and peak inspiratory pressure (PIP), transitioning clinical practice from reactive to proactive approaches.

These advances underscore the vital role of patient-specific models in improving ventilatory management by adapting to individual patient characteristics. The ultimate goal is to develop more robust models capable of identifying personalised strategies and optimising ventilatory settings to enhance clinical outcomes. Therefore, the aim of this study is to establish a simplified, yet effective, relationship based on the equation of motion (Equation 2.4) by integrating patient-specific data to provide a more accurate representation of lung mechanics. The objective is to identify parameters or strategies that can serve as additional information to guide specialists in patient diagnosis and/or treatment.

2.2.4 Researches on SBs

Understanding and monitoring respiratory mechanics is essential for MV. However, conventional models that describe ventilatory mechanics often perform poorly in the SB, which induces PVAs, commonly associated with increased pulmonary effort [1, 3]. Consequently, there is a growing need to develop models that provide useful information about respiratory mechanics in patients experiencing asynchronies to improve ventilator settings and patient outcomes.

In this context, Redmond et al. (2019) [3] compared the performance of several mathematical models used to describe respiratory mechanics and concluded that conventional models must be combined or modified to improve their accuracy when describing the ventilatory dynamics of patients with low sedation levels and the presence of SB. Similarly, Chiew et al. (2015) [28] introduced the concept of “time-varying elastance”, a parameter that accounts for variations in respiratory effort by taking negative values when SB and additional patient efforts occur. This concept enabled a more detailed understanding of ventilatory dynamics, particularly in cycles influenced by asynchronies. In subsequent work, Chiew et al. (2018) [23] extended this approach by emphasising the importance of not only understanding or calculating ventilatory parameters but also quantifying the additional respiratory efforts resulting from asynchronous breaths.

A noteworthy contribution was made by Howe et al. (2020) [17], who developed a model that uses expiratory data to estimate inspiratory mechanics in partially sedated patients or those exhibiting SB. Their approach demonstrated that integrating expiratory information into the modelling process allows for a more accurate breath-by-breath assessment of ventilation parameters, enabling real-time clinical applications. Furthermore, Knopp et al. (2021) [1] investigated these additional respiratory efforts and compared them with measurements of diaphragmatic electrical activity. Their study highlighted the importance of quantifying SB and the WOB, which is crucial for optimising ventilatory manoeuvres, particularly during the weaning process when sedation levels are lower, and SBs are more prevalent.

Addressing the limitations of conventional models that fail to capture variations in pressure-time curves in the presence of SB and PVAs [3, 25], innovative approaches such as pressure waveform reconstruction have emerged [23, 25]. These methods enable more accurate estimation of respiratory mechanics, even in cycles influenced by spontaneous efforts, and have demonstrated reduced variability in parameter identification while enhancing real-time reliability. Such advancements hold great potential for integrating non-invasive tools into clinical workflows, ultimately improving patient-ventilator synchronisation and optimising patient outcomes [23, 27].

Additionally, Ang et al. (2024) [65] explored changes in elastance as a time-varying measure of the respiratory system elastic properties, noting that these variations can reflect the patient evolving condition and signal the need for ventilator adjustments. Understanding these variations is particularly relevant in the context of SB, as it provides valuable insights for optimising ventilator settings and improving patient care. Moreover, identifying and proposing model-based parameters derived from the quantification of elastance over time may offer a non-invasive means to assess pulmonary function, reducing both clinical risk and workload [13, 81].

Despite these advances, certain ventilation modes, such as pressure support ventilation (PSV), have been shown to increase the risk of delivering excessive tidal volumes, potentially leading to higher rates of asynchronies [82]. This highlights the importance of developing decision-support tools to assist clinicians in selecting optimal ventilatory settings and performing appropriate manoeuvres. Inadequate parameter selection can contribute to the occurrence of PVAs, ultimately hindering patient recovery.

A ventilation asynchronous event (AE) occurs when the patient breathing effort is not synchronised with the ventilator support, resulting in poor patient-ventilator interaction, increased WOB, and other adverse effects [10]. Therefore, improving the detection, quantification, and management of SB and PVAs through refined models and advanced analytical techniques is essential for enhancing clinical decision-making and optimising ventilatory support.

2.2.5 Background Summary

The Table 2.1 provides a summary of several approaches aimed at understanding lung mechanics, highlighting their focus and relevance to patient-specific modeling, particularly

in the context of ventilatory support. This overview is essential for understanding the contribution of the present work, which introduces a novel extended model of lung mechanics capable of adjusting ventilatory curves in the presence of RAs. Unlike previous models, this approach refines curve fitting by incorporating new parameters derived from patient-specific data, addressing limitations associated with traditional assumptions about the geometry of pressure-time (P vs. t) curves.

The primary novelty of this work lies in the integration of patient-specific modeling with a new approach for the detection of RAs. Unlike conventional methods that rely on pressure waveform reconstruction—which make assumptions about the geometry of P vs. t curves—the proposed model introduces a different approach that adjusts ventilatory curves by incorporating patient-derived shape functions.

A key advantage of the proposed RA detection tool is its potential to be integrated into real-time monitoring systems in ICU settings. This is possible because the model operates using data that is routinely available in ICUs without the need for additional invasive information. The proposed method offers a conceptually distinct alternative to the reconstruction-based techniques commonly used by other authors [10, 23, 26], and a more detailed discussion comparing these approaches will be presented in Chapter 5.

The literature review highlighted a wide range of computational methods for studying respiratory mechanics (see Table 2.1). It is crucial to distinguish between two main families of models based on their purpose and scope: high-fidelity simulation models (such as CFD-FSI) and low-order, clinically oriented bedside models.

High-fidelity models, reviewed in Table 2.1, are powerful research tools designed for deep mechanistic understanding. They enable detailed investigation of localized phenomena, such as airflow turbulence in specific airways or stress distribution across alveolar walls. However, their direct application in a real-time clinical setting is limited. First, CFD-FSI simulations are computationally intensive, often requiring hours or even days on high-performance computers, which makes them unsuitable for real-time bedside monitoring. Second, they rely on highly detailed, patient-specific anatomical data, typically obtained from advanced 4D imaging, which is not routinely available in the ICU. Finally, their primary function is simulation and theoretical exploration rather than the real-time detection and quantification of clinical events, such as asynchronies, from standard ventilator signals like pressure and flow.

In contrast, the objective of this thesis was to develop a model that meets the criteria of a bedside tool: computationally lightweight, identifiable from standard ventilator data, and capable of providing real-time insights into PVI. For this reason, while acknowledging the immense value of CFD-FSI models in fundamental research, the development path for this work necessarily focused on low-order frameworks such as the Single Compartment Model, which are better suited to the specific challenges of clinical implementation.

Table 2.1: Contribution of the present work

Reference (Year)	Topic	Focus	I1	I2	I3	I4
[76, 77] (1997, 1999)	Simplified model for gas exchange	Perfusion	x			
[78] (2020)	Alveolar and surface tension models	Perfusion	x			
[53, 79] (1973, 2020)	Alveolar and surface tension models	Perfusion	x			
[49, 54, 59, 66–72] (Range: 2006-2020)	CFD - FSI	Ventilation				
[6, 73, 74] (1994, 1999, 2006)	Compartment models	Ventilation	x			
[2, 58] (2009, 2015)	Extended model of lung mechanics	Ventilation	x	x		
[1, 3, 17, 65, 82] (Range: 2017-2024)	Extended model of lung mechanics	Ventilation	x	x	x	
[10, 13, 23, 27, 28, 81] (Range: 2014-2021)	Extended model of lung mechanics	Ventilation	x	x	x	
Present work	New model integrating SB analysis and RA detection	Ventilation	x	x	x	x

^{I1} Is a bedside model?^{I2} Has clinical relevance?^{I3} Analyses spontaneous breathing (SB) or respiratory asynchronies (RAs)?^{I4} Introduce a new RA detection method based on curve fitting

2.3 Conclusions

This chapter provided an overview of the fundamental concepts and relevant research related to MV, laying the groundwork for understanding the contributions of the present study. The theoretical framework introduced the core principles of respiratory mechanics, including definitions of key parameters such as elastance, resistance, and reference pressure, which form the basis of the equation of motion used in the SCM. Additionally, this section highlighted the importance of considering SBs and its impact on the dynamics of ventilatory curves, which is essential for understanding RAs.

The chapter then explored various approaches to modelling lung mechanics, distinguishing between simplified models that primarily focus on gas transport phenomena during perfusion and compartment models that describe ventilatory behavior using reduced-order representations. While these models are computationally efficient and suitable for clinical use, many lack the capability to adequately describe respiratory mechanics in the pres-

ence of RAs. A review of the literature also examined the development of patient-specific models aimed at enhancing MV strategies through personalised therapies. Several studies have highlighted the relevance of bedside models, which balance computational efficiency with clinical applicability. However, despite these advances, many models still encounter challenges when attempting to account for the stochastic variations introduced by SB and RAs.

Finally, the chapter addressed the analysis of ventilatory mechanics in patients with RAs, focusing on efforts to quantify the WOB and develop real-time diagnostic tools. Although promising methodologies have been proposed, these approaches often rely on iterative techniques that may hinder their seamless integration into clinical practice. In summary, this chapter established the theoretical and practical foundations necessary to contextualize the development of a new model that not only improves the representation of ventilatory mechanics in presence of SBs but also proposes a novel method for detecting RAs. These contributions will be further explored and validated in the subsequent chapters.

Chapter 3

Data acquisition process

Respiration is an involuntary physiological process governed by the central nervous system that primarily facilitates the exchange of gases, specifically oxygen (O_2) and carbon dioxide (CO_2) [45, 83]. In the context of MV, the analysis of ventilatory curves is essential for assessing ventilatory and pulmonary mechanics. These curves provide critical insights into respiratory dynamics and the interaction between the lungs and the ventilator. Traditionally, such analyses rely on data extracted directly from the ventilator, allowing for detailed evaluations of parameters such as airway pressure, flow, and volume [17, 23, 39]. However, in resource-limited environments, many healthcare institutions lack the technological infrastructure necessary for direct data extraction, thereby limiting their capacity for comprehensive assessments.

This chapter explores an alternative methodology for acquiring ventilatory data by employing image processing techniques to extract ventilatory curves from video recordings. This approach offers a practical and cost-effective solution for obtaining essential information in settings where direct data extraction is not feasible. The validity of this methodology was established using data from a ventilator emulator developed at Universidad del Valle, confirming the accuracy and reliability of the image-derived curves. Further validation was achieved by replicating the findings of Howe et al. [17], which demonstrated a linear correlation between inspiratory and expiratory phase elastance in ventilated patients, thereby reinforcing the robustness of the image-derived data.

In terms of structure, the chapter first describes the methodology for capturing ventilatory waveforms is described, including the specific image processing techniques employed. Next, the results obtained from the analysis of the ventilatory curves are presented, followed by a discussion of the implications and potential applications of this approach. Finally, the chapter concludes by summarizing the key findings and outlining potential directions for future improvements.

3.1 Methods

This section outlines the key steps involved in acquiring and analyzing ventilatory data using image processing techniques. It begins with a description of the experimental setup used to capture patient data through video recordings. Then, the image processing methods employed to extract data from the ventilator emulator are explained, including the specific images and techniques applied. Lastly, clinical profiles of the patient cohort are presented to provide context for the analysis. To validate this approach, the elastance curves during expiration and inspiration were compared, replicating the findings reported by Howe et al. [17].

3.1.1 Validation of Image Processing with a Ventilator Emulator

The present work employs image processing techniques to acquire mechanical ventilation data, addressing the challenges associated with extracting information directly from ventilators. This approach, also adopted by other researchers to validate their findings [42], has proven especially valuable in resource-constrained hospitals, where access to advanced monitoring technology is often limited. Figure 3.1 shows the setup used to record videos of the ventilatory waveforms.

Before applying image processing to clinical data, the methodology was first validated in a controlled environment using a didactic ventilator emulator developed by the Bionovo research group at Universidad del Valle (Figure 3.2). This setup allowed for a direct comparison between data extracted via image processing and data recorded directly from the emulator sensors.

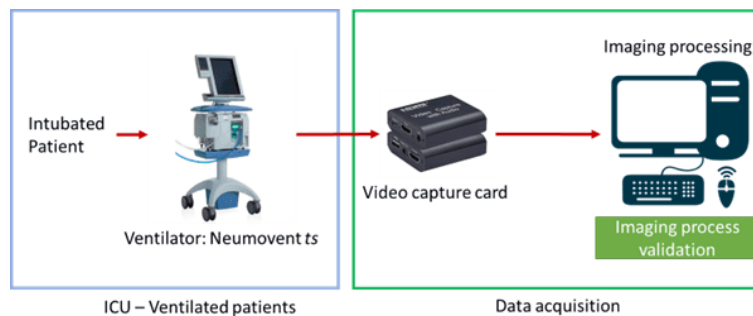


Figure 3.1: Data acquisition setup

The emulator was set to volume-controlled ventilation (VCV) mode and generated ventilatory waveforms displayed on a computer interface. A single, high-resolution (1920×1080 pixel) screenshot capturing 30 seconds of continuous data was saved as a .png file (Figure 3.3). This image of the emulator screen served as the input for the image processing workflow detailed in Figure 3.5, allowing for a robust performance evaluation against the simultaneously recorded sensor data (Figure 3.4).

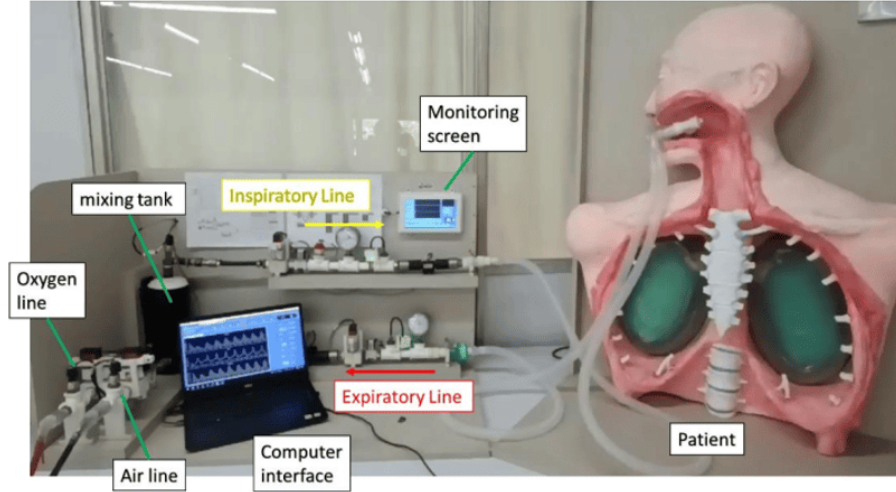


Figure 3.2: Ventilator and patient emulator developed by Universidad del Valle

3.1.2 Clinical Data Acquisition

After validating the methodology, clinical ventilatory data was acquired from patients at the Hospital San José de Buga. This was necessary to address challenges in hospitals where direct data export from ventilators is not available. The setup involved recording the screen of a Neumovent TS ventilator, which was connected to a video capture card via its VGA video output (see Figure 3.1).

Videos were recorded at a resolution of 1920×1080 pixels and 60 fps. A key constraint of this clinical device was its screen limitation of displaying a maximum of 12 seconds of the ventilatory signal at any given time. Therefore, to capture continuous therapy, video frames were extracted sequentially to reconstruct longer data segments for analysis. To ensure consistency across all recordings, an interpolation step was applied so that every patient dataset was resampled at a uniform rate of 100 data points per second of therapy (100Hz). This standardization provided the reference temporal resolution for all subsequent analyses in the whole document.

3.1.3 Evaluation of Image Processing Performance

The image processing methodology was validated using a didactic ventilator emulator developed by the Bionovo research group at Universidad del Valle (Figure 3.2), which simulates a controlled ventilatory environment. This emulator, utilizing a pressurized oxygen tank and a compressor to regulate airway flow, enabled precise testing in volume-controlled ventilation (VCV) mode under the following settings: square-wave inspiratory flow, 15 breaths per minute, an I/E (inspiratory/expiratory time) ratio of 1:2, a 0.6 second inspiratory pause, 1 cmH_2O of PEEP, and a tidal volume of 500 ml. Validation was performed by comparing ventilator screen outputs (Figure 3.3) with sensor-derived data (Figure 3.4), capturing 30 seconds of data directly to a computer without the use of external devices. This 30-second capture, represented by a single 1920×1080 pixel image (Figure

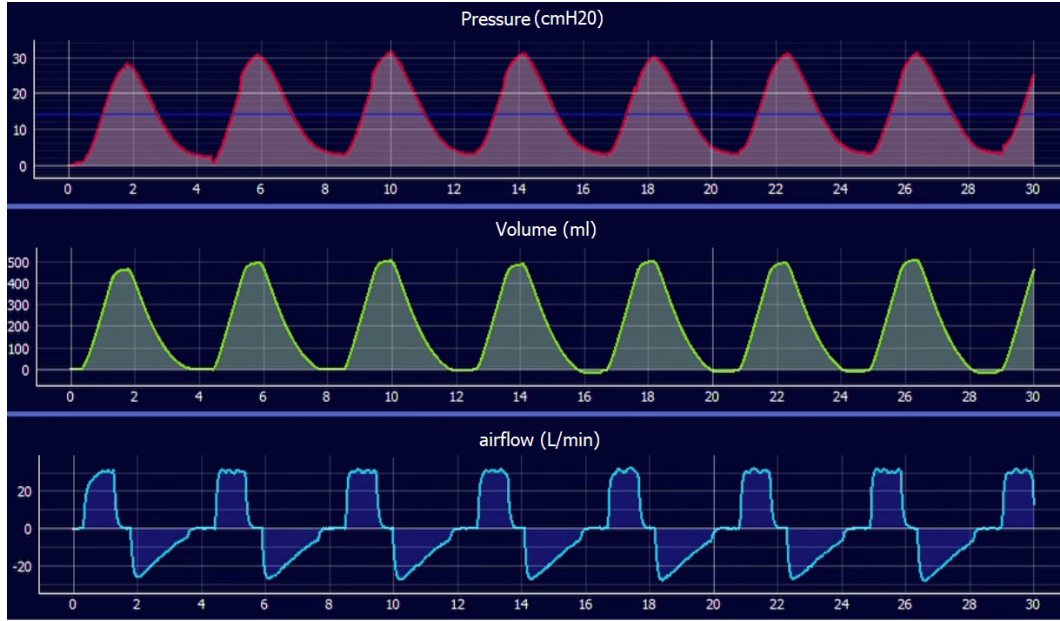


Figure 3.3: Emulator monitoring screen

3.3), was processed and analyzed to ensure the accuracy of the image-derived ventilatory parameters.

The Figure 3.5 is a flowchart describing the image processing procedure. Starting from the initial image (Figure 3.5a), color filtering was applied to produce a binary representation (Figure 3.5b). The pixel positions were then used to reconstruct the curve, resulting in a dispersed dataset (Figure 3.5c). To address the issue of densely packed pixels caused by the thickness of the curve in the original image, a filtering step was applied. This involved sampling the curve data at 15-pixel vertical and 2-pixel horizontal intervals, effectively reducing data density while preserving the overall shape of the curve (Figure 3.5d).

The accuracy of the reconstruction was assessed by comparing it with data extracted using WebPlotDigitizer (Figures 3.5c and 3.5d), an open-source tool available from <https://automeris.io/> that samples data at approximately 15-pixel intervals. Finally, interpolation was applied to ensure a consistent temporal resolution of at least 100 data points per second, resulting in a continuous function relating pressure (P), airflow (Q), and tidal volume (V) to time (t).

3.1.4 Data Analysis

To evaluate the overall consistency between the data derived from image processing and raw data, the coefficient of determination (R^2) was calculated. This metric provided an overall measure of how closely the sensor-based measurements aligned with the image-processed data. Subsequently, the Mean Squared Error (MSE) was computed to quantify the average squared difference between the values produced by each method. This evaluation was conducted both across the entire dataset and on a point-by-point basis, with the

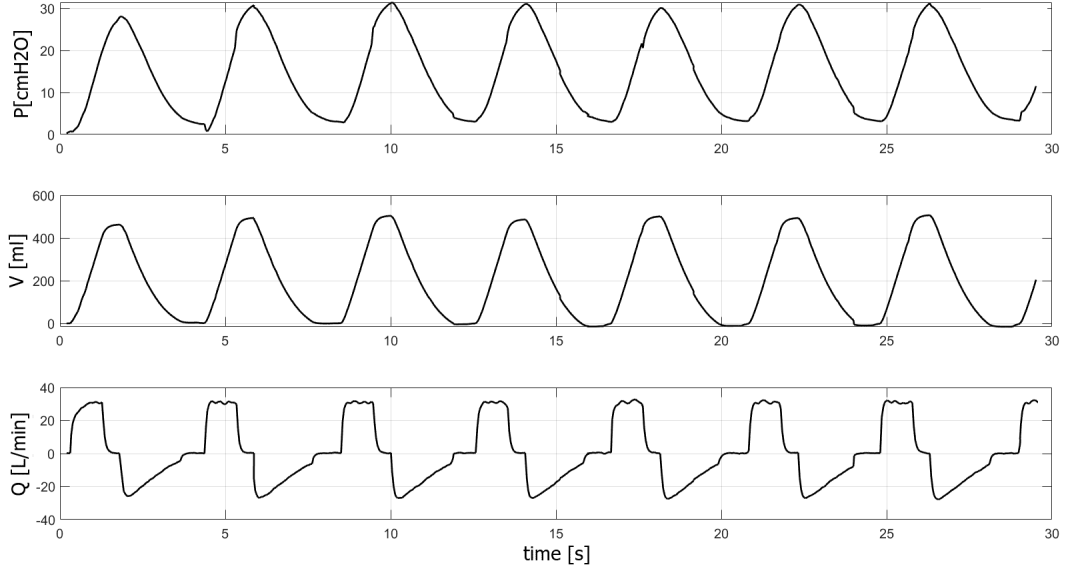


Figure 3.4: Sensor-derived ventilatory data from the emulator

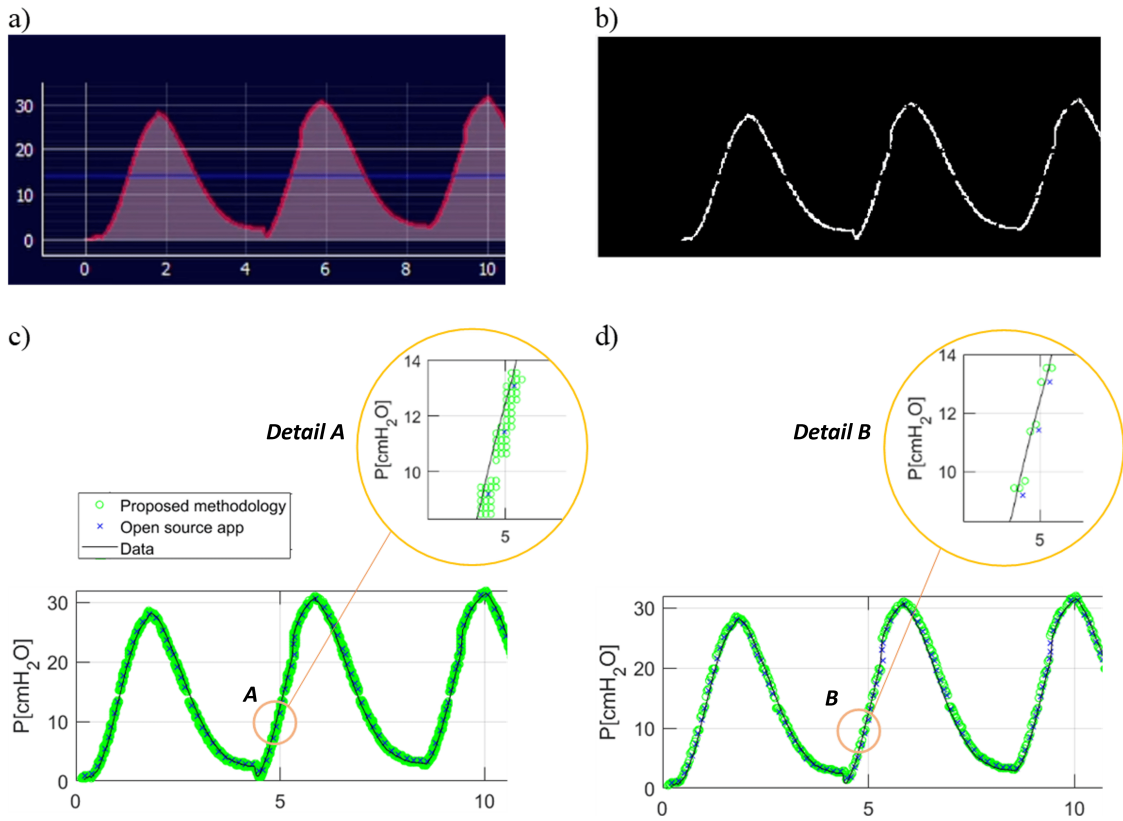


Figure 3.5: Image Processing Flowchart: a) Original Image (Pressure vs. Time), b) Binarized Image, c) Pixel-Based Reconstruction, d) Filtered Data

Interquartile Range (IQR) used to assess the dispersion of errors. A low error dispersion would indicate a strong agreement between the two methods.

Furthermore, Bland–Altman plots were used to visualize the differences between the two measurement methods relative to their mean. These plots are particularly useful for evaluating agreement between measurement techniques by displaying the magnitude of the differences against the average of the two measurements. The distribution of these differences was analyzed, and the limits of agreement (bias ± 1.96 standard deviations) were calculated to identify any systematic bias or variability. This comprehensive analysis was designed to demonstrate a strong correlation and the absence of significant discrepancies between the sensor-derived and image-processed data, thereby validating the reliability of image processing as a viable technique for data extraction.

3.1.5 Replication of Results Using Image Processing

Building upon the initial validation using the Universidad del Valle emulator, a further comparison was conducted by replicating part of the findings reported by Howe et al. [17], who demonstrated a linear correlation between inspiratory and expiratory elastance in mechanically ventilated patients.

Table 3.1: Dataset

Patient	sex	Age [years]	Clinical Diagnostic	Tidal Volume [L]	PEEP [cmH ₂ O]	Ventilatory mode
P1	Male	50	Traumatic brain injury	0.55	8.0	VCV
P2	Female	30	Renal failure	0.42	7.0	
P3	Female	58	Pneumonia	0.32	10.0	
P4	Female	24	Cerebral palsy	0.40	6.0	
P5	Male	38	Subarachnoid haemorrhage	0.53	9.0	
P6	Female	78	COPD	0.41	6.0	
P7	Male	18	Trauma	0.50	5.0	
P8	Female	44	Alveolar haemorrhage	0.35	12.0	

It is important to note that, while Howe et al. used data obtained directly from ventilators, this study successfully reproduced those results using image-processed data. To accomplish this, one minute of recorded therapy from each of eight fully sedated patients was analyzed, as detailed in Table 3.1 and illustrated in Figure 3.6. For each patient, Howe et al. applied Equation 2.4 and reported a linear relationship between inspiratory and expiratory elastance values within the range of 15–45 cmH_2O , with an R^2 coefficient of 0.94. The waveform analysis presented in Figure 3.6 aims to replicate Howe’s results.

3.2 Results

The Figure 3.7a presents the reconstructed pressure (P), volume (V), and airflow (Q) curves, derived from both the proposed image processing flowchart (outlined in Figure 3.5)

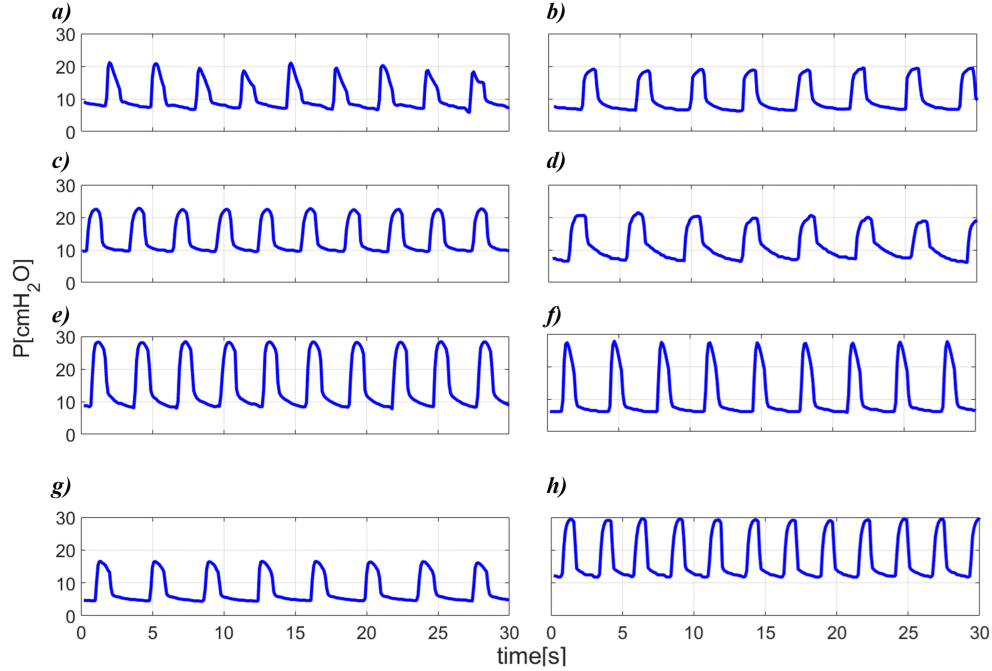


Figure 3.6: Pressure waveform: a) P1, b) P2, c) P3, d) P4, e) P5, f) P6, g) P7, h) P8

and WebPlotDigitizer, an open-source tool. Visual inspection reveals a strong agreement between the curves, suggesting that both methods effectively capture ventilatory data.

As shown in Table 3.2, the R^2 values for all reconstructed curves, calculated using the original data (Figure 3.7a), exceed 0.99. This confirms the reliability of both techniques for extracting ventilatory information. To facilitate a more meaningful comparison of the Mean Squared Error (MSE), the analysis was conducted using normalized graphs (Figure 3.7b), as normalization enables clearer interpretation than raw values.

A point-by-point comparison of the reconstructed curves (Figure 3.8b) reveals that the highest MSE values are concentrated around sharp transitions or inflection points, particularly during the transition between inspiration and expiration. Despite these localized variations, the overall MSE values for pressure, volume, and airflow, as presented in Table 3.3, remain low, reinforcing the accuracy of both reconstruction methods (the flowchart in Figure 3.5 and WebPlotDigitizer).

Data in Table 3.3 indicates that both the proposed methodology and the open-source tool yield comparable median MSE values, demonstrating high accuracy in reconstructing

Table 3.2: R^2 for Reconstructed Ventilatory Curves

	Pressure (P)	Volume (V)	Airflow (Q)
Proposed flowchart (Figure 3.5)	0.998	0.997	0.992
WebPlotDigitizer Open-Source app	0.998	0.997	0.997

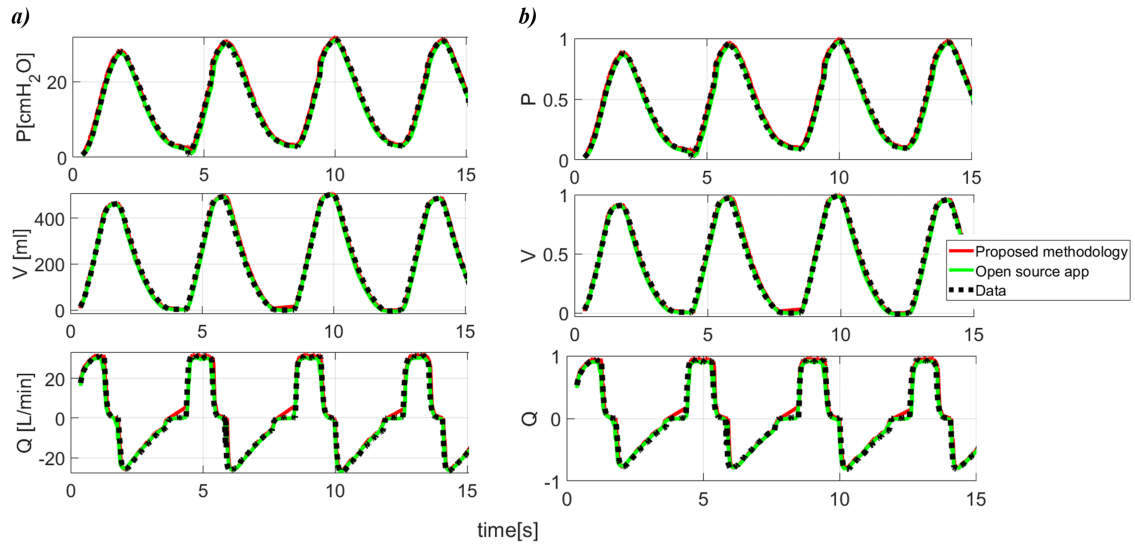


Figure 3.7: Comparison of Reconstructed Ventilatory Curves: a) Original Waveforms; b) Normalized Graphics

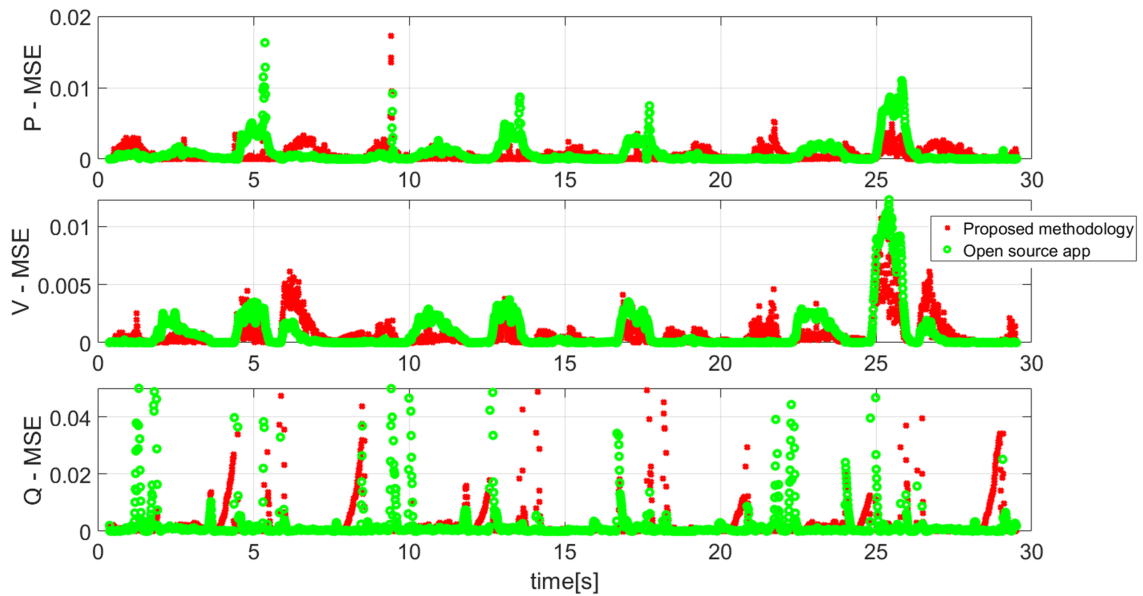


Figure 3.8: Performance Evaluation: MSE of Image Processing Methods Against Sensor-Derived Data

ventilatory curves. However, the open-source tool shows slightly lower median MSE values and narrower interquartile ranges (IQRs).

Table 3.3: MSE for Reconstructed Curves Compared with Sensor Data

	Pressure (P)	Volume (V)	Airflow (Q)
	MSE: Med [IQR]		
Proposed flowchart (Figure 3.5)	0.0003 [0.0001 - 0.0008]	0.0002 [0.0001-0.0018]	0.0005 [0.0001 - 0.0013]
WebPlotDigitizer Open-Source app	0.0002 [0.0000 - 0.0009]	0.0001 [0.0002 - 0.0012]	0.0004 [0.0002 - 0.0012]

Bland-Altman plots, generated using the normalized data (Figure 3.7b) and shown in Figure 3.9, offer refined validation of the alignment between reconstructed and sensor-measured data. These plots display minimal bias, with limits of agreement closely centered around zero for both methods. In particular, pressure and volume curves exhibit agreement limits near 0.05 and -0.05, indicating strong concordance (Figures 3.9a, 3.9b, 3.9d, and 3.9e). Airflow curves (Figures 3.9c and 3.9f), although still centered around zero, show a broader agreement range of approximately -0.2 to 0.2. Nonetheless, all values remain within acceptable limits, confirming the reliability of both approaches. The open-source tool exhibited slightly tighter agreement bounds and reduced variability.

3.3 Elastance analysis using Image Processing

The elastance analysis, presented in Figure 3.10, demonstrated a linear relationship between the inspiratory (E_i) and expiratory (E_e) elastance, consistent with the findings of Howe et al. [17]. A strong agreement was observed within the elastance range evaluated by Howe et al. (15–45 cmH_2O/L), yielding an R^2 value of 0.943, which aligns closely with their reported results. This study further extended the analysis to a broader elastance range (4.7–50.7 cmH_2O/L), while still maintaining a strong correlation ($R^2 = 0.903$). The successful replication of Howe’s findings highlights the reliability of image processing as a robust method for ventilatory data extraction.

3.4 Conclusions

A pivotal aspect of this study involved validating the feasibility and robustness of image processing techniques for extracting ventilatory curves. Both the flowchart illustrated in Figure 3.5 and the use of open-source software, such as WebPlotDigitizer, demonstrated substantial accuracy and reliability in data acquisition. This conclusion is supported by high R^2 values (Table 3.2), low MSE values 3.3, and Bland-Altman analyses (Figure 3.9), which indicate that discrepancies between sensor-derived and image-processed data remain within acceptable limits.

These results establish the open-source application as a dependable and accessible tool for advancing the development of predictive models. Moreover, the successful replication

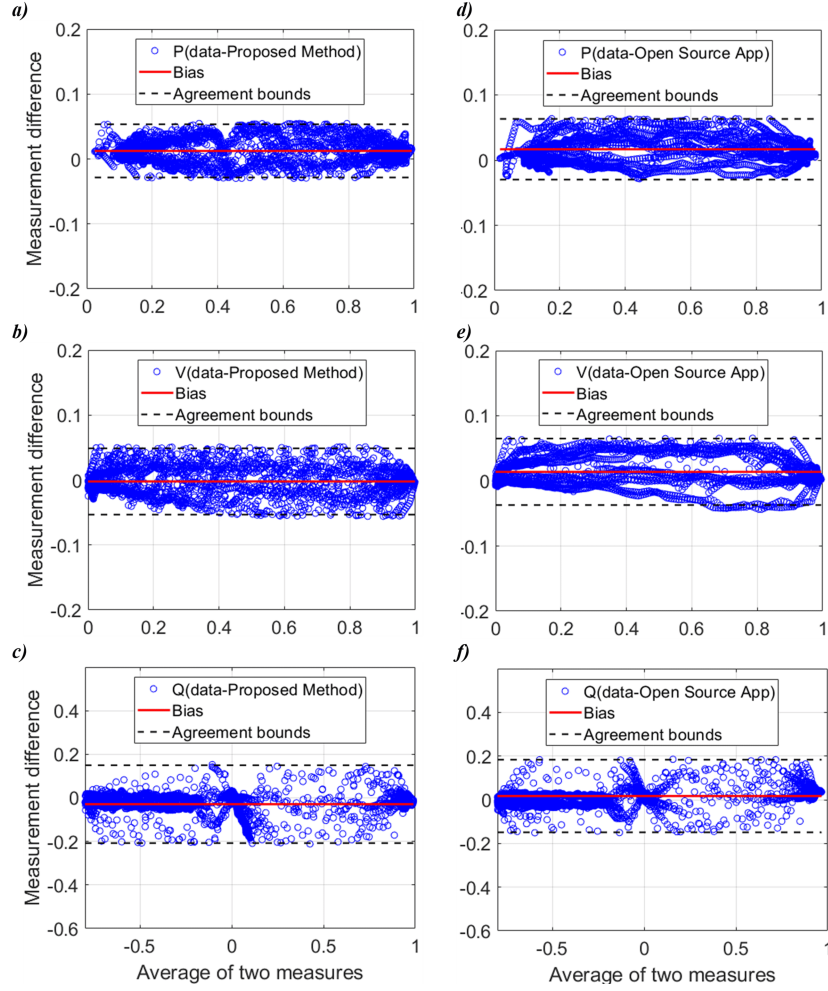


Figure 3.9: Bland-Altman Analysis of Agreement Between Sensor Data and Image-Derived Methods for Pressure (a and d), Volume (b and e), and Airflow (d and f)

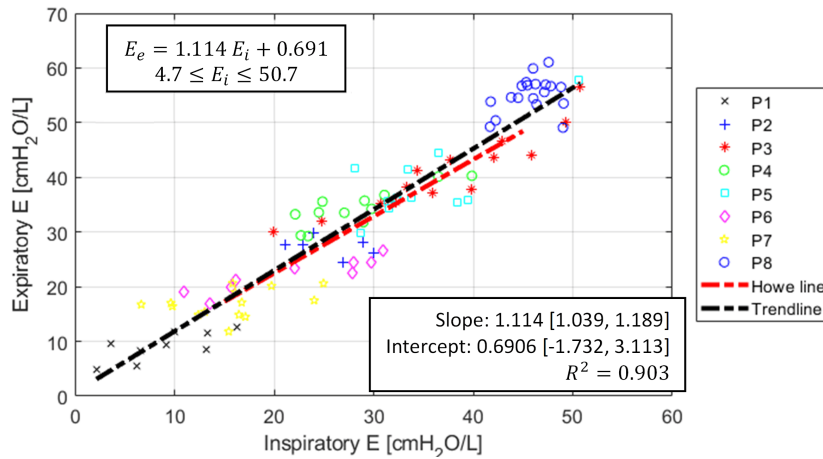


Figure 3.10: Expiratory Elastance vs Inspiratory Elastance linear regression

of the results reported by Howe et al. [17] (Figure 3.10), with a correlation coefficient of 0.943 closely approximating their findings, further validates the effectiveness of the image processing methodology.

Despite this validation, the study acknowledges certain limitations and opportunities for future work associated with image processing. Although the methodology proved effective in validating the fidelity of the data conversion, variables such as image resolution, video quality, pixel sampling rates, and interpolation methods were not systematically analyzed for their potential impact on data accuracy. Furthermore, the validation was conducted using synchronous waveforms, due to the nature of the emulator available at the time of the tests. A valuable next step for future research would be to perform additional validation studies using an emulator capable of generating standardized asynchronous waveforms. This would allow for a quantitative analysis to determine precisely how the accuracy of the reconstruction behaves in the presence of specific, controlled asynchronies.

Chapter 4

Proposing a new Model

This chapter builds upon the SCM as a foundational framework for analyzing ventilatory mechanics. A significant advancement was achieved by incorporating the approach proposed by Morton et al. [43], which introduced the use of shape functions to refine the representation of ventilatory curves. While Morton proposed a model that effectively captured certain dynamic aspects, it exhibited limitations in accurately fitting ventilatory curves when SB and RAs were present. To address these challenges, new shape functions were developed to enhance the model adaptability. However, even with these improvements, further refinement was necessary to achieve greater precision. Therefore, Morton approach was integrated with a variation of the methodology proposed by Guttman et al. [44], which utilizes the division of curves into equal-volume slices for mechanical property analysis. In the proposed model, this slicing technique was applied to the pressure curve rather than the volume curve, enabling a more detailed characterization of ventilatory dynamics. This adaptation culminated in the development of the Recruitment Distention Elastance Analysis with Slice (RDEA+Slice) model, which significantly improved the model ability to capture the complex ventilatory mechanics observed in the pressure-versus-time (P vs. t) curve.

To evaluate the accuracy and reliability of this refined model, retrospective data from 8 patients (6 minutes of therapy per patient) were analyzed, with the data partitioned into two independent datasets: one for initial model development and the other for validation. Model accuracy was assessed using the coefficient of determination (R^2), which measured the correlation between the fitted curve and actual data, and the Mean Residual Error (MRE), which quantified the average error in capturing key ventilatory dynamics, including SB efforts. As a result of this analysis, a new equation was derived, demonstrating superior precision in fitting ventilatory curves affected by RAs. The RDEA+Slice model was employed in Chapter 5 to propose a parameter that can assist in the detection of RAs, contributing to the development of more effective real-time diagnostic tools in intensive care unit (ICU) settings.

4.1 Methods

This study develops a method for accurately fitting ventilatory curves in the presence of SB, building upon two foundational models. The first is the SCM, which has been refined by various researchers [3, 4, 17, 62] to better represent mechanical ventilation (MV). The second is Morton model [43], which introduced the use of shape functions to capture the complexities of ventilatory mechanics, offering a framework for refining these functions to enhance curve fitting in the presence of SBs.

Leveraging these models, this research proposes a series of advancements to address critical gaps in analyzing pressure-time ventilatory curves. Initially, the Recruitment Elastance Analysis (REA) and Distention Elastance Analysis (DEA) models were developed, refining the shape functions introduced by Morton et al. [43]. These models aimed to improve the accuracy of ventilatory dynamics representation. Building on these refinements, a third model, termed Recruitment and Distention Elastance Analysis (RDEA), was formulated to integrate the effects of both recruitment and distention elastance simultaneously. However, subsequent analysis highlighted limitations in the ability of the REA, DEA, and RDEA models to fully capture all identified RAs.

To address these limitations, a modified version of the slice method, originally proposed by Guttman et al. [44], was incorporated, leading to the development of the Recruitment and Distention Elastance Analysis with Slice (RDEA+Slice) model. This enhanced model significantly improves the accuracy of fitting ventilatory curves in the presence of SBs. Figure 4.1 provides a schematic overview of the progression of these models, illustrating their derivation from the base models and the rationale behind their development.

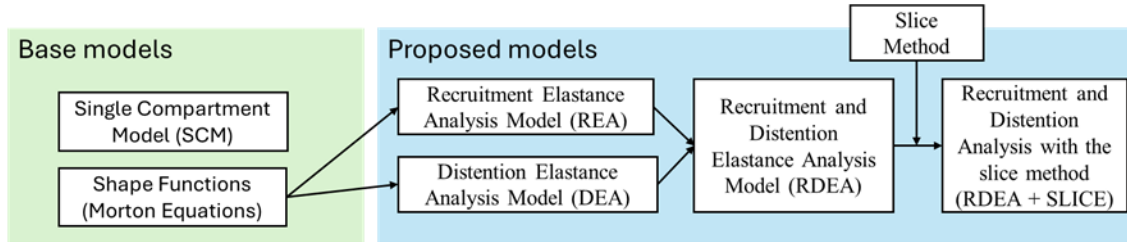


Figure 4.1: Evolution from Base Models to Proposed Models

Source: Ruiz et al. (2025) [84]

To evaluate the behavior and accuracy of the proposed models in replicating ventilatory curves affected by SB, patient-specific ventilator data were used. As defined in Section 4.1.7, two datasets were utilized, each comprising data from four patients with approximately six minutes of recorded therapy; the first dataset was used to develop the model fitting functions, while the second was employed to test the proposed equations. Model accuracy was subsequently assessed using specific metrics designed to quantify improvements in replicating the pressure-time curve, providing a comprehensive evaluation of the model capability to capture the complexities introduced by SBs.

4.1.1 Shape functions approach

To enhance the SCM, Morton et al. [43] introduced shape functions, as shown in equation 4.1. This approach, similar to modifications observed in studies by Knopp et al. [1] and Langdon et al. [7], adds adaptability to the SCM by incorporating additional terms that account for the specific challenges presented by SB. By refining shape functions and improving model precision, Morton's method provides a more robust framework for representing ventilatory dynamics in the presence of SB, thereby serving as a valuable tool for individualized patient modeling.

$$P(t) = (E_1 \cdot \phi_1 + E_2 \cdot \phi_2) \cdot V(t) + (R_1 \cdot \theta_1 + R_2 \cdot \theta_2) \cdot Q(t) + P_0, \quad (4.1)$$

where ϕ_1 , ϕ_2 , θ_1 , and θ_2 are shape functions defined by equations 4.2.

$$\phi_1 = (V(t) - V_m)^2, \quad V_m = 1L, \quad (4.2a)$$

$$\phi_2 = \frac{P(t)}{60}, \quad (4.2b)$$

$$\theta_1 = 1, \quad (4.2c)$$

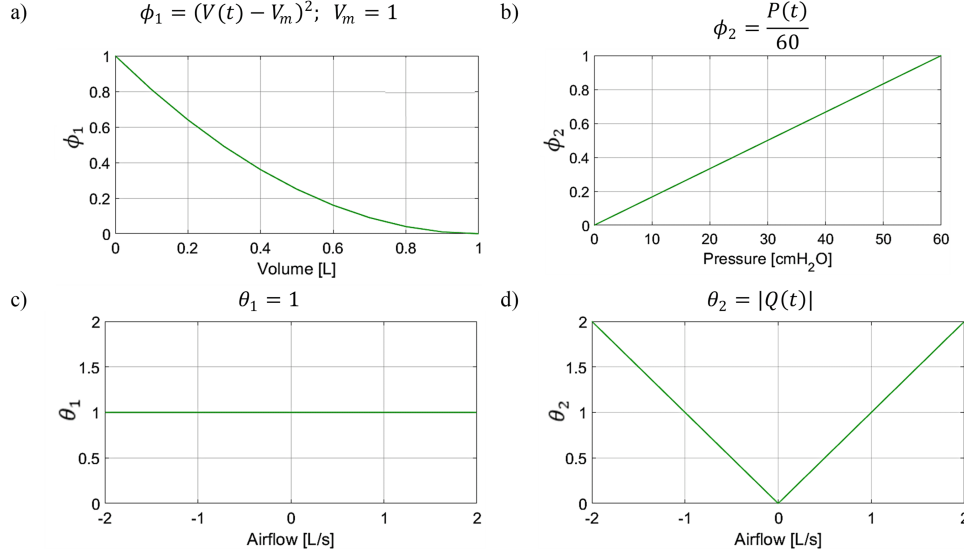
$$\theta_2 = |Q(t)|. \quad (4.2d)$$

In the work of Morton et al. [40, 43], the parameter E_1 was defined as Recruitment Elastance, representing the elastance associated with alveolar recruitment. This parameter quantified the rate at which alveoli were recruited as volume increased. Similarly, E_2 was defined as Distention Elastance, describing the elastance related to alveolar expansion, thus modeling the increase in elastance caused by applied pressure. Finally, R_1 and R_2 represented Rohrer Resistance, providing a framework for modeling both linear and nonlinear aspects of airflow resistance. Figure 4.2 illustrates the shape functions proposed by Morton et al., which served as the foundation for developing a new model specifically designed for implementation in patients experiencing SB [84]. Equation 4.1 can also be expressed in matrix form, as follows:

$$\begin{pmatrix} P_1 \\ P_2 \\ \vdots \\ P_n \end{pmatrix} = \begin{pmatrix} \phi_{11}V_1 & \phi_{21}V_1 & \theta_{11}Q_1 & \theta_{21}Q_1 & 1 \\ \phi_{12}V_2 & \phi_{22}V_2 & \theta_{12}Q_2 & \theta_{22}Q_2 & 1 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \phi_{1n}V_n & \phi_{2n}V_n & \theta_{1n}Q_n & \theta_{2n}Q_n & 1 \end{pmatrix} \begin{pmatrix} E_1 \\ E_2 \\ R_1 \\ R_2 \\ P_0 \end{pmatrix}. \quad (4.3)$$

4.1.2 Recruitment Elastance Analysis Model (REA)

The REA model focuses on refining the shape function ϕ_1 (Figure 4.2a) to better capture the dynamics of SB. The original function from Morton et al. [43], Equation 4.2a, is a convex parabola that can only model an elastance that increases as volume changes.


 Figure 4.2: Morton Shape Functions. a) ϕ_1 , b) ϕ_2 , c) θ_1 , and d) θ_2

However, a key feature of SB efforts is the potential for airway pressure to drop during respiratory cycle waveform. This phenomenon implies a transient negative elastance [25], which the original convex shape of ϕ_1 is mathematically incapable of representing. To address this specific limitation, the REA model proposes a new formulation that inverts the concavity of the parabola, allowing it to model these pressure drops:

$$\phi_1 = 1 - N \cdot (V(t) - 1)^2. \quad (4.4)$$

This inverted, negatively concave shape allows the recruitment elastance term to decrease as volume increases, providing the necessary mathematical flexibility to fit the pressure drops characteristic of SB efforts. A family of shape functions is defined by Equation 4.4, controlled by a parameter N ranging from -1 to 2 and illustrated in Figure 4.3. Each dotted line represents a specific N value. The objective was to determine the optimal value of N that yielded the highest R^2 coefficient, as described previously.

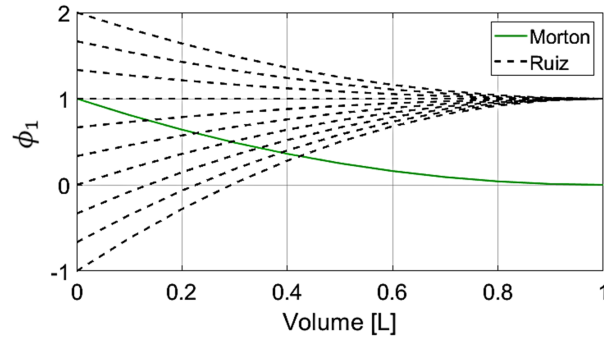


Figure 4.3: Shape function proposal for REA

Source: Ruiz et al. (2025) [84]

4.1.3 Distention Elastance Analysis Model (DEA)

The DEA model refines the shape function ϕ_2 , which relates elastance to airway pressure (distention). The original function from Morton et al. [43], Equation 4.2b, assumes a purely linear relationship, where elastance increases in direct proportion to pressure. While this is a reasonable approximation for passive ventilation, the complex dynamics during patient-ventilator asynchrony can result in highly non-linear pressure-distention relationships. To provide the model with the flexibility to capture these non-linearities, the DEA model transforms the linear term into a variable power function:

$$\phi_2 = (P(t)/60)^M. \quad (4.5)$$

This modification introduces a parameter M , ranging from 0 to 5, which generates a family of functions illustrated in Figure 4.4. Each dotted line in the figure represents a specific M value. The goal was to determine the optimal value of M that produced the highest R^2 coefficient, allowing the model to adapt to the specific non-linear characteristics of each patient breathing pattern.

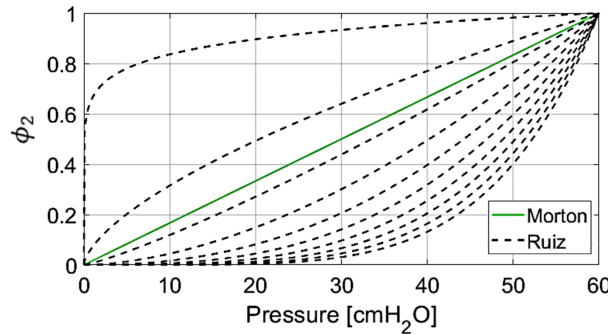


Figure 4.4: Shape function proposal for DEA

Source: Ruiz et al. (2025) [84]

4.1.4 Recruitment and Distention Elastance Analysis Model (RDEA)

By synthesizing the REA and DEA frameworks, the RDEA model aimed to optimize the N and M parameters simultaneously. The base SCM already provides a physiological interpretation of elastance (E) and resistance (R), which Morton et al. [43] extended by decomposing elastance into Recruitment Elastance (E_1), related to the opening of collapsed alveoli, and Distention Elastance (E_2), associated with stiffening from tissue overstretching, while modeling resistance with the Rohrer formulation to account for non-linear, turbulent airflow (R_1 and R_2). The main challenge in this work was adapting that framework, originally designed for sedated patients, to the complex dynamics of SB, where the patient respiratory muscles actively contribute to the mechanics.

To address this, the N coefficient was introduced to modify the recruitment shape function (ϕ_1), enabling the model to represent negative elastance, a phenomenon that

occurs when the patient inspiratory effort assists the ventilator, reducing the apparent stiffness of the respiratory system. Likewise, the M coefficient modifies the distention shape function (ϕ_2), adjusting the non-linearity of the pressure–stiffness relationship to reflect how patient–ventilator interaction alters lung mechanics. Both coefficients were optimized jointly within the calibrated range of -2 to 2 to capture meaningful variability without unnecessarily enlarging the search space. By incorporating these parameters, the RDEA model moves beyond simple curve fitting, aiming to capture the underlying physiological interactions between the patient and the ventilator during SB, while improving the R^2 coefficient compared to separate REA or DEA analyses.

4.1.5 RDEA + SLICE method

To enhance the accuracy of the RDEA model, a method similar to that of Guttman et al. [44] was incorporated. This approach, known as the “slice method,” traditionally divides tidal volume into equal segments to analyze volume-dependent compliance and resistance. However, to better represent SBs and RAs—phenomena that standard models often fail to capture—the slice method was modified, as illustrated in Figure 4.5.

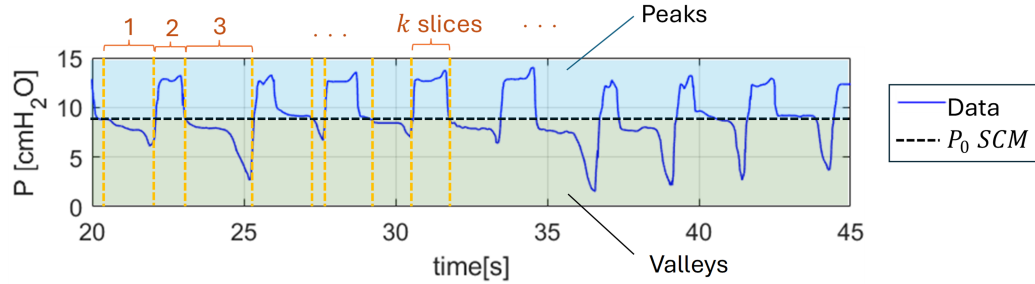


Figure 4.5: RDEA+Slice model

Source: Ruiz et al. (2025) [84]

To better represent SBs and RAs, the slice method was modified. Instead of dividing by equal-volume segments, the domain was segmented based on the intersections between the pressure waveform and a reference pressure P_0 . It is essential to clarify that this reference P_0 is a global and constant value, determined by applying the SCM (Equation 2.4) to the entire data series using the least-squares method (Equation 2.7). This global value, represented by the dashed line in Figure 4.5, is used solely as a threshold for segmentation.

These intersections define slices, indexed as k , that encompass both the peaks and valleys of the waveform. The governing equation for each slice k is shown in Equation 4.6. For each of these slices, a new set of local parameters E_{1k} , E_{2k} , R_{1k} , R_{2k} , and a local P_{0k} is calculated using Equation 2.7. This approach gives the RDEA+Slice model a time-variant nature, where the parameters are piecewise-constant. This dynamic adaptation is crucial for accurately capturing the changing mechanics of SB and asynchronies.

$$P_k(t) = (E_{1k} \cdot \phi_{1k} + E_{2k} \cdot \phi_{2k}) \cdot V_k(t) + (R_{1k} \cdot \theta_{1k} + R_{2k} \cdot \theta_{2k}) \cdot Q_k(t) + P_{0k}. \quad (4.6)$$

4.1.6 Model Analysis

To evaluate the accuracy of the models in replicating observed patient data, the Mean Relative Error (MRE) was employed. This metric, previously utilized by Zaniol et al. [41], quantifies the average relative discrepancy between the original patient pressure data and the pressure values predicted by the evaluated models. Essentially, it measures how well each model reconstructs the patient pressure waveform. The MRE is calculated using the following equation:

$$MRE = \frac{1}{n} \sum_{i=1}^n \left| \frac{P_{\text{model},i} - P_{\text{data},i}}{P_{\text{data},i}} \right|. \quad (4.7)$$

Here, P_{data} represents the measured pressure data from the patients, and P_{model} denotes the pressure values derived from the models under evaluation, including the SCM, Morton model, REA, DEA, RDEA, and RDEA+Slice. While the coefficient of determination (R^2) provides a global overview of how well the models fit the overall data trend, the MRE offers a more detailed assessment. Specifically, it highlights the precision of each model in capturing finer dynamics, such as SB efforts or asynchrony events. This detailed analysis of residual errors provided a clearer understanding of the improvements in accuracy achieved by the proposed models, particularly in handling the variability introduced by spontaneous breathing.

4.1.7 Patients data

To improve the replication of ventilatory curves in the presence of SB, a random selection and partitioning process was applied to retrospective patient data. Data were obtained from 8 patients connected to Neumovent TS ventilators, with each patient undergoing six minutes of recorded therapy. This data collection was conducted using the experimental setup described in Chapter 3. The complete dataset was then randomly divided into two distinct groups: dataset 1 (Table 4.1) and dataset 2 (Table 4.2). Dataset 1 served as the basis for model development, as outlined in the methodology flowchart (Figure 4.1), while dataset 2 was used for model validation, assessing each model's ability to replicate ventilatory curves with SB and to determine the most effective model.

A review of Tables 4.1 and 4.2 shows that the primary ventilation mode was Pressure Support Ventilation/Continuous Positive Airway Pressure (PSV/CPAP), suitable for patients capable of spontaneous breathing. The most commonly used backup mode was Volume Control Ventilation (VCV), followed by Pressure Control Ventilation (PCV). Additionally, Pressure Support Ventilation with Guaranteed Tidal Volume (PSV + VT Aseg) and VCV were used in two patients—one from each dataset. Positive End-Expiratory Pressure (PEEP) was maintained between 5 and 8 cmH_2O for all patients.

A clinical evaluation of Figure 4.6 identified multiple types of asynchronies within datasets 1 and 2. It is important to note that the definitions and terminology of these asynchronies were established in Chapter 2. Flow asynchrony (FA), characterized by a

Table 4.1: Dataset 1

Patient	Sex	Age [years]	Clinical Diagnostic	PEEP [cmH ₂ O]	Ventilatory mode	PSV [cmH ₂ O]	Backup mode
P1	Male	60	Pulmonary edema	6.0	PSV/CPAP	10.0	VCV
P2	Female	66	Exacerbated COPD	8.0	PSV/CPAP	8.0	PCV
P3	Male	64	Heart attack	7.0	VCV	-	-
P4*	Female	91	Neural surgery	6.0	PSV/CPAP	7.0	VCV

*Weaning patient

Source: Ruiz et al. (2025) [84]

Table 4.2: Dataset 2

Patient	Sex	Age [years]	Clinical Diagnostic	PEEP [cmH ₂ O]	Ventilatory mode	PSV [cmH ₂ O]	Backup mode
S1	Female	70	Respiratory Failure	6.0	PSV/CPAP	8.0	VCV
S2*	Male	75	Neural surgery	5.0	PSV/CPAP	10.0	VCV
S3*	Female	83	Neural surgery	6.0	PSV/CPAP	12.0	VCV
S4	Female	87	Respiratory Failure	6.0	PSV + VT Aseg	8.0	VCV

*Weaning Patient

Source: Ruiz et al. (2025) [84]

mismatch between flow demand and delivery, was identified in patients P1, P2, P4, S1, S2, S3, and S4. Premature cycling (PC), involving early termination of inspiration, was present in patients P1, P2, P4, S2, S3, and S4. Patient S1 exhibited double cycling (DC), marked by extended inspiratory efforts. Ineffective efforts (IE), defined as failed triggering attempts, were seen in patients P4, S1, and S4. Double triggering (DT), where a second breath is initiated due to an additional inspiratory effort, occurred in patients S2 and S3. Reverse triggering (RT), in which a ventilator-delivered breath triggers a muscular response, was observed in patient P3. No cases of auto-triggering (AT) were found in any of the patients.

4.2 Results and Discussion

A grid search was conducted to determine the optimal values of coefficients N and M . For each model, a broad parameter space was explored, ranging from -20 to 20 with a step size of 0.1 . At each point in this grid, the model was fitted to the training

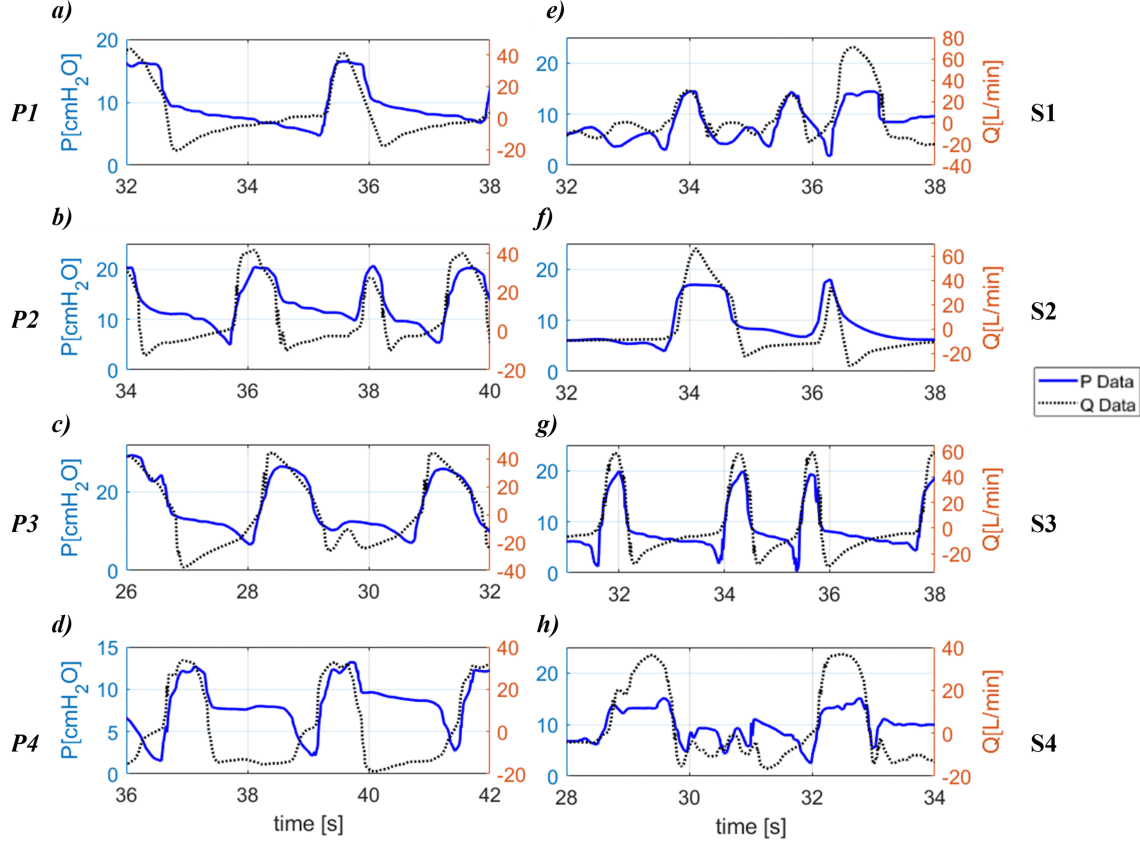


Figure 4.6: Pressure (P) and airflow (Q) versus time for each patient. a) P1, b) P2, c) P3, d) P4, e) S1, f) S2, g) S3, h) S4

Source: Ruiz et al. (2025) [84]

dataset (Dataset 1), and the coefficient of determination (R^2) was calculated. The main goal was to find coefficient values that maximized the average R^2 across all patients in the dataset. This analysis revealed stable, high-performing parameter regions. The final coefficients selected for the models were chosen from these regions to define a generalized and functionally improved model, recognizing that these correspond to consistent local maxima rather than a single guaranteed global maximum.

To establish the baseline performance of the SCM and the Morton model [43] within the study dataset, an initial evaluation was carried out. Figures 4.7a–4.7d show the results of applying these models to patients in Dataset 1. For patients P1 and P2 (Figures 4.7a and 4.7b, respectively), both models successfully reproduced the respiratory frequencies but struggled to accurately capture inspiratory peaks and pressure drops—particularly in the regions highlighted by the orange dotted circles. These limitations became even more apparent in the simulation of patient P4 (Figure 4.7d), where the models failed to replicate the pressure valleys entirely.

In patient P3 (Figure 4.7c), an inspiratory effort occurring at the end of the expiratory phase was identified. This asynchrony posed a significant modeling challenge, leading to the SCM’s failure to reproduce the ventilatory curve accurately. However, the Morton

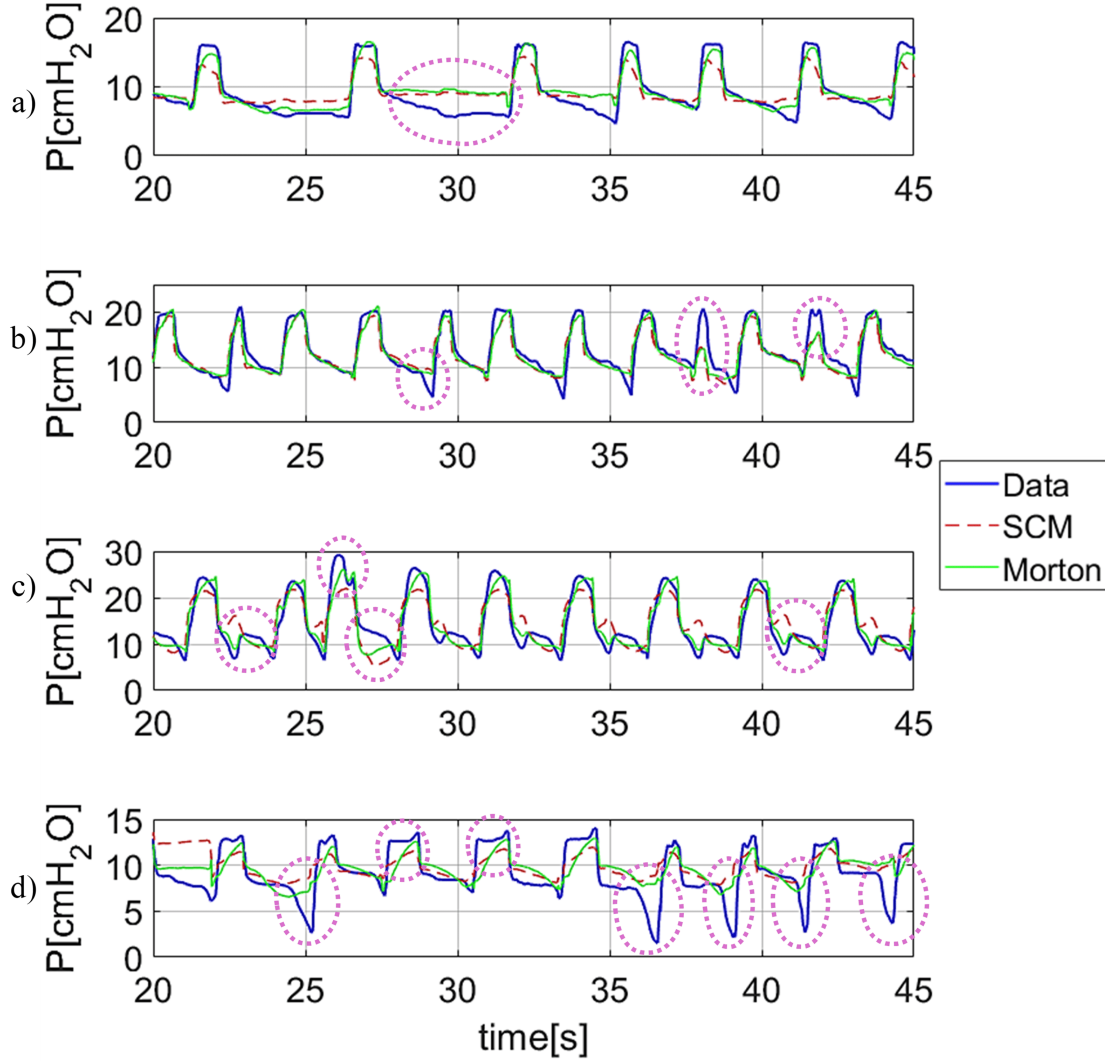


Figure 4.7: SCM and Morton Comparison. a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4

model, which incorporates shape functions, demonstrated a superior ability to model the pressure waveform, as will be further illustrated in Table 4.4. This outcome underscores the potential of adaptable shape functions for effectively modeling ventilatory curves in the presence of spontaneous breathing.

4.2.1 The REA Model

During the development of the REA model, multiple values of N were evaluated to modify the shape function ϕ_1 , with the goal of optimizing the R^2 coefficient within the family of functions defined by Equation 4.4. The influence of these N values on the R^2 coefficient was assessed by comparison with the baseline models, as illustrated in Figures 4.8a–4.8d. For patients P2, P3, and P4 (Figures 4.8b, 4.8c, and 4.8d, respectively), the

proposed REA model exhibited a higher R^2 coefficient within the range of $0 < N \leq 1$. Even in the case of patient P1 (Figure 4.8a), where the optimal point fell outside this range, the REA model still outperformed the baseline approaches. As a result, an N value of 0.98 was selected, representing the average of the maximum R^2 values observed across dataset 1, as shown in Figures 4.8a–4.8d.

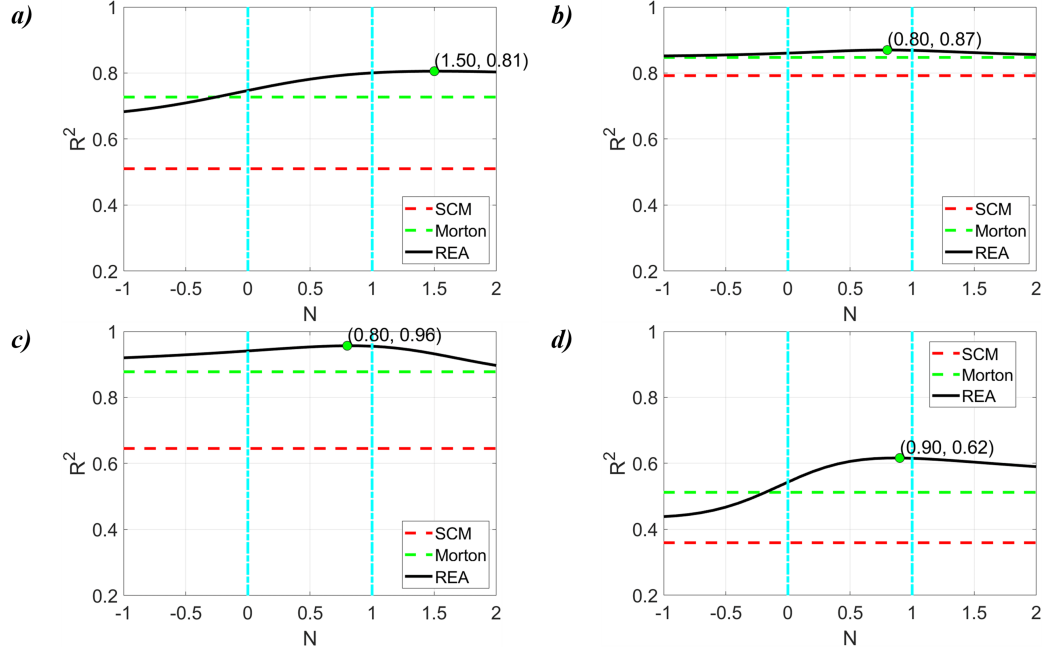


Figure 4.8: R^2 values for shape function $\phi_1 = 1 - N(V - 1)^2$. a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4

Source: Ruiz et al. (2025) [84]

4.2.2 The DEA Model

To develop the DEA model and assess the impact of distention elastance, the methodology from the previous analysis was applied to modify ϕ_2 based on varying values of M within the family of functions defined by Equation 4.5. Figure 4.9 illustrates the variation in R^2 in response to changes in M for patients P1–P4 (Figures 4.9a–4.9d, respectively). The DEA model produced slightly higher R^2 values than the baseline models within the range $1.5 < M \leq 3$. Although patient P4 (Figure 4.9d) showed a peak R^2 value outside this range, it still exceeded that of the baseline models. Consequently, an M value of 2.48 was selected, representing the average of the maximum R^2 values observed across dataset 1.

4.2.3 The RDEA Model

Recognizing that the REA and DEA models produced R^2 coefficients with room for improvement (Figures 4.8 and 4.9), a combined approach was implemented to evaluate

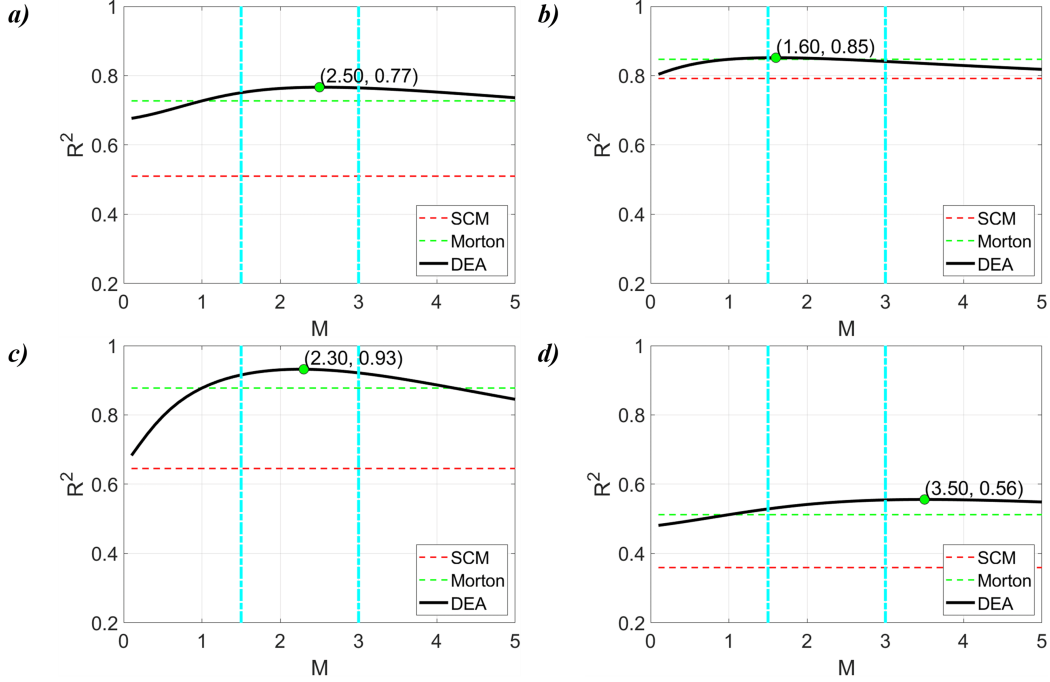


Figure 4.9: R^2 for shape function $\phi_2 = (P/60)^M$. a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4

Source: Ruiz et al. (2025) [84]

the effect of simultaneously modifying ϕ_1 (Equation 4.4) and ϕ_2 (Equation 4.5) on the R^2 value. The objective was to achieve a higher R^2 coefficient in this combined Recruitment Distension Elastance Analysis (RDEA) model compared to the individual models. The optimal combination of N and M coefficients that maximized R^2 was identified, resulting in the surfaces and contour plots shown in Figures 4.10a–4.10d for patients P1–P4.

The surfaces displayed in Figure 4.10 reveal two distinct regions for each patient where the R^2 coefficient is elevated. These regions are defined by the ranges $0 < N \leq 1.5$ and $0.5 < M \leq 1.5$ for the first, and $-1.5 < N \leq 0$ and $-0.2 < M \leq 1.5$ for the second. To select the optimal values, the average of the maximum R^2 values observed in Figures 4.10a–4.10d was computed, yielding $N = -0.35$ and $M = -0.48$. This process defined a new equation that integrates both shape functions and combines modifications in Recruitment and Distension Elastance.

4.2.4 Analysis and Summary of REA, DEA, and RDEA Model Results

Once the N and M values were chosen based on the aforementioned procedure, the shape functions for each of the proposed models are presented in Table 4.3, and their performance is shown in Figure 4.3, focusing on the patient dataset 1.

Upon initial observation, the proposed models (Figure 4.11) appear to offer subtle

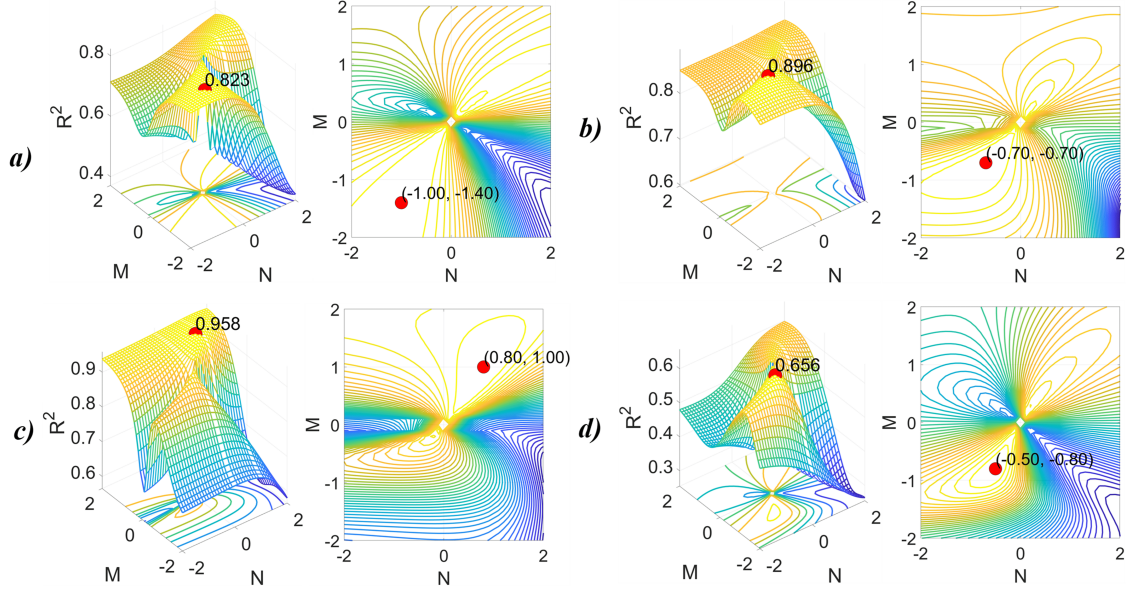


Figure 4.10: R^2 for shape functions $\phi_1 = 1 - N.(V - 1)^2$ and $\phi_2 = (P/60)^M$ combined. a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4

Source: Ruiz et al. (2025) [84]

Table 4.3: Shape functions proposal summary

REA	DEA	RDEA
$\phi_1 = 1 - 0.98(V - 1)^2$	$\phi_1 = \text{Eq Morton 4.2a}$	$\phi_1 = 1 + 0.35(V - 1)^2$
$\phi_2 = \text{Eq Morton 4.2b}$	$\phi_2 = \left(\frac{P}{60}\right)^{2.48}$	$\phi_2 = \left(\frac{P}{60}\right)^{-0.48}$

Source: Ruiz et al. (2025) [84]

improvements compared to the baseline models (Figure 4.7). Notably, in patient P3 (Figure 4.11c), the proposed models demonstrated a significant enhancement in capturing SB events, which were poorly represented by the baseline models, particularly the SCM.

However, a closer examination of patients P1, P2, and P4 (Figures 4.11a, 4.11b, and 4.11d, respectively) reveals persistent challenges in accurately replicating the expiratory phase. Specifically, the models struggle to represent mild pressure drops, as seen in patient P1, and more pronounced pressure drops, as observed in patient P4. Table 4 presents the R^2 coefficients of the evaluated models (REA, DEA and RDEA), where it can be observed that although there is an increase for the proposed models, the values remain low and can still be improved. This indicates a need for further refinement to accurately model these expiratory phase dynamics. To address this, a new model integrating the 'slice method,' as defined in Equation 4.6, is proposed, aiming to enhance the capture of these critical ventilatory behaviors.

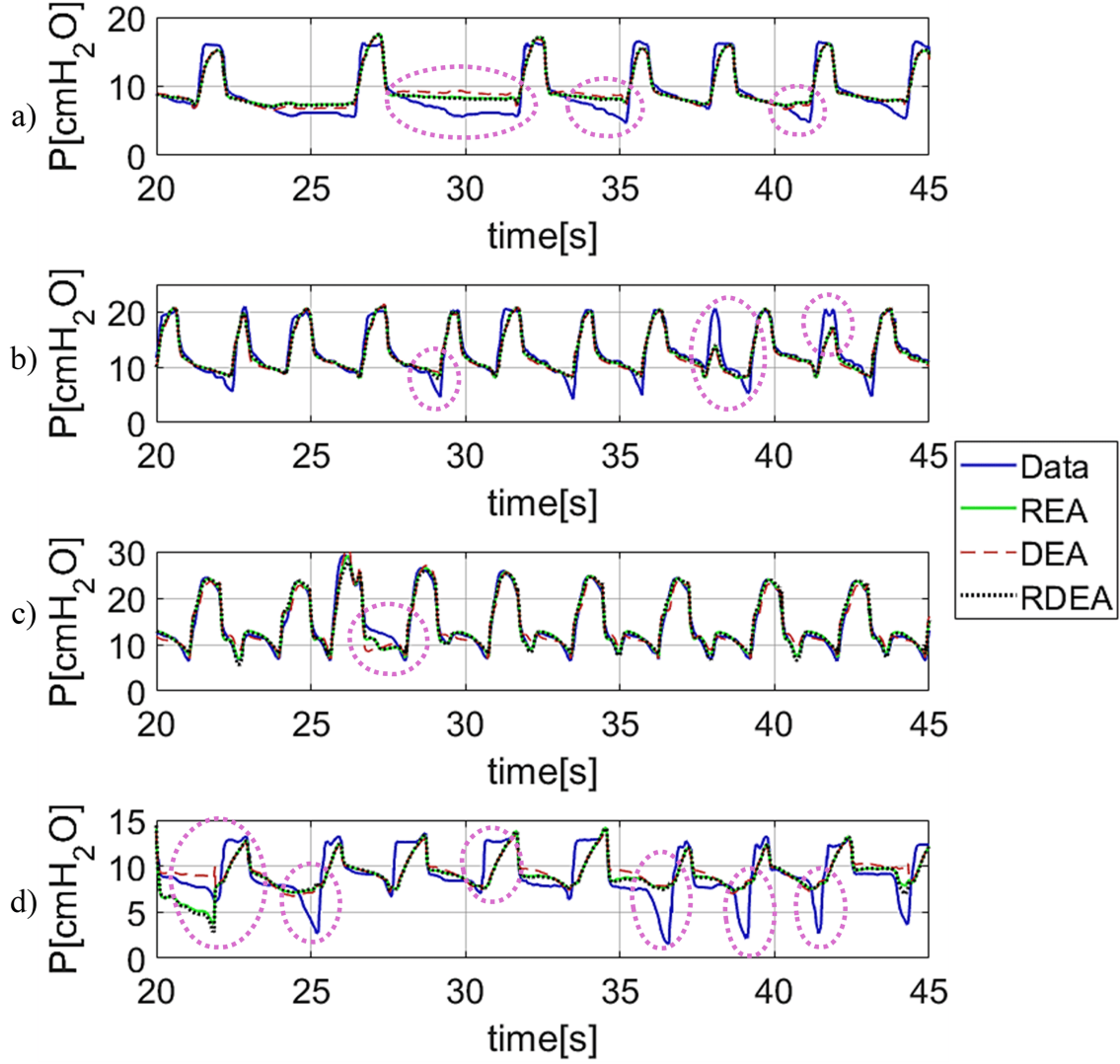


Figure 4.11: REA, DEA and RDEA comparison a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4

Table 4.4: R^2 for SCM, Morton and proposed models Dataset 1

	SCM	Morton	REA	DEA	RDEA	RDEA+Slice
P1	0.52	0.73	0.80	0.77	0.82	0.98
P2	0.80	0.85	0.87	0.85	0.89	0.94
P3	0.65	0.88	0.96	0.93	0.92	0.99
P4	0.36	0.51	0.62	0.55	0.65	0.96

Source: Ruiz et al. (2025) [84]

4.2.5 Evaluating RDEA + Slice model

The Figures 4.12a through 4.12d illustrate the effectiveness of integrating the Slice method into the RDEA model using dataset 1. The results show a significant improvement

in fitting the ventilatory curves of patients exhibiting spontaneous breathing (SB) patterns. The R^2 coefficients for the RDEA + Slice model indicate substantial gains over the other models evaluated (Table 4.1). Notably, this approach accurately captures the regions below P_0 , which were not well-represented by previous models.

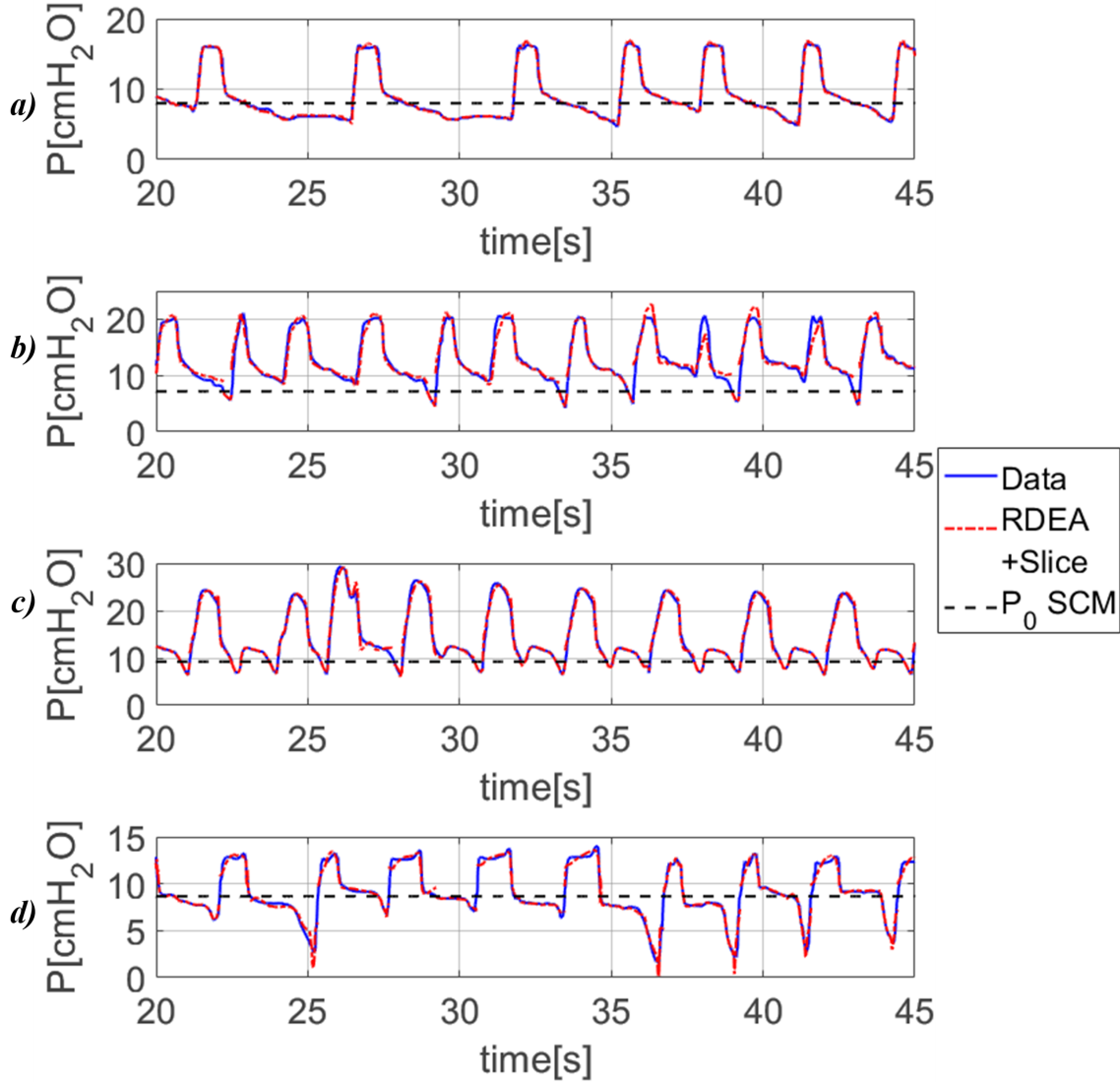


Figure 4.12: RDEA + Slice method, dataset 1. a) Patient P1, b) Patient P2, c) Patient P3, d) Patient P4

The robustness of the RDEA + Slice approach was further validated using dataset 2 (Table 4.2). As shown in Figure 4.13, incorporating the Slice method into the RDEA model significantly improves the replication of pressure peaks and valleys. The Table 4.5 confirms the findings from dataset 2, reflecting the trends observed in dataset 1 (Table 4.4). The RDEA + Slice model consistently achieves the highest R^2 values, emphasizing the importance of incorporating the Slice method for accurately modeling ventilatory dynamics in the presence of respiratory asynchronies. To further assess the model's precision, the Mean Relative Error (MRE) was evaluated, as presented in Table 4.6.

Table 4.5: R^2 for SCM, Morton, and proposed models – Dataset 2

	SCM	Morton	REA	DEA	RDEA	RDEA+Slice
S1	0.25	0.31	0.37	0.32	0.38	0.93
S2	0.73	0.82	0.82	0.81	0.83	0.97
S3	0.87	0.91	0.91	0.90	0.92	0.97
S4	0.21	0.54	0.62	0.53	0.55	0.90

Source: Ruiz et al. (2025) [84]

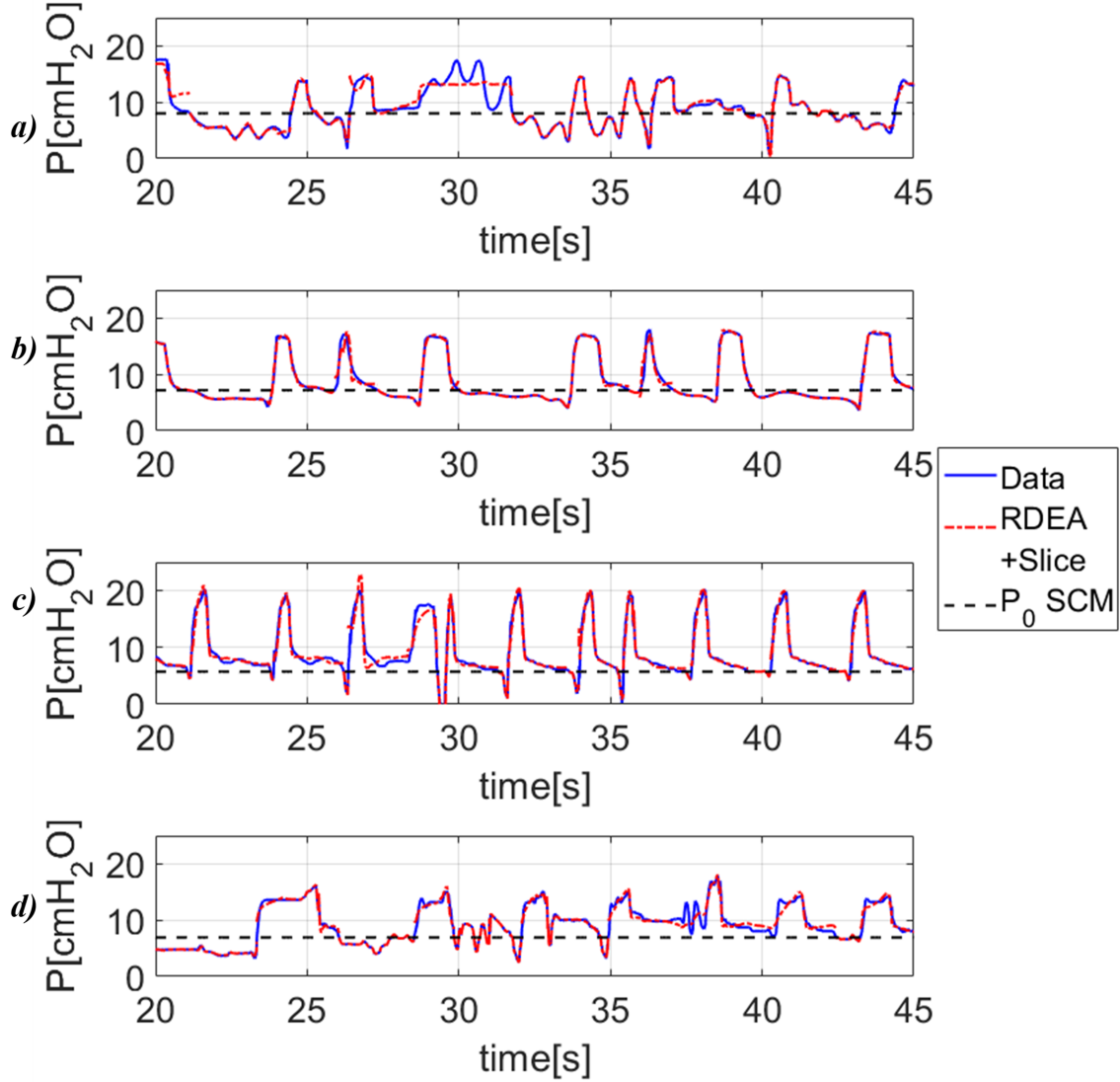


Figure 4.13: RDEA + Slice method, dataset 2. a) Patient S1, b) Patient S2, c) Patient S3, d) Patient S4

The RDEA + Slice model consistently produced the lowest Mean Relative Error (MRE) among all models evaluated (Table 4.6). This superior performance is attributed to the integration of the Slice method, which accurately captures both peaks and valleys in the

ventilatory curves. As a result, the model closely mirrors the dynamic changes in the pressure-time (P vs. t) curves, effectively addressing the limitations found in the SCM, Morton, REA, DEA, and RDEA models. This improvement—evaluated across breathing cycles ranging from 95 to 156—yielded MRE values often less than half those observed in the SCM and Morton models.

Table 4.6: Comparison of MRE for all evaluated models

		Mean Residual Error (MRE): Med [IQR]					
Breathing Cycles		SCM	Morton	REA	DEA	RDEA	RDEA +Slice
P1	108	0.153	0.106	0.092	0.105	0.088	0.012
		[0.075-0.249]	[0.056-0.204]	[0.045-0.183]	[0.053-0.196]	[0.041-0.173]	[0.005-0.027]
P2	156	0.078	0.061	0.055	0.062	0.036	0.032
		[0.035-0.158]	[0.028-0.117]	[0.026-0.099]	[0.030-0.114]	[0.015-0.076]	[0.012-0.067]
P3	136	0.160	0.119	0.054	0.072	0.051	0.015
		[0.081-0.290]	[0.062-0.186]	[0.022-0.100]	[0.035-0.139]	[0.022-0.104]	[0.005-0.035]
P4	123	0.113	0.096	0.071	0.091	0.071	0.020
		[0.054-0.206]	[0.036-0.214]	[0.031-0.171]	[0.035-0.199]	[0.034-0.150]	[0.009-0.039]
S1	98	0.185	0.160	0.144	0.151	0.139	0.019
		[0.082-0.336]	[0.068-0.307]	[0.061-0.294]	[0.061-0.304]	[0.049-0.290]	[0.007-0.042]
S2	95	0.133	0.081	0.102	0.099	0.079	0.014
		[0.061-0.267]	[0.042-0.168]	[0.041-0.199]	[0.045-0.186]	[0.035-0.157]	[0.007-0.040]
S3	130	0.082	0.051	0.052	0.069	0.054	0.019
		[0.041-0.154]	[0.021-0.113]	[0.022-0.107]	[0.031-0.124]	[0.027-0.107]	[0.008-0.043]
S4	107	0.116	0.122	0.074	0.109	0.115	0.020
		[0.049-0.234]	[0.058-0.214]	[0.034-0.149]	[0.055-0.190]	[0.051-0.218]	[0.007-0.047]

Source: Ruiz et al. (2025) [84]

4.2.6 Model Identification

To verify that the evaluated models are uniquely identifiable, the rank and determinant of the matrix $[\underline{A}^T \cdot \underline{A}]$ (see Equation 2.7) were calculated. These results, evaluated using dataset 2, are presented in Table 4.7. As shown, the matrix rank is 3 for the SCM model and 5 for all other models, consistent with the expected values derived from Equations 2.4, 4.1, and 4.6.

Additionally, the determinant of the matrix $[\underline{A}^T \cdot \underline{A}]$ was found to be significantly different from zero, confirming that the system of equations includes linearly independent vectors. This indicates that each model has enough information to determine a unique solution, thereby ensuring model identifiability.

Table 4.7: Model Identifiability: Determinant and Rank

Patient	S1		S2	
Model	$\det(A^T A)$	$\text{rank}(A)$	$\det(A^T A)$	$\text{Rank}(A)$
SCM	4.05E+11	3.0	2.01E+11	3.0
Morton	4.11E+14	5.0	1.02E+14	5.0
REA	6.81E+14	5.0	1.81E+14	5.0
DEA	3.89E+12	5.0	2.08E+12	5.0
RDEA	2.86E+16	5.0	1.89E+16	5.0
RDEA+Slice:	345.22	5.0	85.52	5.0
Med [IQR]	[43.7, 624.88]	[5.0, 5.0]	[22.14, 923.84]	[5.0, 5.0]
Patient	S3		S4	
SCM	7.60E+10	3.0	3.26E+10	3.0
Morton	1.65E+13	5.0	4.99E+12	5.0
REA	1.02E+13	5.0	8.13E+12	5.0
DEA	6.41E+11	5.0	1.36E+11	5.0
RDEA	9.25E+14	5.0	9.00E+14	5.0
RDEA+Slice:	137.91	5.0	71.24	5.0
Med [IQR]	[42.39, 212.04]	[5.0, 5.0]	[18.47, 350.22]	[5.0, 5.0]

Source: Ruiz et al. (2025) [84]

It is important to note that Table 4.7 reports the RDEA+Slice model results as median and interquartile range (IQR), since this evaluation is performed individually for each slice k . As a result, the RDEA+Slice model exhibits lower determinant values compared to the other models, which was expected because each slice was computed using a smaller subset of the data, whereas the other models perform estimations using the full dataset.

For each slice k , two main factors determine good conditioning. First, the slice must include a number of data points well above the number of estimated parameters (five in this case), so that the system is sufficiently overdetermined. Second, and more importantly, the volume (V) and airflow (Q) signals must exhibit enough dynamic variation within the slice. Periods where these signals remain nearly constant, such as during an inspiratory pause or a pressure plateau, lead to strong collinearity among the regressor columns and result in ill-conditioned matrices. In this study, ensuring a minimum of 15 data points per slice yielded nonzero determinants and linearly independent vectors, as shown in Table 4.7.

4.3 Conclusions

With the development and validation of the RDEA + Slice model, this chapter has presented a new mathematical framework based on an analysis that highlighted the limitations of conventional models in capturing the dynamics of spontaneous breathing. The proposed model demonstrated significantly improved numerical accuracy, as reflected by high R^2 coefficients and low Mean Relative Errors (MREs) when compared to the SCM.

This study introduced and evaluated four innovative modeling approaches, expanding upon the shape function methodology originally proposed by Morton et al. [43]. The

SCM and Morton models served as benchmarks for comparison. Although the Morton model was not initially designed for spontaneous breathing (SB), it was adapted based on the assumption that its shape functions could be tuned to better represent SB dynamics. As a result, new shape functions were developed, targeting Recruitment Elastance and Distension Elastance, which led to the creation of three enhanced models: REA, DEA, and RDEA.

A key contribution of this development stage was the systematic identification of parameter ranges for the shape functions. Through a grid search, this work determined the specific, robust ranges for coefficients N and M that consistently maximized model performance (R^2) across the patient dataset. The characterization of these operating regions, which define the behavior of the new shape functions, is a principal and practical finding of this research.

Despite these advancements, the models still faced limitations in accurately capturing certain SB characteristics. To address this, a fourth model, RDEA + Slice, was developed by incorporating a modified version of the slice method introduced by Guttman et al. [44]. This model substantially improved the accuracy of ventilatory curve representation in the presence of SB, achieving lower Mean Relative Errors (MREs) and narrower error distributions compared to the baseline models. This enhanced precision positions the RDEA + Slice model as a strong candidate for integration into predictive algorithms, potentially enabling the development of advanced clinical decision support tools.

Furthermore, this work establishes a practical guideline for the reliable implementation of the proposed slice-based methodology. A core finding is that a minimum of 15 data points per slice is required to ensure both model identifiability and the numerical stability of the solution. Adhering to this data-richness criterion is presented as an essential condition for obtaining physiologically meaningful parameters from each respiratory slice. While other advanced techniques could be explored to further analyze robustness, this finding provides a foundational and validated requirement for the successful application of the RDEA+Slice model.

However, several limitations of this study should be acknowledged and addressed in future work. Most notably, auto-triggering (AT) asynchrony was not considered, which restricts the model applicability to all asynchrony types. Future studies should include AT to broaden the model capabilities. Additionally, the analysis was based on a relatively small dataset from eight patients, each contributing between 95 and 196 respiratory cycles. Increasing both the sample size and therapy duration will be essential for improving the generalizability and robustness of the findings. Lastly, since this study focused exclusively on PSV/CPAP ventilation modes, future research should explore a broader range of ventilation settings and clinical conditions to enhance the versatility and applicability of the proposed models.

Chapter 5

Obtaining an Asynchrony Index

The previous chapter presented a novel model, RDEA+Slice, capable of capturing and fitting ventilatory curves from patients exhibiting RAs. This represents a significant advancement over conventional models, which, despite their widespread use, suffer from a major limitation: the inability to accurately replicate or fit such curves. As a result, these models may lead to the loss of critical information regarding patient respiratory mechanics.

Several studies have emphasized the importance of estimating respiratory elastance to detect mismatches between patient effort and ventilator support. Authors such as Poole et al. (2014) [10], Damanhuri et al. (2016) [26], and Chiew et al. (2018) [23] developed model-based methods that either reconstruct airway pressure signals or evaluate breath-by-breath variations in elastance to identify periods of poor ventilator synchrony, using metrics based on the area under the elastance-vs-time curve. A common element among these approaches is the assumption that deviations in the estimated elastance curve reflect the presence and magnitude of patient-driven activity.

While prior studies have focused on elastance-based methods to assess patient–ventilator interaction, this work introduces a novel approach by proposing a signal decomposition method based on frequency-domain analysis. The airway pressure signal is modeled as the sum of a baseline component generated by ventilator-synchronized breaths and an additive disturbance caused by spontaneous respiratory efforts. Using the Fourier transform, the pressure waveform is decomposed into a low-frequency component, primarily associated with passive ventilator-driven breathing, and a high-frequency component that captures irregular perturbations due to spontaneous efforts. By comparing the area under the time-varying elastance curve before and after filtering, an Asynchrony Event percentage (AE%) was obtained, providing a quantitative measure of the mismatch between the ventilator and the patient spontaneous efforts.

However, the AE% signal alone, being a time-varying metric, was not sufficient to provide a simple, clinically meaningful classification of the patient state. Therefore, an Asynchrony Index (AI%) was developed to condense this dynamic information into a single score for each patient. The calculation and interpretation of this index depended on two key parameters: a Tolerance Range to define significant AE% deviations, and a final Decision Threshold to classify the patient as either synchronous or asynchronous. To avoid arbitrary

selection, these parameters were selected using two primary datasets, each containing 6-minute recordings from four patients: a baseline cohort of sedated (synchronous) patients, and a second cohort exhibiting spontaneous breathing and asynchronies. A comprehensive analysis was performed where the Tolerance Range was defined to maximize the Area Under the Curve (AUC) of a Receiver Operating Characteristic (ROC) analysis. Subsequently, the Decision Threshold was identified from the resulting ROC curve to ensure the best diagnostic performance in a clinical context. Finally, a third dataset was used to validate the performance of the defined classifier index. This evaluation demonstrated that the proposed method is capable of detecting specific types of mismatches between patient effort and ventilator support. However, it also revealed limitations in identifying certain other forms of asynchrony, as will be discussed.

5.1 Methods

Several model-based methods have been developed to detect PVAs by analyzing airway pressure signals. Some approaches rely on geometric reconstruction, identifying landmarks in the pressure waveform to extrapolate a "synchronous" curve [26]. Other studies have highlighted that deviations in the patient time-varying elastance are a key indicator of patient effort and ventilator mismatch [10, 21, 23, 81]. These methods typically quantify asynchrony by applying thresholds to the area under the elastance-time curve. While valuable, these approaches can be sensitive to variable waveform morphologies.

In contrast, the present method proposes a signal processing framework. We interpret the measured airway pressure signal in the presence of asynchronies as a combination of two components: a baseline, low-frequency signal representing the synchronous, ventilator-driven mechanics, and an additive, high-frequency disturbance or "noise" representing the spontaneous respiratory activity, as illustrated in Figure 5.1.

This interpretation allows for the separation of these two components using frequency-domain tools. To achieve this, a low-pass filter was applied to the original pressure signal. The cutoff frequency was set to 0.8 Hz, a value selected based on physiological rationale. This frequency is high enough to preserve the fundamental frequency of a typical respiratory rate (approx. 0.25-0.33 Hz for 15-20 breaths/min) and its primary harmonics, which define the morphology of a synchronous breath (see Figure 5.7). Simultaneously, it is low enough to attenuate the high-frequency components characteristic of asynchronous efforts. This process yields two distinct signals: the *Original Pressure* and the *Filtered Pressure* (representing the synchronous component).

Building on the demonstrated relevance of elastance, the next step quantifies the difference between these two pressure signals. The time-varying elastance parameter E_2 was calculated for each slice k using Equation 5.1, which is derived from the RDEA+Slice model presented in the previous chapter.

$$E_{2k}(t) = \frac{P(t) - P_{0k} - (R_{1k} \cdot \theta_1 + R_{2k} \cdot \theta_2) \cdot Q_k(t)}{V(t) \cdot \phi_2} - E_{1k} \cdot \frac{\phi_1}{\phi_2}. \quad (5.1)$$

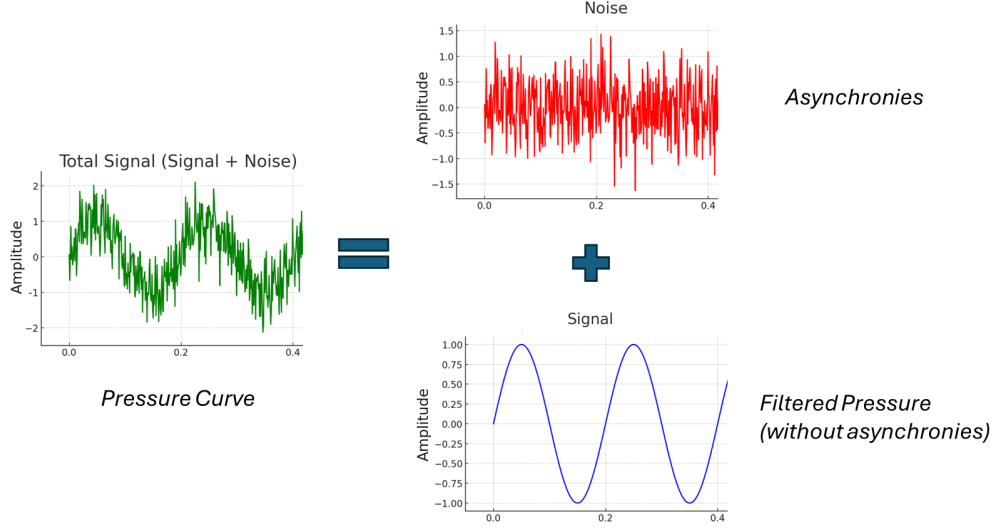
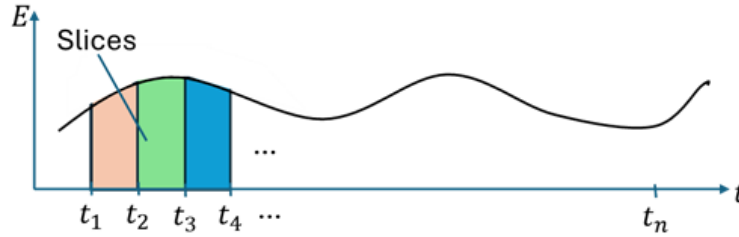


Figure 5.1: Pressure signal interpretation in the presence of RAs

5.1.1 Derivation of Asynchrony Event Percentage (AE%)

Equation 5.1 was applied to both the *Original Pressure* and *Filtered Pressure* signals to obtain their respective time-varying elastance curves, $E_{\text{Original}}(t)$ and $E_{\text{Filtered}}(t)$. An example of the time-varying elastance profile is shown in Figure 5.2. By itself, this curve does not provide sufficient information to reliably detect asynchronies. Therefore, we analyzed the cumulative area under the elastance-time curve, as defined in Equation 5.2.


 Figure 5.2: E vs t example

Then, the cumulative area under each curve was calculated, resulting in two new signals, $\Psi_{\text{Original}}(t)$ and $\Psi_{\text{Filtered}}(t)$. From these, the Asynchrony Event Percentage (AE%) was defined as the point-by-point percentage difference between them (Equation 5.3)

$$\Psi(t) = \int_{t_0}^t E(\tau) d\tau \quad (5.2)$$

$$AE\%(t) = \left| \frac{\Psi_{\text{Original}}(t) - \Psi_{\text{Filtered}}(t)}{\Psi_{\text{Filtered}}(t)} \right| \cdot 100. \quad (5.3)$$

The resulting AE% is a time-dependent signal that quantifies the magnitude of mismatch at any given moment (Figure 5.3). However, because it fluctuates continuously, it does not provide a single, easily interpretable metric for a patient overall condition. A clinician needs a summary index, not another complex waveform to monitor.

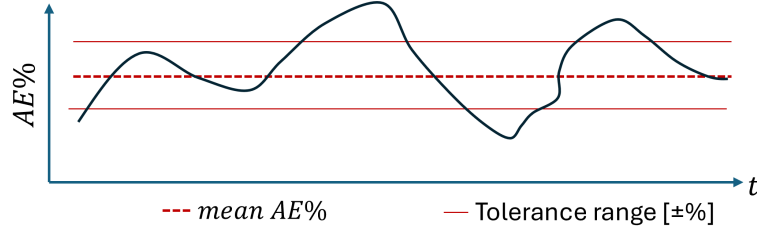


Figure 5.3: AE% vs t example

5.1.2 Derivation of the Asynchrony Index (AI%)

To enhance clinical relevance, the time-varying AE% signal was condensed into a single, global metric: the Asynchrony Index (AI%). The derivation of this index required the data-driven determination of two key parameters: a Tolerance Band (see Figure 5.3) for calculating the AI% score from the AE% signal, and a final Decision Threshold to classify a patient state based on that score.

To avoid arbitrary selection and to ensure the most robust classification, these parameters were systematically selected. This was performed using two primary datasets to establish the ground truth: Dataset 1, comprising four sedated (synchronous) patients, and Dataset 2, comprising four patients with frequent asynchronies. Each patient record consisted of six minutes of therapy.

First, to find the Tolerance Range, a sensitivity analysis was performed. The Tolerance Range was varied systematically, and for each value, an AI% score was calculated for every patient. A full Receiver Operating Characteristic (ROC) curve analysis was then conducted for each band, and the Area Under the Curve (AUC) was recorded. The best Tolerance Band was identified as the value that yielded the maximum AUC, thus defining the most diagnostically powerful version of the AI% score.

Secondly, once the best Tolerance Range was fixed, its corresponding ROC curve was used to determine the best Decision Threshold, which was selected as the point on the curve offering the best clinical balance between sensitivity and specificity, prioritizing the minimization of false negatives. The final classifier, defined by these two parameters, was then validated on a third, independent dataset to assess its generalization performance. The AI% was formally defined as:

$$AI\% = \frac{N_{out}}{N_{total}} \cdot 100. \quad (5.4)$$

where N_{out} is the number of samples lying outside the defined optimal tolerance band, and N_{total} is the total number of samples considered. This formulation provides a single, clinically relevant score to classify a patient's ventilatory state.

5.1.3 Patient Data

To compute the AI%, a total of three datasets were analyzed, each consisting of recordings from four patients undergoing six minutes of mechanical ventilation therapy. Data collection took place at Fundación San José de Buga, following the protocol described in Chapter 3. Datasets 1 and 2 (see Tables 5.1 and 5.2) include patients who were either fully sedated (Figure 5.4) or exhibited spontaneous breathing efforts (Figure 5.5), respectively.

Table 5.1: Patient Dataset 1

Patient	Sex	Age [years]	Clinical Diagnostic	Tidal Volume [L]	PEEP [cmH ₂ O]	Inspiratory time [s]	I:E relation	Ventilatory mode
P1	Female	78	COPD	0.41	6.0	0.85	1:2.9	VCV
P2	Female	58	Pneumonia	0.32	10.0	1.0	1:2.0	
P3	Female	78	Respiratory failure	0.42	9.0	1.00	1:2.3	
P4	Female	44	Alveolar hemorrhage	0.35	12.0	0.85	1:2.0	

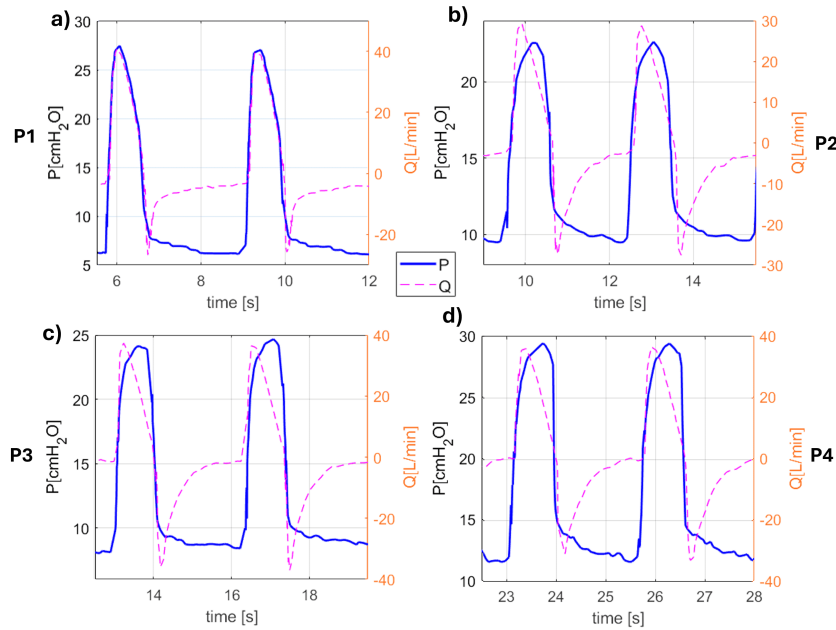


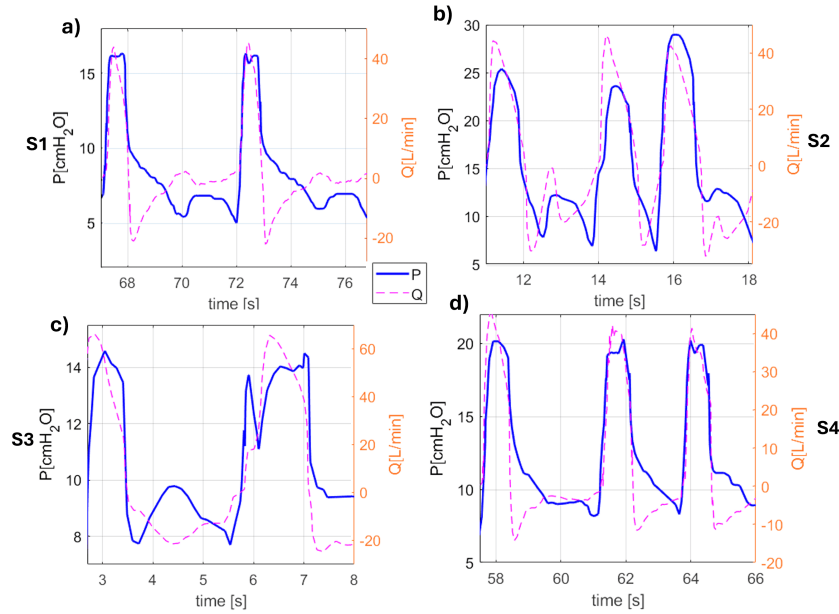
Figure 5.4: P and Q vs t for Patient Dataset 1

These two datasets were analyzed in the frequency domain to identify significant differences and to define a threshold range for which the AE% metric effectively indicates

asynchronous breathing. Additionally, the $AI\%$ was computed for both datasets to assess its behavior under varying ventilatory conditions. Dataset 2 (Table 5.2) includes patients with documented asynchrony events of various types. In Patient S1 (Figure 5.5a), an ineffective effort (IE) was observed, characterized by a small drop in airway pressure and corresponding flow changes, indicating a clear inspiratory effort that failed to trigger a ventilator breath. Patient S2 (Figure 5.5b) exhibited double triggering (DT), with two consecutive breaths occurring in close succession and minimal expiratory time between them, caused by a persistent inspiratory effort that activated the ventilator twice.

Table 5.2: Patient Dataset 2

Patient	Sex	Age [years]	Clinical Diagnostic	Tidal Volume [L]	PEEP [cmH ₂ O]	Inspiratory time [s]	I:E relation	Ventilatory mode	Backup mode
S1	Male	60	Pulmonary edema	-	6.0	-	-	PSV/CPAP	VCV
S2	Male	64	Heart attack	0.51	7.0	1.0	1:2.7	VCV	-
S3	Female	70	Respiratory Failure	-	6.0	-	-	PSV/CPAP	VCV
S4	Female	66	Exacerbated COPD	-	8.0	-	-	PSV/CPAP	PCV


 Figure 5.5: P and Q vs t for Patient Dataset 2

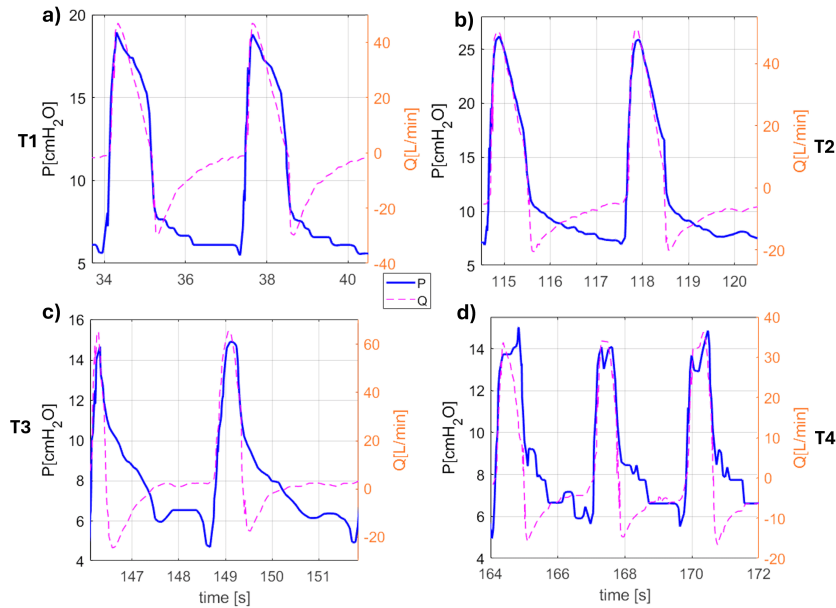
Patient S3 (Figure 5.5c) presented a combination of asynchrony types, including flow asynchrony (FA), recognizable by a distinct “sawtooth” pattern in the flow waveform, indicating that the ventilator’s flow delivery did not meet the patient’s inspiratory demand. This patient also exhibited premature cycling (PC), where the inspiratory phase ended before the flow reached zero, along with additional episodes of double triggering, as a second inspiratory effort immediately followed the first. Similarly, Patient S4 (Figure 5.5d)

experienced both PC and FA; the former was identified by the early termination of inspiration before the patient's effort was complete, while the latter manifested as an irregular and fragmented flow pattern, reflecting a mismatch between ventilator support and patient demand.

To provide an additional point of comparison, a third dataset (Table 5.3) was analyzed. This dataset includes two synchronous patients (T1 and T2) and two asynchronous patients (T3 and T4). The purpose of this third dataset was to validate the patterns and thresholds previously identified and to assess the robustness of the proposed method in distinguishing between synchronous and asynchronous ventilation.

Table 5.3: Patient Dataset 3

Patient	sex	Age [years]	Clinical Diagnostic	Tidal Volume [L]	PEEP [cmH ₂ O]	Inspiratory time [s]	I:E relation	Ventilatory mode	backup breathing mode
T1	Male	19	Respiratory Failure	0.52	6.0	1.00	1:2.3	VCV	-
T2	Male	67	COPD	0.50	8.0	0.85	1:2.5	VCV	-
T3	Female	50	Renal Failure	-	6.0	-	-	PSV/CPAP	VCV
T4	Female	87	Respiratory Failure	-	6.0	-	-	PSV + VT Aseg	VCV


 Figure 5.6: P and Q vs t for Patient Dataset 3

In the third dataset, the asynchronous patients also exhibited characteristic signs of ventilator mismatch. Patient T3 (Figure 5.5c) demonstrated evidence of IE and mild FA, with untriggered inspiratory attempts and slight irregularities in the flow waveform.

Patient T4 (Figure 5.5d) showed more pronounced events, including DT and clear signs of FA, consistent with prolonged inspiratory efforts and poor synchronization with the ventilator cycle.

These three datasets provided a structured framework for developing, calibrating, and validating the proposed asynchrony detection method. By comparing fully synchronous cases with clearly asynchronous patterns, it was possible to define and test the performance of the AE% (Equation 5.3) and AI% (Equation 5.4) metrics under diverse clinical conditions, laying the groundwork for their potential application in real-time patient monitoring scenarios.

5.2 Results

A frequency-domain analysis of Datasets 1 and 2 was performed to evaluate the spectral characteristics of the pressure signals. The resulting plots suggest a distinct difference in behavior between the two groups. While the frequency spectrum obtained for Dataset 1 (Figure 5.7) exhibits well-defined frequency components and amplitudes, the spectrum for Dataset 2 (Figure 5.8) shows a signal with increased irregularity and noise content, as expected due to the presence of SB efforts.

This observation served as one of the motivations for implementing a filtering process aimed at attenuating the noisy components associated with asynchronous activity. To achieve this, a cutoff frequency (F_c) of 0.8Hz was selected with the goal of isolating a cleaner pressure signal representative of purely ventilator-driven behavior. As previously detailed, this frequency was chosen as it preserves the fundamental frequency and primary harmonics of a typical respiratory rate while effectively removing the high-frequency noise associated with asynchronous effort. The high-frequency content, interpreted as noise or asynchrony-related fluctuations, was removed through filtering and is shown in Figure 5.9 for Dataset 1 and Figure 5.10 for Dataset 2.

5.2.1 Evaluating the AE% and AI%

Figures 5.11 and 5.12 present a comparison between the original and filtered pressure curves for Datasets 1 and 2, respectively. For Dataset 1, although some changes in the waveform are noticeable, the alterations are relatively minor. In contrast, Dataset 2 shows a more substantial difference between the original and filtered signals, with several pressure peaks being suppressed by the chosen cutoff frequency. This behavior is consistent with the presence of asynchrony-related disturbances in the unfiltered signal.

Based on the original and filtered pressure signals, Equation 5.3 was applied, and the resulting values of AE% over time are presented in Figures 5.13 and 5.14. These figures provide a detailed visualization of the temporal behavior of the AE% for the synchronous and asynchronous patient cohorts, respectively, revealing key differences in their signal dynamics. In the synchronous cohort (Figure 5.13), the AE% signals are characterized by relatively smooth, low-frequency fluctuations. While patients P2 and P3 (Figures 5.13b

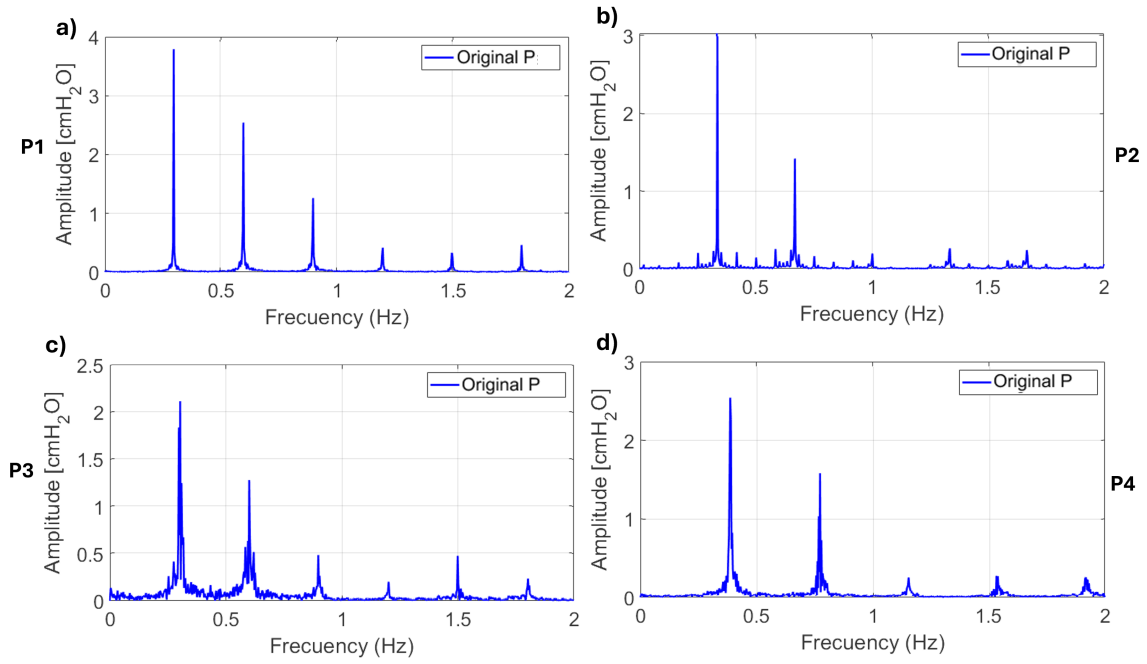


Figure 5.7: Frequency analysis dataset 1: Patient a)P1, b)P2, c)P3 and d)P4

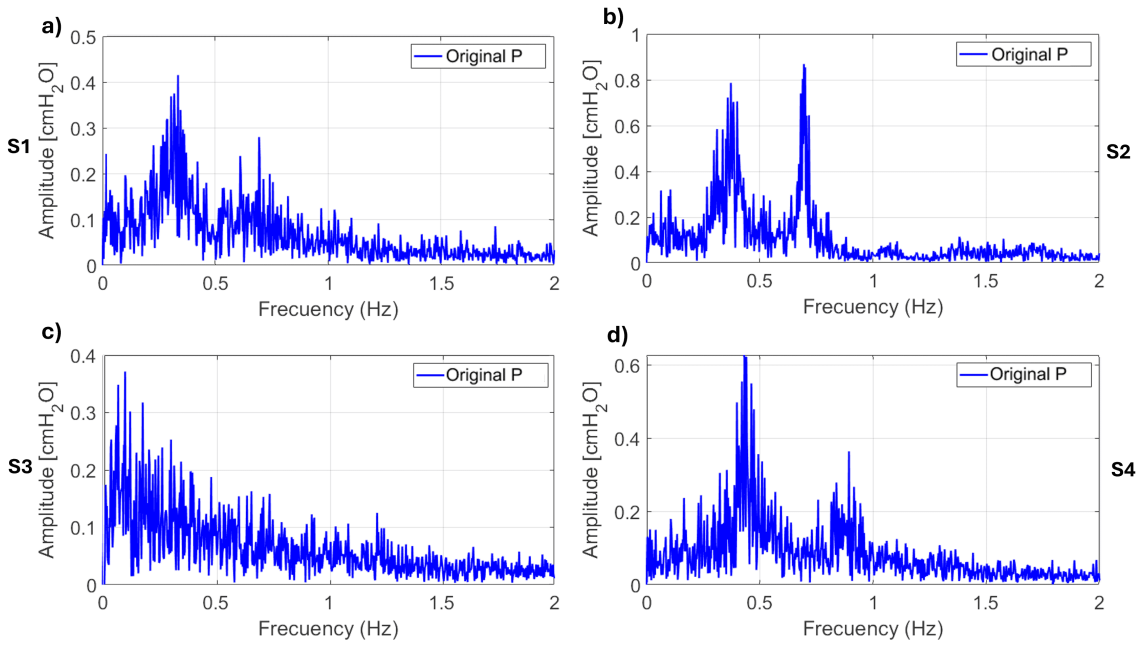


Figure 5.8: Frequency analysis dataset 2: Patient a)S1, b)S2, c)S3 and d)S4

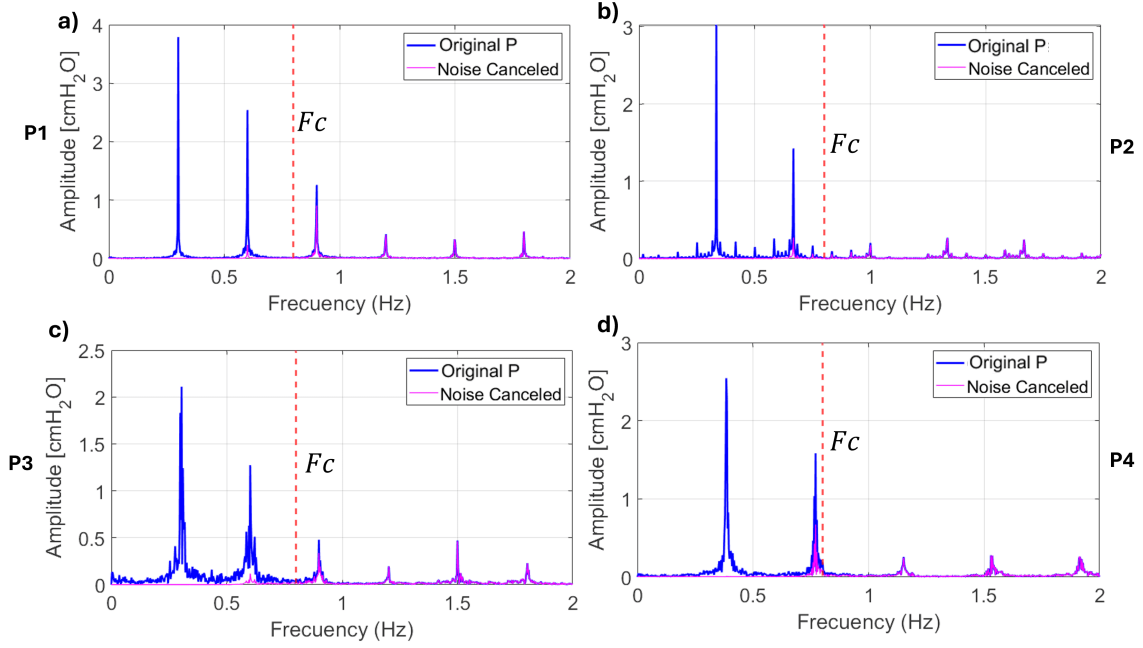


Figure 5.9: Cutoff frequency (F_c) dataset 1: Patient a)P1, b)P2, c)P3 and d)P4

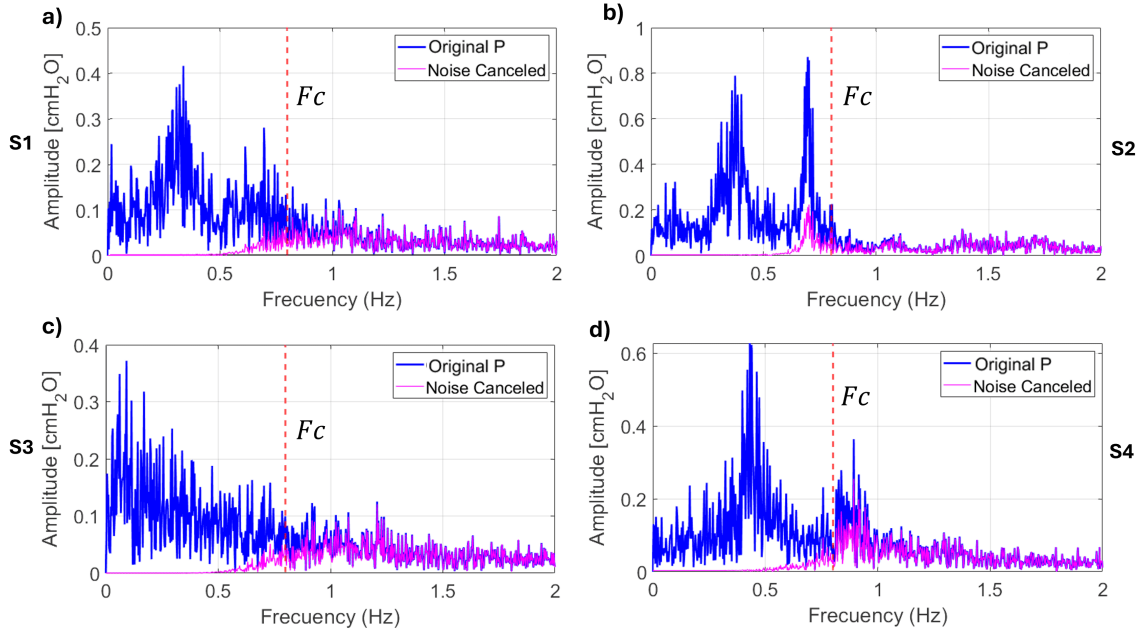


Figure 5.10: Cutoff frequency (F_c) dataset 2: Patient a)S1, b)S2, c)S3 and d)S4

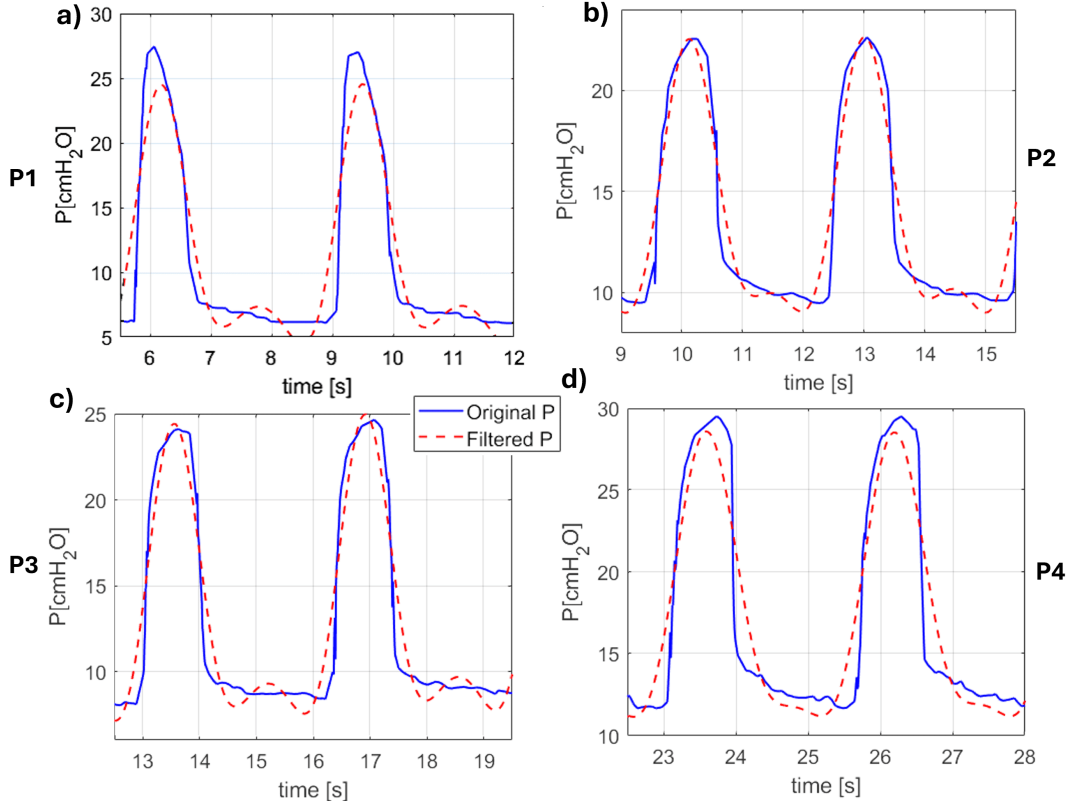


Figure 5.11: Original and filtered signal dataset 1: Patient a)P1, b)P2, c)P3 and d)P4

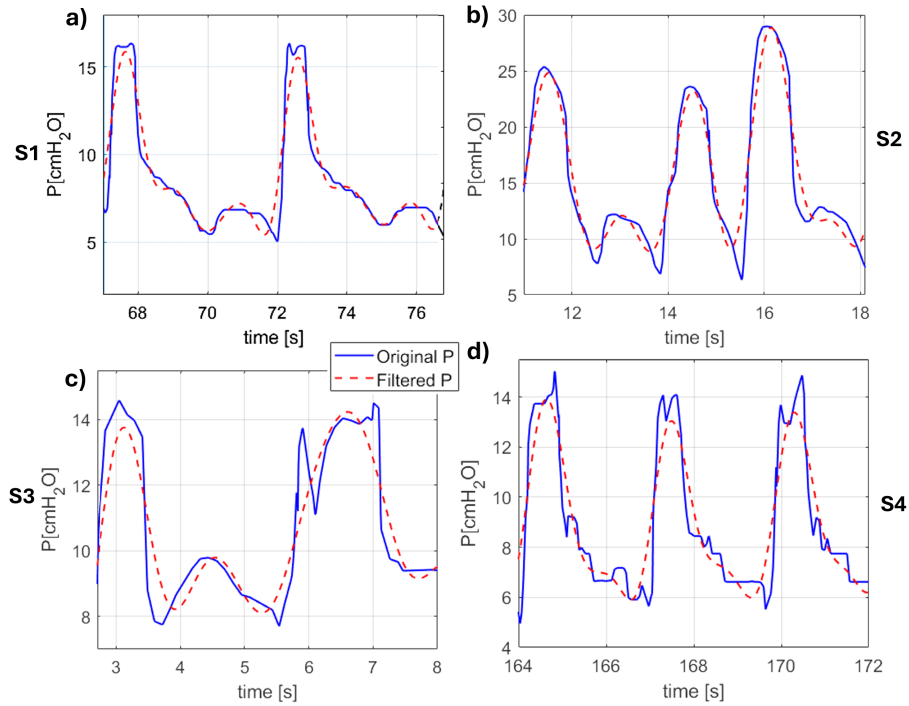


Figure 5.12: Original and filtered signal dataset 2: Patient a)S1, b)S2, c)S3 and d)S4

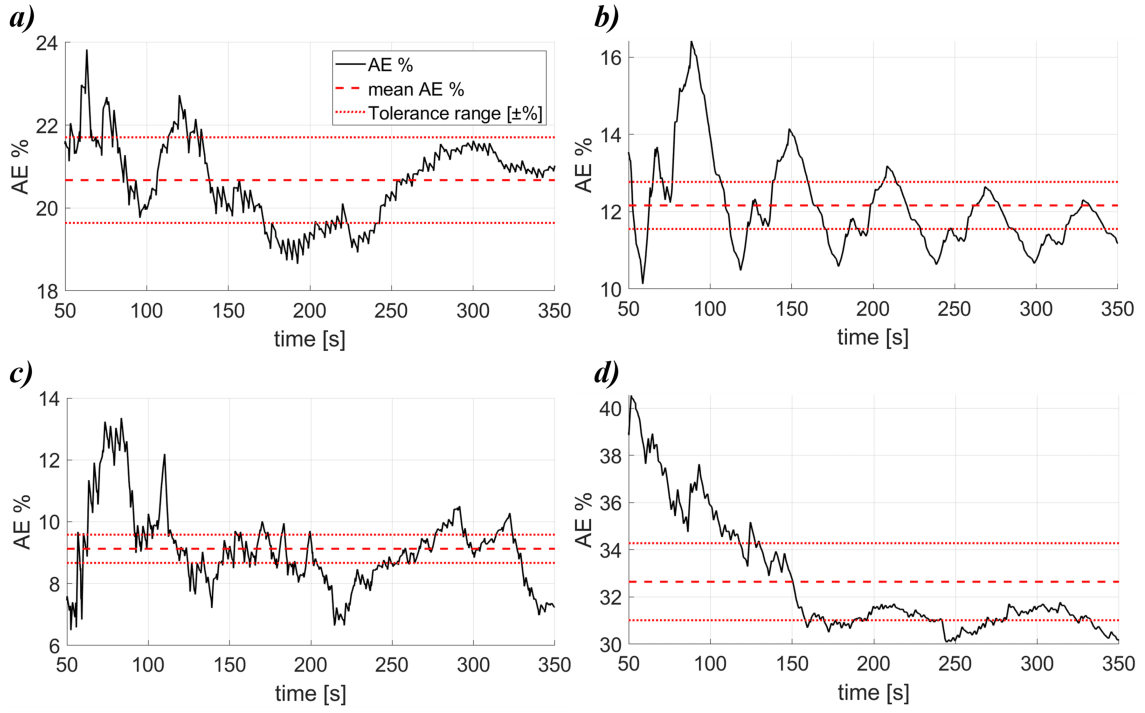


Figure 5.13: Asynchrony events on dataset 1: Patient a)P1, b)P2, c)P3 and d)P4

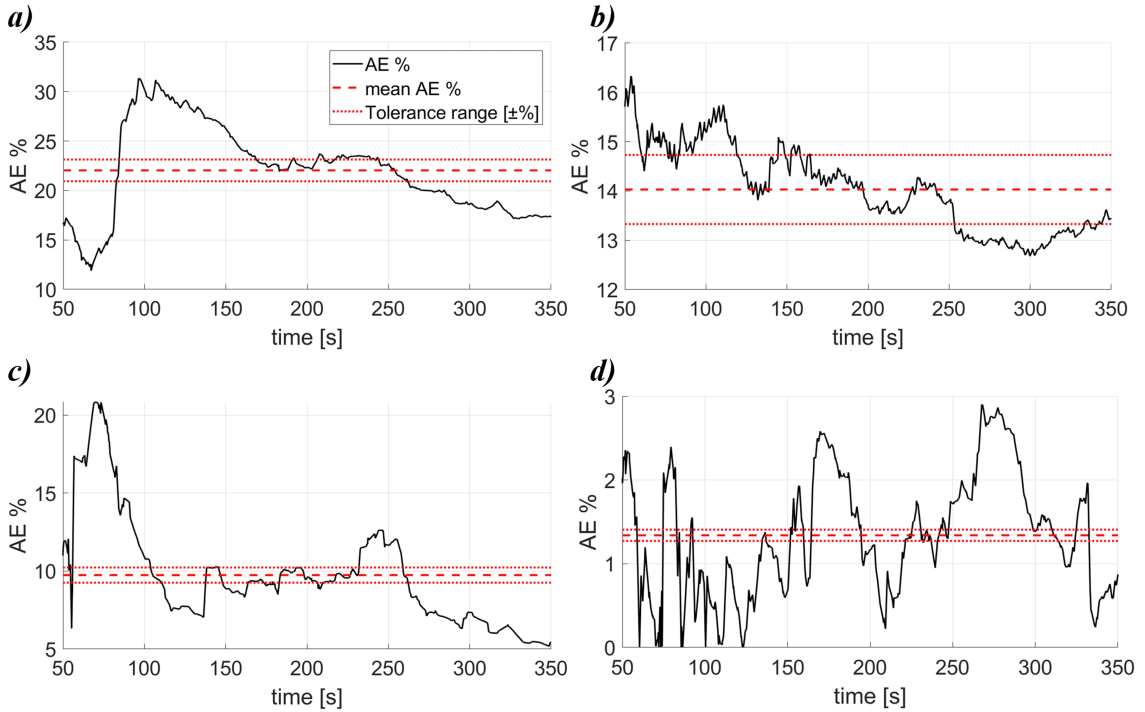


Figure 5.14: Asynchrony events on dataset 2: Patient a)S1, b)S2, c)S3 and d)S4

and 5.13c) exhibit stable behavior around their mean, patients P1 and P4 (Figures 5.13a and 5.13d) show a significant non-stationarity, with their AE% values drifting in a clear downward trend over the 6-minute period.

In contrast, the asynchronous cohort (Figure 5.14) displays more complex and varied patterns, generally characterized by abrupt, high-frequency events. Patients S1 and S3 (Figures 5.14a and 5.14c), for example, show large and distinct transient excursions that rise and fall rapidly, corresponding to clear periods of significant asynchrony. The case of Patient S4 (Figure 5.14d) is particularly illustrative: while its mean AE% is very low (approximately 1.5%), the signal is highly volatile and erratic, with numerous sharp spikes. This behavior visually confirms that a simple average of AE% is an insufficient metric and reinforces the necessity of the AI%, which is designed specifically to quantify these frequent changes from the mean. Notably, Patient S2 appears visually stable and similar to the synchronous cohort, which is consistent with the finding that this patient represented a challenging, borderline case for the classifier.

Then, to define the ranges to classify a synchronous and an asynchronous patient, a sensitivity analysis was conducted to understand the relationship between the AE% Tolerance Range and the resulting AI%. Figure 5.15 plots this relationship for each of the 8 patients in the primary training datasets.

The results in Figure 5.15 show a clear separation between the two patient groups. The

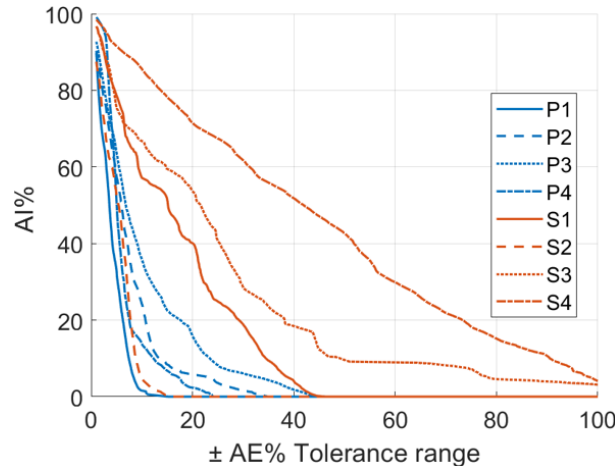


Figure 5.15: Sensitivity analysis showing the AI% as a function of the selected AE% Tolerance range for synchronous (P1-P4, blue) and asynchronous (S1-S4, orange) patients.

AI% for synchronous patients (blue curves) drops sharply to zero with a relatively narrow tolerance range (typically $< 25\%$), indicating their AE% signal exhibits low variability. In contrast, the AI% for asynchronous patients (red curves) decays much more slowly, demonstrating a high and sustained signal variability that is not easily contained. This clear discrimination, particularly within the 5-20% range, provides strong visual evidence that the AI% metric could be a robust indicator of asynchrony and justifies the subsequent search for an optimal parameter set within this region.

The analysis revealed that the diagnostic performance of AI%, measured by the Area Under the Curve (AUC), depended on the selected Tolerance Range. Figure 5.16a illustrates the relationship between the Tolerance Range and the resulting AUC of the ROC analysis. The evaluation identified a maximum AUC of 0.875, obtained with a Tolerance Range of 5.0%. Figure 5.16b presents the final ROC curve for the AI% classifier using this 5% Tolerance Band, showing a strong diagnostic performance clearly superior to that of a random classifier. Based on this curve, the optimal Decision Threshold was determined to be 76%.

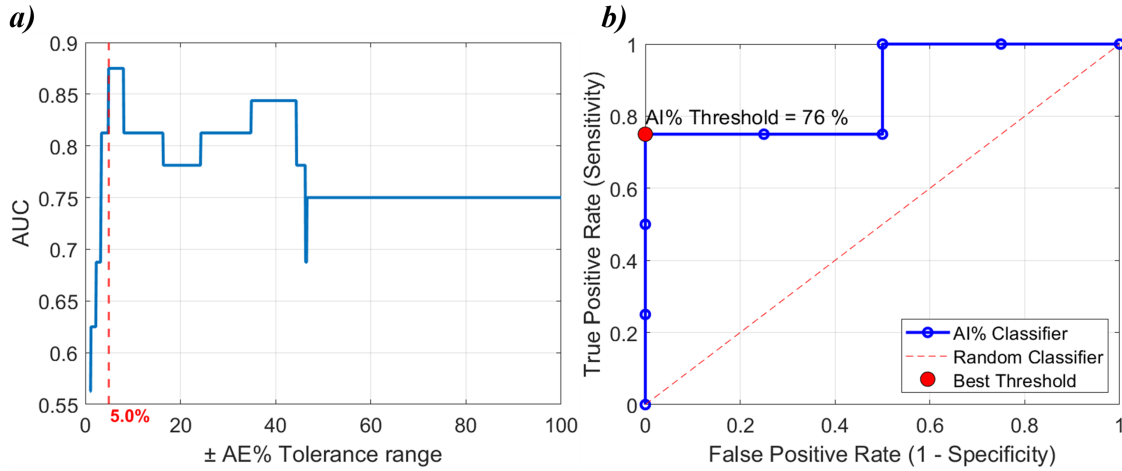


Figure 5.16: a) AUC of the AI% classifier as a function of the selected Tolerance Band, b) Final ROC Curve for the best AI% classifier (AUC = 0.87).

5.2.2 Performance of the Asynchrony Index and Clinical Interpretation

The ROC analysis provides a quantitative validation of the AI% as a diagnostic tool. The final optimized model establishes a clear, mathematically-derived decision rule: a patient is classified as asynchronous if their AI% (calculated using the optimal 5% Tolerance Band) exceeds a Decision Threshold of 76%. At this operating point, the classifier achieves a powerful performance profile with a sensitivity of 75% and a perfect specificity of 100% on the studied dataset. In practical terms, a specificity of 100% indicates that the model correctly identified every synchronous patient, producing zero false alarms. Table 5.4 shows the AI% of dataset 1 and 2.

However, a detailed analysis of individual patient scores suggests that a minor adjustment to this threshold can enhance its clinical utility (see Table 5.4). At the 76% threshold, Patient S3, a known asynchronous case with an AI% of 76.16%, is narrowly misclassified as synchronous (a false negative). In a clinical setting, the consequence of a false negative

Table 5.4: Asynchrony Index Values

Dataset 1		Dataset 2	
Patient	AI [%]	Patient	AI [%]
P1	33.07	S1	78.59
P2	58.12	S2	52.49
P3	63.88	S3	76.16
P4	51.01	S4	91.52

(a missed asynchrony) is significantly more detrimental than a false positive (a false alarm prompting clinician review). Therefore, prioritizing sensitivity is a safer clinical strategy.

For this reason, a clinically-adjusted Decision Threshold of 70% is proposed. This slightly lower threshold improves the classifier sensitivity by correctly capturing borderline cases, thereby maintaining the detection rate of asynchronous patients of 75% (3 out of 4) in this cohort. This adjustment maintains an excellent specificity of 100% (0 out of 4 false positives), representing a more robust and secure profile for clinical application. It is important, to acknowledge the limitations of this index. The model performance may be less effective for certain types of asynchrony that do not produce strong, sustained deviations in the AE% signal. This is exemplified by Patient S2 who, despite clinical evidence of asynchrony, yielded a lower AI% of 52.5%. This highlights that asynchronies such as double triggering (DT) or ineffective effort (IE), which can manifest as subtle or merged pressure waveforms, may not be reliably detected by this method. Future work should aim to incorporate additional features to improve the detection of these specific event types.

5.3 Discussion

To validate the previously obtained findings, the same methodology was applied to Dataset 3 (see Table 5.3), which, as mentioned earlier, includes two synchronous patients (T1 and T2) and two asynchronous patients (T3 and T4). A frequency-domain analysis was first performed on this dataset, yielding results that were consistent with those observed in Datasets 1 and 2 (Figure 5.17). Using the same cutoff frequency as before (Figure 5.18), the pressure signal was filtered to isolate the ventilator-driven component (Figure 5.19).

With the original and filtered pressure curves, the AE% over time was computed using Equation 5.3, and the corresponding results are shown in Figure 5.20. Additionally, the AI% was calculated using Equation 5.4, and the final values are summarized in Table 5.5. This analysis served to corroborate the robustness and applicability of the proposed method across different patient conditions.

The analysis of Dataset 3 supports the effectiveness of the proposed detection method. Notably, Patient T4, who presented clear signs of asynchrony, was correctly identified with an AI% well above the 70% threshold. Likewise, the method successfully recognized patients T1 and T2 as synchronous, with AI% values remaining near zero. The model

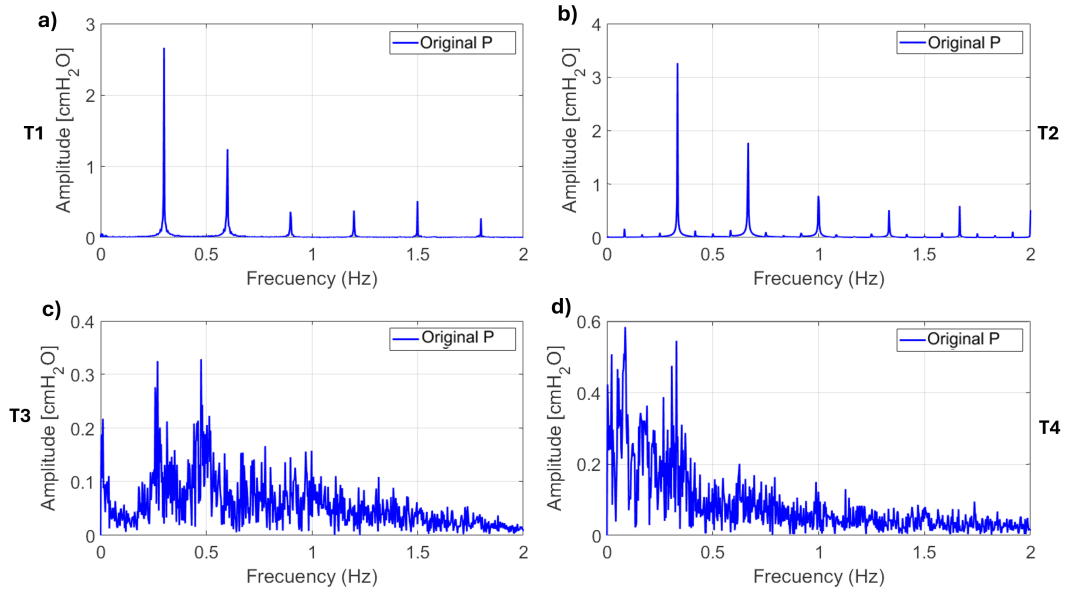


Figure 5.17: Frequency analysis dataset 3: Patient a)T1, b)T2, c)T3 and d)T4

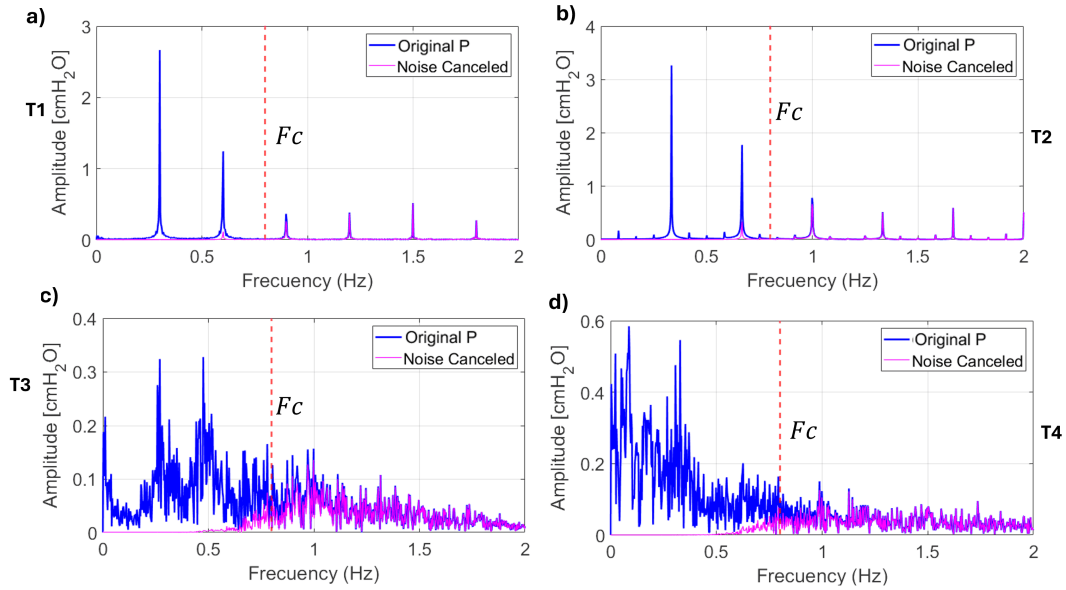


Figure 5.18: Cutoff frequency (F_c) dataset 3: Patient a)T1, b)T2, c)T3 and d)T4

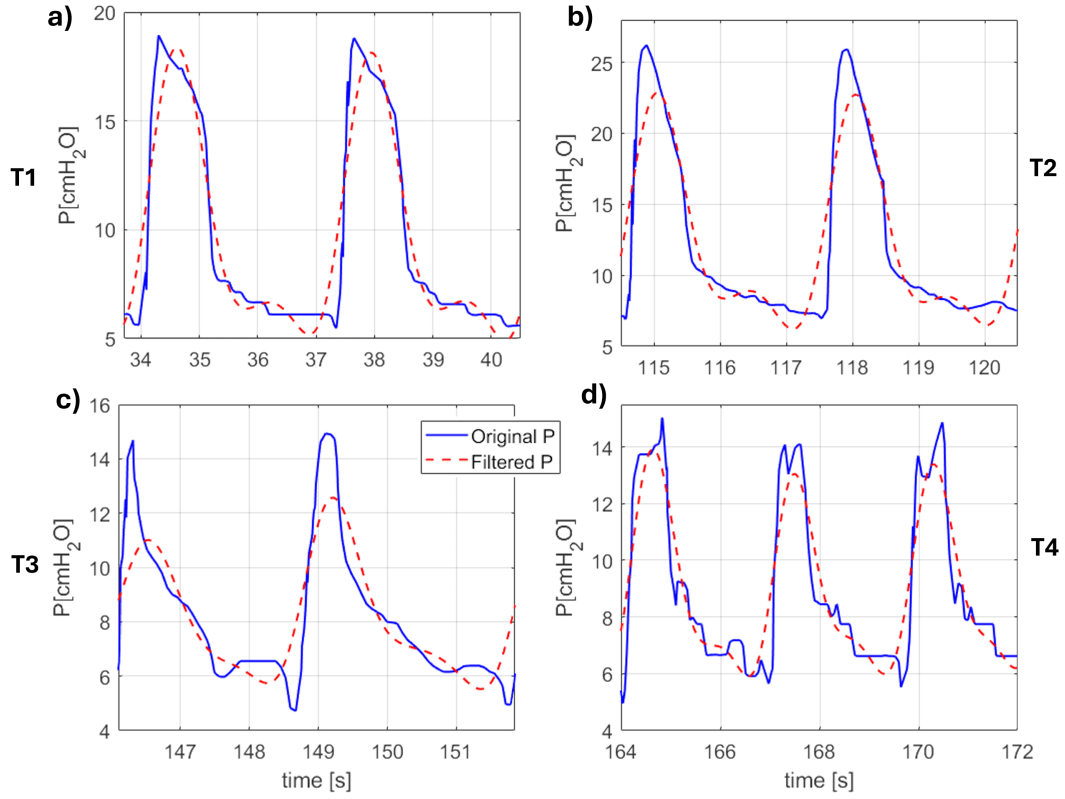


Figure 5.19: Original and filtered signal dataset 3: Patient a)T1, b)T2, c)T3 and d)T4

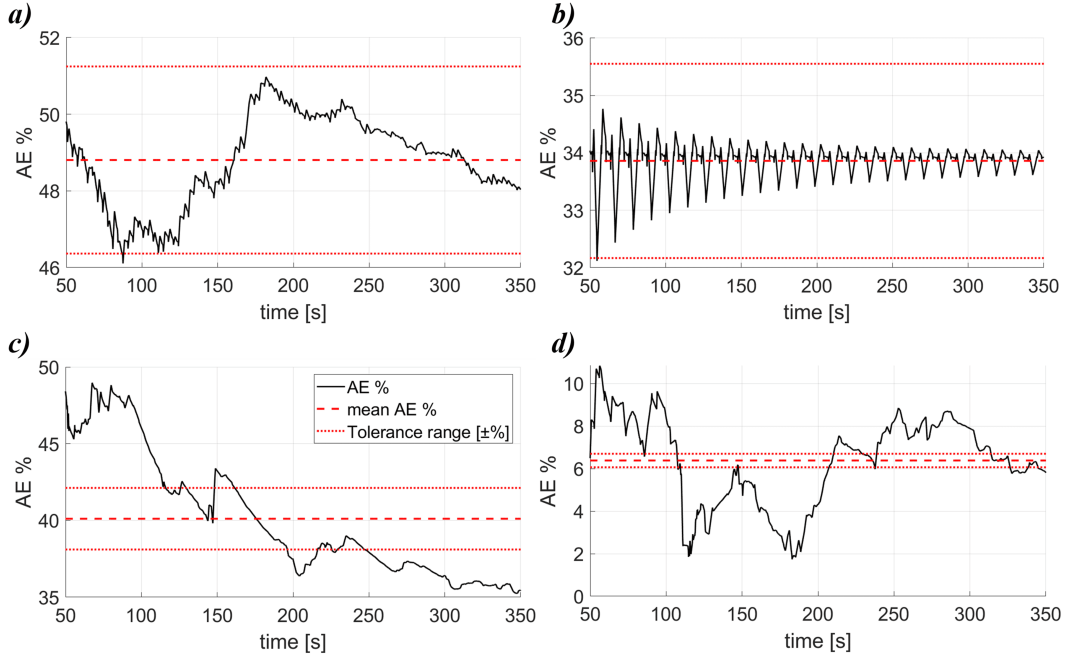


Figure 5.20: Asynchrony events on dataset 3: Patient a)T1, b)T2, c)T3 and d)T4

performance on the more challenging asynchronous patients, S2 and T3, provides valuable insight into both the strengths and limitations of the index. The case of Patient T3 is particularly informative. Patient T3 (Table 5.5) yielded an AI% of 69.91%, falling just below the 70% clinically-adjusted threshold. This borderline result strongly validates the decision to lower the threshold from the mathematical of 76% (which would have missed this case by a wider margin) to a more sensitive clinical cutoff. It suggests that while the binary classification for T3 was synchronous, the index was sensitive enough to identify it as a high-risk, borderline case. For future real-time implementations, this highlights the potential of creating a "warning zone" to alert clinicians to patients approaching the asynchrony threshold.

In contrast, Patient S2 represents a clearer limitation of the pressure-based approach. Despite clinical evidence of asynchrony (DT), this patient AI% was significantly lower and was not detected. This is likely because certain asynchrony types, such as DT, may not always produce the significant pressure waveform alterations required for detection by this method. These findings suggest that while the AI% is a robust indicator for many forms of asynchrony, incorporating complementary signals, such as P-V or V-Q loop analysis, may be necessary to improve detection accuracy for these more subtle cases. Further studies with larger datasets would also be essential to establish more generalized and finely-tuned thresholds.

Table 5.5: Asynchrony Index Values Dataset 3

Dataset 3	
Patient	AI [%]
T1	0.28
T2	0.03
T3	69.91
T4	88.87

The literature presents powerful pressure reconstruction techniques to estimate an 'ideal' synchronous breath from an asynchronous one, though their methodologies differ. The approach by Damanhuri et al. [26] is geometric, relying on identifying specific landmarks on the expiratory slope to extrapolate and fill the 'M-wave'. In contrast, the method by Chiew et al. [23] is model-based, using an iterative process that repeatedly refits the SCM to converge on a passive waveform. While effective, the geometric nature of the first method can be sensitive to atypical waveform morphologies, and the iterative nature of the second assumes the underlying model is a sufficient representation.

A different approach is the time-varying elastance area method used by Poole et al. [10]. This method is effective but depends on statistical thresholds (e.g., $\pm 50\%$) around a moving median value, which may not capture slow, dynamic changes in a patient condition and can be skewed if asynchronies become frequent. The AI% method proposed in this thesis offers a conceptually distinct alternative. It is neither geometric nor iterative, but rather a signal processing approach. By treating asynchronous events as high-frequency 'noise' superimposed on a low-frequency baseline signal, it avoids reliance on specific morphological landmarks or iterative model convergence. This makes it potentially more robust

to variations in breathing patterns. However, as demonstrated with patients S2 and T3, this strength is also its primary limitation: asynchronies that do not produce a significant 'noise' signal in the pressure waveform, such as IE or some forms of DT, are likely to be missed. This contrasts with methods that analyze flow or volume curves, which might be more sensitive to these specific events. Therefore, the proposed AI% should be considered a complementary tool, particularly effective for detecting FA and PC.

5.4 Conclusions

A novel respiratory AI% was proposed and evaluated, with potential applicability in clinical settings when integrated into real-time monitoring systems. The method is based on quantifying variability in the cumulative elastance signal by comparing original and filtered airway pressure waveforms. A key strength of this study was the systematic definition of two critical parameters: the Tolerance Range (5%), which maximized the diagnostic performance in terms of AUC, and the Decision Threshold (70%), which provided an optimal balance between sensitivity and specificity. This combination ensured that borderline cases, such as patient T3 ($\text{AI}\% = 69.91$), were correctly flagged as high-risk rather than overlooked, demonstrating the clinical value of adopting a slightly more conservative threshold compared to the mathematically derived one (76%).

Overall, the AI% proved effective in distinguishing synchronous from asynchronous patients, with particularly strong performance in identifying flow asynchrony (FA) and premature cycling (PC). However, the method showed limitations in detecting certain forms of double triggering (DT), as evidenced by patient P2, who exhibited clinically evident DT but whose AI% value fell below the diagnostic threshold. This underscores that asynchronies that do not generate sustained, high-frequency perturbations in the pressure waveform remain challenging for this pressure-based approach.

For future work, extending the analysis to larger and more diverse patient cohorts will be essential to refine the tolerance and threshold values across populations. Moreover, integrating complementary signals such as flow-volume loops or neural drive estimates could enhance the detection of subtle asynchronies. Such developments would strengthen the AI% as a clinically reliable and comprehensive tool, not only for detecting asynchrony but also for guiding ventilator adjustments in real time.

Chapter 6

Conclusions and Future Works

This research successfully met the general objective of obtaining clinically relevant mechanical ventilatory parameters for the diagnosis and treatment of older adults with Acute Respiratory Distress Syndrome (ARDS). The study culminated in the development and validation of a new mathematical model, the Recruitment and Distention Elastance Analysis + Slice (RDEA+Slice) model. This advanced framework, which integrates novel shape functions for recruitment and distention elastance with an adaptation of the slice method, demonstrated a superior ability to estimate patient-specific respiratory mechanics, especially in the presence of spontaneous breathing (SB) efforts and patient-ventilator asynchronies (PVAs). The parameters derived from this model, along with the proposed asynchrony indices, provide a quantitative basis to potentially support clinical decision-making and personalize ventilatory therapy.

A new mathematical model was proposed, building upon analysis of the SCM. The development was progressive starting from the foundational SCM. The shape function methodology proposed by Morton et al. [43] was adopted to enhance the model ability to capture non-linear respiratory mechanics. A key contribution of this work was the systematic analysis performed to adapt these functions for SB. Through a grid search (exploring parameters N and M in a range of -20 to 20), optimal operating regions for the shape functions were identified. While the non-convex nature of the problem means a global optimum is not guaranteed, the identification of these robust, high-performing parameter ranges is a valuable finding in itself. Furthermore, a biophysical interpretation for the new tuning coefficients was proposed: N modifies the recruitment function to model the effect of patient effort and capture negative elastance, while M adjusts the distention function to account for how PVI alters non-linear lung stiffness. The final step was the integration of a pressure-based slice method, which segments the breathing cycle to analyze its dynamics with high temporal resolution. This methodological process culminated in the proposal of the RDEA+Slice model, a robust framework that captures the complex dynamics of asynchrony, thus achieving the first specific objective.

The numerical accuracy of the proposed model was significantly improved over the SCM within the target study group of older adults with ARDS. Comparative evaluation demonstrated that the RDEA+Slice model consistently achieves higher R^2 values (often

exceeding 0.90) and considerably lower Mean Relative Errors (MRE) compared to the SCM and other evaluated models. This improvement in accuracy was especially notable in replicating ventilatory waveforms affected by asynchronies, where traditional models fail. The model validation using real patient data confirmed its ability to estimate patient-specific respiratory mechanics with high fidelity. These results fulfill the second specific objective by demonstrating the model enhanced performance in the defined clinical context.

This work proposed and validated two indices: Asynchrony Event Percentage (AE%) and Asynchrony Index (AI%) to evaluate the patient respiratory state. These indices were derived from an analysis of elastance profiles obtained from the RDEA+Slice model was used as the foundation for a novel detection index. First, a signal processing approach was employed, treating asynchronies as high-frequency "noise" superimposed on a baseline synchronous signal. A low-pass filter with a cutoff frequency of 0.8 Hz was used to separate these components. This frequency was selected based on a physiological rationale: it preserves the fundamental frequency and primary harmonics of a normal breath while attenuating the abrupt fluctuations of asynchrony. From the difference between the original and filtered signals, the time-varying AE% was calculated. To condense this signal into a single, clinically relevant score, the AI% was developed. The two key parameters of this index—the Tolerance Range and the Decision Threshold—were determined through a systematic, two-level optimization process using ROC analysis, which identified a 5% tolerance band and a clinically-adjusted 70% decision threshold as optimal. The development and application of this index fulfill the third specific objective by providing a quantitative framework to assess the patient respiratory state.

Unlike the pressure reconstruction techniques of Damanhuri et al. [26] and Chiew et al. [23], which aim to generate an 'ideal' passive waveform by computationally removing the asynchronous components, the RDEA+Slice model's primary goal is to accurately fit the actual, measured waveform in its entirety. This also contrasts with other approaches that attempt to mathematically isolate and model the patient's effort as a separate component [27]. The novelty of the RDEA+Slice framework lies in its unique hybrid approach. It combines the flexibility of adaptive shape functions to account for non-linear mechanics with the granularity of a pressure-based slice method. This combination allows the model to capture the complex dynamics of asynchronies without attempting to remove them, thereby providing a high-fidelity representation of the true patient-ventilator interaction. It thus serves not as a tool to estimate purely passive mechanics, but as a robust platform for analyzing the mechanics of the asynchronous breath itself, which was foundational for developing the AI%.

This thesis presented a complete, three-phase methodology (Figure 1.2), from data acquisition to a final diagnostic index. While each phase was validated independently, it is important to discuss the robustness of the interconnected workflow. The comprehensive validation of the image processing phase (Chapter 3), which demonstrated extremely high fidelity ($R^2 > 0.99$) against sensor data, ensures that the error introduced at the input of the analysis pipeline is minimal. Furthermore, the design of the final Asynchrony Index (AI%) provides intrinsic resilience to minor modeling inaccuracies. As the AI% is derived from a relative percentage difference (the AE%), any small, systematic errors in the baseline elastance estimation (phase 2) tend to be cancelled out. The index is thus more sensitive

to the dynamic, high-frequency differences between the original and filtered signals—which represent asynchrony—than to the absolute accuracy of the underlying model. This inherent robustness in both the initial data capture and the final metric design provides strong confidence in the method overall stability.

As a natural extension of this research, future work should focus on applying the proposed model and indices to larger and more diverse datasets encompassing a wider range of ventilatory modes and clinical conditions. The specific optimal values found for the shape function coefficients (N and M) and the AI% parameters (5% Tolerance Band, 70% Decision Threshold) are specific to this cohort and require validation on larger, more diverse datasets to ensure generalizability. This also applies to the empirically-determined requirement of a minimum of 15 data points per slice for the RDEA+Slice model, which, while functionally validated in this work (Table 4.7), would benefit from a formal sensitivity analysis. To address the limitations of the pressure-only approach, the AI% should be enhanced by incorporating complementary signals. Analyzing flow waveforms or Pressure-Volume loops could significantly improve the detection of subtle events like DT and IE. Furthermore, a systematic sensitivity analysis should be performed on the filter’s cutoff frequency (F_c) to quantify its impact on the AI% and further refine its selection.

Another important direction for future work lies in the development of predictive models for respiratory asynchronies. Leveraging the elastance-based approach introduced in this study—together with machine learning techniques and temporal trend analysis—could enable early detection of asynchrony patterns before they become clinically apparent. Such predictive capabilities would be highly valuable in ICU settings, where real-time alerts could assist clinicians in anticipating patient-ventilator mismatch and adjusting therapy proactively. Integrating predictive asynchrony detection into ICU monitoring systems could enhance patient safety, reduce time under MV, and improve overall outcomes by enabling timely, personalized interventions.

Although proposing a novel data extraction method was not the primary focus of this research, the study demonstrated that image processing is a reliable and effective tool for extracting ventilatory curves from mechanical ventilators, particularly in resource-constrained environments. Both the custom-developed methodology and the open-source WebPlotDigitizer software exhibited high fidelity in reconstructing key ventilatory parameters, achieving R^2 values exceeding 0.99 and maintaining low Mean Squared Error (MSE) values. The validation of this approach—both against a ventilator emulator and through the replication of Howe’s results—confirms its potential for application in clinical settings with limited technological resources. However, further work is needed to explore the influence of image resolution, pixel sampling, and video quality on the accuracy of the extracted data. Furthermore, since the initial validation was performed on synchronous waveforms, a valuable extension would be to quantify the method’s performance on standardized asynchronous curves ensuring broader applicability across diverse scenarios.

References

- [1] J. L. Knopp, J. G. Chase, K. T. Kim, and G. M. Shaw, “Model-based estimation of negative inspiratory driving pressure in patients receiving invasive NAVA mechanical ventilation,” *Computer Methods and Programs in Biomedicine*, vol. 208, p. 106300, 2021. [Online]. Available: <https://doi.org/10.1016/j.cmpb.2021.106300>
- [2] J. H. T. Bates, *Lung Mechanics An Inverse Modeling Approach*, 1st ed. New York: Cambridge University Press, 2009.
- [3] D. P. Redmond, Y. S. Chiew, V. Major, and J. G. Chase, “Evaluation of model-based methods in estimating respiratory mechanics in the presence of variable patient effort,” *Computer Methods and Programs in Biomedicine*, vol. 171, pp. 67–79, 2019.
- [4] N. S. Damanhuri, Y. S. Chiew, P. D. Docherty, N. A. Othman, G. M. Shaw, T. Desai, and J. G. Chase, “Negative Lung Elastance in Mechanically Ventilated Spontaneously Breathing Patient,” *IFAC-PapersOnLine*, vol. 50, no. 1, pp. 15 179–15 184, 2017. [Online]. Available: <https://doi.org/10.1016/j.ifacol.2017.08.2269>
- [5] S. E. Morton, J. L. Dickson, J. G. Chase, P. D. Docherty, S. L. Howe, G. M. Shaw, and M. Tawhai, “Basis function identification of lung mechanics in mechanical ventilation for predicting outcomes of therapy changes: A first virtual patient,” *IFAC-PapersOnLine*, vol. 51, no. 15, pp. 299–304, 2018. [Online]. Available: <https://doi.org/10.1016/j.ifacol.2018.09.151>
- [6] S. Tomlinson, D. Tilley, and C. Burrows, “Computer Simulation of the Human Breathing Process,” *IEEE ENGINEERING IN MEDICINE AND BIOLOGY*, vol. 94, pp. 115–124, 1994.
- [7] R. Langdon, P. D. Docherty, Y. Shiong, and J. G. Chase, “Extrapolation of a non-linear autoregressive model of pulmonary mechanics,” *Mathematical Biosciences journal*, vol. 17, no. 7, pp. 1–8, 2016.
- [8] J. G. Chase, J. Preiser, J. L. Dickson, A. Pironet, Y. S. Chiew, C. G. Pretty, G. M. Shaw, B. Benyo6, K. Moeller, S. Safaei, M. Tawhai, P. Hunter, and T. Desai, “Next generation, personalised, model based critical care medicine: a state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them,” *BioMedical Engineering*, vol. 17, no. 24, pp. 1–29, 2018.

- [9] J. S. Alqahtani, M. D. AlAhmari, K. H. Alshamrani, A. M. Alshehri, M. A. Althumayri, A. A. Ghazwani, A. O. AlAmoudi, A. Alsomali, M. H. Alenazi, Y. R. AlZahrani, A. S. Alqahtani, S. M. AlRabeeah, and Y. M. Arabi, "Patient-Ventilator Asynchrony in Critical Care Settings: National Outcomes of Ventilator Waveform Analysis," *Heart and Lung*, vol. 49, no. 5, pp. 630–636, 2020. [Online]. Available: <https://doi.org/10.1016/j.hrtlng.2020.04.002>
- [10] S. F. Poole, Y. S. Chiew, D. P. Redmond, S. M. Davidson, N. S. Damanhuri, C. Pretty, P. D. Docherty, T. Desai, G. M. Shaw, and J. G. Chase, *Real-time breath-to-breath asynchrony event detection using time-varying respiratory elastance model*. IFAC, 2014, vol. 19, no. 3. [Online]. Available: <http://dx.doi.org/10.3182/20140824-6-ZA-1003.00228>
- [11] M. Amato, C. Barbas, D. Medeiros, R. Magaldi, G. Schettino, G. Lorenzi-Filho, R. Kairalla, D. Deheinzelin, C. Munoz, R. Oliveira, T. Takagaki, and C. Carvalho, "Effect of a Protective-Ventilation Strategy on Mortality in the Acute Respiratory Distress Syndrome," *N Engl J Med*, vol. 22, p. 55, 1998.
- [12] V. J. Major, Y. S. Chiew, G. M. Shaw, and J. G. Chase, "Biomedical engineer's guide to the clinical aspects of intensive care mechanical ventilation," *BioMedical Engineering Online*, vol. 17, no. 1, 2018. [Online]. Available: <https://doi.org/10.1186/s12938-018-0599-9>
- [13] J. W. W. Lee, Y. S. Chiew, X. Wang, C. P. Tan, M. B. Mat Nor, N. S. Damanhuri, and J. G. Chase, "Stochastic Modelling of Respiratory System Elastance for Mechanically Ventilated Respiratory Failure Patients," *Annals of Biomedical Engineering*, vol. 49, no. 12, pp. 3280–3295, 2021.
- [14] M. Briel, M. Meade, A. Mercat, R. G. Brower, D. Talmor, S. D. Walter, A. S. Slutsky, E. Pullenayegum, Q. Zhou, D. Cook, L. Brochard, J.-C. M. Richard, F. Lamontagne, N. Bhatnagar, T. E. Stewart, and G. Guyatt, "Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome Systematic Review and Meta-analysis," *JAMA: The Journal of the American Medical Association*, vol. 303, no. 9, pp. 865–873, 2010.
- [15] Acute Respiratory Distress Syndrome Network, R. Brower, M. Matthay, A. Morris, D. Schoenfeld, B. Thompson, and A. Wheeler, "Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome," *N Engl J Med*, vol. 45, no. 1, pp. 19–20, 2001.
- [16] S. E. Morton, J. L. Knopp, J. G. Chase, P. Docherty, S. L. Howe, K. Möller, G. M. Shaw, and M. Tawhai, "Optimising mechanical ventilation through model-based methods and automation," *Annual Reviews in Control*, vol. 48, pp. 369–382, 2019. [Online]. Available: <https://doi.org/10.1016/j.arcontrol.2019.05.001>
- [17] S. L. Howe, J. G. Chase, D. P. Redmond, S. E. Morton, K. T. Kim, C. Pretty, G. M. Shaw, M. H. Tawhai, and T. Desai, "Inspiratory respiratory mechanics

- estimation by using expiratory data for reverse-triggered breathing cycles,” *Computer Methods and Programs in Biomedicine*, vol. 186, p. 105184, 2020. [Online]. Available: <https://doi.org/10.1016/j.cmpb.2019.105184>
- [18] E. C. Goligher, E. L. Costa, C. J. Yarnell, L. J. Brochard, T. E. Stewart, G. Tomlinson, R. G. Brower, A. S. Slutsky, and M. P. Amato, “Effect of lowering vt on mortality in acute respiratory distress syndrome varies with respiratory system elastance,” *American Journal of Respiratory and Critical Care Medicine*, vol. 203, no. 11, pp. 1378–1385, 2021.
- [19] I. C. Muñoz, A. M. Hernández, and M. Á. Mañanas, “Estimation of work of breathing from respiratory muscle activity in spontaneous ventilation: A pilot study,” *Applied Sciences (Switzerland)*, vol. 9, no. 10, 2019.
- [20] A. M. Nakato, D. d. F. Ribeiro, A. C. Simão, R. P. Da Silva, and P. Nohama, “Impact of spontaneous breathing trials in cardiorespiratory stability of preterm infants,” *Respiratory Care*, vol. 66, no. 2, pp. 286–291, 2021.
- [21] K. T. Kim, J. Knopp, and J. G. Chase, “Quantifying patient spontaneous breathing effort using model-based methods,” *Biomedical Signal Processing and Control*, vol. 69, no. May, p. 102809, 2021. [Online]. Available: <https://doi.org/10.1016/j.bspc.2021.102809>
- [22] Q. Sun, C. Zhou, and J. G. Chase, “Parameter updating of a patient-specific lung mechanics model for optimising mechanical ventilation,” *Biomedical Signal Processing and Control*, vol. 60, p. 102003, jul 2020.
- [23] Y. S. Chiew, C. P. Tan, J. G. Chase, Y. W. Chiew, T. Desaive, A. M. Ralib, and M. B. Mat Nor, “Assessing mechanical ventilation asynchrony through iterative airway pressure reconstruction,” *Computer Methods and Programs in Biomedicine*, vol. 157, pp. 217–224, 2018.
- [24] J. L. Knopp, Y. S. Chiew, D. Georgopoulos, G. M. Shaw, and J. G. Chase, “Ubiquity of models describing inspiratory effort dynamics in patients on pressure support ventilation,” *IFAC Journal of Systems and Control*, vol. 27, p. 100250, 2024. [Online]. Available: <https://doi.org/10.1016/j.ifacsc.2024.100250>
- [25] V. Major, S. Corbett, D. Redmond, A. Beatson, D. Glassenbury, Y. S. Chiew, C. Pretty, T. Desaive, Á. Szlávecz, B. Benyó, G. M. Shaw, and J. G. Chase, “Respiratory mechanics assessment for reverse-triggered breathing cycles using pressure reconstruction,” *Biomedical Signal Processing and Control*, vol. 23, pp. 1–9, 2016. [Online]. Available: <http://dx.doi.org/10.1016/j.bspc.2015.07.007>
- [26] N. S. Damanhuri, Y. S. Chiew, N. A. Othman, P. D. Docherty, C. G. Pretty, G. M. Shaw, T. Desaive, and J. G. Chase, “Assessing respiratory mechanics using pressure reconstruction method in mechanically ventilated spontaneous breathing patient,” *Computer Methods and Programs in Biomedicine*, vol. 130, pp. 175–185, 2016. [Online]. Available: <http://dx.doi.org/10.1016/j.cmpb.2016.03.025>

- [27] G. R. Arunachalam, Y. S. Chiew, C. P. Tan, A. M. Ralib, and M. B. M. Nor, “Patient asynchrony modelling during controlled mechanical ventilation therapy,” *Computer Methods and Programs in Biomedicine*, vol. 183, 2020.
- [28] Y. S. Chiew, C. Pretty, P. D. Docherty, B. Lambermont, G. M. Shaw, T. Desaive, and J. G. Chase, “Time-varying respiratory system elastance: A physiological model for patients who are spontaneously breathing,” *PLoS ONE*, vol. 10, no. 1, pp. 1–13, 2015.
- [29] European Respiratory Society, *The Global Impact of Respiratory Disease*. United for Lung Health, 2017, vol. 2. [Online]. Available: https://www.who.int/gard/publications/The_Global_Impact_of_Respiratory_Disease_ES.pdf
- [30] MinSalud, “Infección Respiratoria Aguda,” Ministerio de Salud Colombiano, Tech. Rep., 2017. [Online]. Available: <https://www.ins.gov.co/buscador-eventos/Informesdeevento/InformeIRAFinal2017.pdf>
- [31] D. P. Redmond, “Respiratory Mechanics and Patient Effort in Mechanical Ventilation,” Ph.D. dissertation, University of Canterbury, 2017. [Online]. Available: <http://hdl.handle.net/10092/11594>
- [32] K. T. Kim, “Clinical Utilisation of Respiratory Elastance in Clinical Environments,” Ph.D. dissertation, University of Canterbury, 2020. [Online]. Available: <https://hdl.handle.net/10092/101200>
- [33] V. M. Ranieri, G. D. Rubenfeld, B. T. Thompson, N. D. Ferguson, E. Caldwell, E. Fan, L. Camporota, and A. S. Slutsky, “Acute respiratory distress syndrome: The Berlin definition,” *JAMA - Journal of the American Medical Association*, vol. 307, no. 23, pp. 2526–2533, 2012.
- [34] J. F. Dasta, T. P. McLaughlin, S. H. Mody, and C. T. Piech, “Daily cost of an intensive care unit day - The contribution of mechanical ventilation,” *Critical Care Medicine*, vol. 33, 2005.
- [35] S. Larraza, N. Dey, D. S. Karbing, J. B. Jensen, M. Nygaard, R. Winding, and S. E. Rees, “A mathematical model approach quantifying patients’ response to changes in mechanical ventilation: Evaluation in volume support,” *Medical Engineering and Physics*, vol. 37, no. 4, pp. 341–349, 2015. [Online]. Available: <http://dx.doi.org/10.1016/j.medengphy.2014.12.006>
- [36] C. Y. Shuen Ang, Y. S. Chiew, X. Wang, M. B. Mat Nor, M. E. Cove, and J. G. Chase, “Predicting mechanically ventilated patients future respiratory system elastance – A stochastic modelling approach,” *Computers in Biology and Medicine*, vol. 151, no. PA, p. 106275, 2022. [Online]. Available: <https://doi.org/10.1016/j.compbiomed.2022.106275>
- [37] C. Zhou, J. G. Chase, J. Knopp, Q. Sun, M. Tawhai, K. Möller, S. J. Heines, D. C. Bergmans, G. M. Shaw, and T. Desaive, “Virtual patients for mechanical ventilation

- in the intensive care unit,” *Computer Methods and Programs in Biomedicine*, vol. 199, p. 105912, 2021. [Online]. Available: <https://doi.org/10.1016/j.cmpb.2020.105912>
- [38] R. H. Kallet, H. Zhuo, V. Yip, A. Gomez, and M. S. Lipnick, “Spontaneous breathing trials and conservative sedation practices reduce mechanical ventilation duration in subjects with ARDS,” *Respiratory Care*, vol. 63, no. 1, pp. 1–10, 2018.
- [39] S. E. Morton, J. L. Knopp, M. H. Tawhai, P. Docherty, S. J. Heines, D. C. Bergmans, K. Möller, and J. G. Chase, “Prediction of lung mechanics throughout recruitment maneuvers in pressure-controlled ventilation,” *Computer Methods and Programs in Biomedicine*, vol. 197, 2020.
- [40] S. E. Morton, J. Dickson, J. G. Chase, P. Docherty, T. Desai, S. L. Howe, G. M. Shaw, and M. Tawhai, “A virtual patient model for mechanical ventilation,” *Computer Methods and Programs in Biomedicine*, vol. 165, pp. 77–87, 2018. [Online]. Available: <https://doi.org/10.1016/j.cmpb.2018.08.004>
- [41] N. M. Zainol, N. S. Damanhuri, N. A. Othman, Y. S. Chiew, M. B. M. Nor, Z. Muhammad, and J. G. Chase, “Estimating the incidence of spontaneous breathing effort of mechanically ventilated patients using a non-linear auto regressive (NARX) model,” *Computer Methods and Programs in Biomedicine*, vol. 220, p. 106835, 2022. [Online]. Available: <https://doi.org/10.1016/j.cmpb.2022.106835>
- [42] T. Leros, J. L. Knopp, L. Holder-Pearson, E. F. Guy, and J. G. Chase, “An identifiable model of lung mechanics to diagnose and monitor COPD,” *Computers in Biology and Medicine*, vol. 152, no. November 2022, p. 106430, 2023. [Online]. Available: <https://doi.org/10.1016/j.compbiomed.2022.106430>
- [43] S. E. Morton, J. L. Knopp, J. G. Chase, K. Möller, P. Docherty, G. M. Shaw, and M. Tawhai, “Predictive Virtual Patient Modelling of Mechanical Ventilation: Impact of Recruitment Function,” *Annals of Biomedical Engineering*, vol. 47, no. 7, pp. 1626–1641, 2019.
- [44] J. Guttmann, L. Eberhard, B. Fabry, D. Zappe, H. Bernhard, M. Lichtwarck-Aschoff, M. Adolph, and G. Wolff, “Determination of volume-dependent respiratory system mechanics in mechanically ventilated patients using the new slice method,” *Technology and Health Care*, vol. 2, no. 3, pp. 175–191, 1994.
- [45] J. D. Stucki, N. Hobi, A. Galimov, A. O. Stucki, N. Schneider-Daum, C.-M. Lehr, H. Huwer, M. Frick, M. Funke-Chambour, T. Geiser, and O. T. Guenat, “Medium throughput breathing human primary cell alveolus-on-chip model,” *Sci Rep*, vol. 8, no. 1, p. 14359, 2018. [Online]. Available: <http://www.nature.com/articles/s41598-018-32523-x>
- [46] F. Bermejo, “Sistema de Asistencia para la Configuración De Ventiladores OAF en Neonatología,” Ph.D. dissertation, Instituto Tecnológico de Buenos Aires, 2002.

- [47] S. Howe, “Measurement of lung mechanics during spontaneous tidal breathing in out-patient care,” Ph.D. dissertation, University of Canterbury, 2020. [Online]. Available: <https://hdl.handle.net/10092/100910>
- [48] National Cancer Institute, “Bronchi, Bronchial Tree, & Lungs,” [Online]. Available: <https://training.seer.cancer.gov/anatomy/respiratory/passages/bronchi.html>, accessed 24-01-2022.
- [49] P. Aghasafari and R. Pidaparti, “Influence of tidal-volume setting, emphysema and ARDS on human alveolar sacs mechanics,” *Acta Mechanica Sinica*, vol. 34, no. 5, pp. 983–993, jul 2018.
- [50] H. Ashfaq, *Understanding Mechanical Ventilation. A Practical Handbook*, 2nd ed. London: Springer Verlag London Limited, 2010.
- [51] E. Correger, G. Murias, E. Chacon, A. Estruga, B. Sales, J. Lopez-Aguilar, J. Montanya, U. Lucangelo, O. Garcia-Esquirol, A. Villagra, J. Villar, R. M. Kacmarek, M. J. Burgueño, and L. Blanch, “Interpretación de las curvas del respirador en pacientes con insuficiencia respiratoria aguda,” *Medicina Intensiva*, vol. 36, no. 4, pp. 294–306, may 2012.
- [52] R. Boulding, R. Stacey, R. Niven, and S. J. Fowler, “Dysfunctional breathing: a review of the literature and proposal for classification,” *Eur Respir Rev*, vol. 25, no. 141, pp. 287–294, 2016. [Online]. Available: <http://err.ersjournals.com/lookup/doi/10.1183/16000617.0088-2015>
- [53] K. G. Andersen, A. Rambaut, W. I. Lipkin, E. C. Holmes, and R. F. Garry, “The proximal origin of SARS-CoV-2,” *Nat Med*, vol. 26, no. 4, pp. 450–452, 2020. [Online]. Available: <http://www.nature.com/articles/s41591-020-0820-9>
- [54] W. Zhang, Y. Xiang, C. Lu, C. Ou, and Q. Deng, “Numerical modeling of particle deposition in the conducting airways of asthmatic children,” *Medical Engineering and Physics*, vol. 76, pp. 40–46, 2020. [Online]. Available: <https://linkinghub.elsevier.com/retrieve/pii/S1350453319302425>
- [55] M. I. Sigurdsson, K. Sigvaldason, T. S. Gunnarsson, A. Moller, and G. H. Sigurdsson, “Acute respiratory distress syndrome : nationwide changes in incidence , treatment and mortality over,” *Acta Anaesthesiologica Scandinavica*, pp. 37–45, 2013.
- [56] G. D. Rubenfeld, E. Caldwell, E. Peabody, J. Weaver, D. P. Martin, D. Ph, M. Neff, E. J. Stern, and L. D. Hudson, “Incidence and Outcomes of Acute Lung Injury,” *N Engl J Med*, vol. 353, no. 16, pp. 1685–1693, 2005.
- [57] D. R. Hess, “Approaches to Conventional Mechanical Ventilation of the Patient With Acute Respiratory Distress Syndrome,” *Respiratory Care*, vol. 56, no. 10, pp. 1555–1572, oct 2011.

- [58] N. S. Damanhuri, “Multi-Scale Pulmonary Modelling and Clinical Applications,” Ph.D. dissertation, University of Canterbury, 2015. [Online]. Available: <http://hdl.handle.net/10092/11594>
- [59] L. Chen and X. Zhao, “Characterization of air flow and lung function in the pulmonary acinus by fluid-structure interaction in idiopathic interstitial pneumonias,” *PLoS ONE*, vol. 14, no. 3, p. e0214441, 2019. [Online]. Available: <https://dx.plos.org/10.1371/journal.pone.0214441>
- [60] A. B. Otis, W. O. Fenn, and H. Rahn, “Mechanics of Breathing Man,” *J Appl Physiol*, vol. 2, no. 11, 1950.
- [61] S. Saha and S. Mukherjee, “Investigation of severity of lung fibrosis by dynamic modelling of human respiratory system,” *International Journal of Advanced Research in Electrical, Electronics and Instrumentation Energy*, vol. 2, pp. 4837–4844, 2013.
- [62] K. T. Kim, J. Knopp, B. Dixon, and G. Chase, “Quantifying neonatal pulmonary mechanics in mechanical ventilation,” *Biomedical Signal Processing and Control*, vol. 52, pp. 206–217, 2019. [Online]. Available: <https://doi.org/10.1016/j.bspc.2019.04.015>
- [63] A. Lauzon and J. H. Bates, “Estimation of time-varying respiratory parameters by recursive least squares,” *Journal of Applied Physiology*, vol. 71, no. 3, pp. 1159–1165, 1991.
- [64] W. Souza Leite, A. Novaes, M. Bandeira, E. Olympia Ribeiro, A. M. dos Santos, P. H. de Moura, C. C. Morais, C. Rattes, M. K. Richtmoe, J. Souza, G. H. C. de Lima, N. S. P. Modolo, A. C. E. Gonçalves, C. A. R. Gonzalez, M. do Amparo Andrade, A. D. de Andrade, D. C. Brandão, and S. L. Campos, “Patient-ventilator asynchrony in conventional ventilation modes during short-term mechanical ventilation after cardiac surgery: Randomized clinical trial,” *Multidisciplinary Respiratory Medicine*, vol. 15, 2020.
- [65] C. Y. S. Ang, Y. S. Chiew, X. Wang, E. H. Ooi, M. E. Cove, Y. Chen, C. Zhou, and J. G. Chase, “Patient-ventilator asynchrony classification in mechanically ventilated patients: Model-based or machine learning method?” *Computer Methods and Programs in Biomedicine*, vol. 255, p. 108323, 2024. [Online]. Available: <https://doi.org/10.1016/j.cmpb.2024.108323>
- [66] E. G. Tsega, “Computational Fluid Dynamics Modeling of Respiratory Airflow in Tracheobronchial Airways of Infant, Child, and Adult,” *Computational and Mathematical Methods in Medicine*, pp. 1–9, 2018.
- [67] W. M. Faizal, N. N. N. Ghazali, C. Y. Khor, I. Anjum, and M. Z. Zainon, “Computational fluid dynamics modelling of human upper airway: A Review,” *Computer Methods and Programs in Biomedicine* *fdsfsdfs*, no. January, 2020.

- [68] J. W. De Backer, W. G. Vos, A. Devolder, S. L. Verhulst, P. Germonpré, F. L. Wuyts, P. M. Parizel, and W. De Backer, “Computational fluid dynamics can detect changes in airway resistance in asthmatics after acute bronchodilation,” *Journal of Biomechanics*, vol. 41, no. 1, pp. 106–113, 2008. [Online]. Available: <https://linkinghub.elsevier.com/retrieve/pii/S0021929007003181>
- [69] X. L. Yang, Y. Liu, R. M. C. So, and J. M. Yang, “The effect of inlet velocity profile on the bifurcation COPD airway flow,” *Computers in Biology and Medicine*, vol. 36, no. 2, pp. 181–194, 2006. [Online]. Available: <https://linkinghub.elsevier.com/retrieve/pii/S0010482504001465>
- [70] A. Farghadan, F. Coletti, and A. Arzani, “Topological analysis of particle transport in lung airways: Predicting particle source and destination,” *Computers in Biology and Medicine*, vol. 115, p. 103497, 2019. [Online]. Available: <https://linkinghub.elsevier.com/retrieve/pii/S0010482519303622>
- [71] J. Xi, J. Kim, X. A. Si, R. A. Corley, S. Kabilan, and S. Wang, “CFD Modeling and Image Analysis of Exhaled Aerosols due to a Growing Bronchial Tumor: towards Non-Invasive Diagnosis and Treatment of Respiratory Obstructive Diseases,” *Theranostics*, vol. 5, pp. 443–455, 2015. [Online]. Available: <https://www.thno.org/v05p0443.htm>
- [72] Q. Gu, S. Qi, Y. Yue, J. Shen, B. Zhang, W. Sun, W. Qian, M. S. Islam, S. C. Saha, and J. Wu, “Structural and functional alterations of the tracheobronchial tree after left upper pulmonary lobectomy for lung cancer,” *BioMed Eng OnLine*, vol. 18, no. 1, p. 105, 2019. [Online]. Available: <https://biomedical-engineering-online.biomedcentral.com/articles/10.1186/s12938-019-0722-6>
- [73] W. A. Zin and R. F. M. Gomes, “Mechanical models of the respiratory system: linear models,” in *Basics of Respiratory Mechanics and Artificial Ventilation*. Springer Milan, 1999, pp. 87–94.
- [74] N. Flores, “Simulación por software de las curvas generadas en ventilación mecánica por control de presión,” *Red de Revistas Científicas de América Latina*, no. 9, pp. 85–96, 2006.
- [75] A. Ben-Tal, “Simplified models for gas exchange in the human lungs,” *Journal of Theoretical Biology*, vol. 238, no. 2, pp. 474–495, 2006.
- [76] L. Shekerdemian and D. Bohn, “Cardiovascular effects of mechanical ventilation,” *Archives of Disease in Childhood*, vol. 80, no. 5, pp. 475–480, may 1999.
- [77] L. Chiari, G. Avanzolini, and M. Ursino, “A Comprehensive Simulator of the Human Respiratory System: Validation with Experimental and Simulated Data,” *Annals of Biomedical Engineering*, vol. 25, pp. 985–999, 1997.
- [78] A. Jbaily, S. Frank, and A. J. Szeri, “Pulmonary mechanics and gas exchange: a mathematical framework,” *International Journal of Engineering Science*, vol. 154, pp. 103–276, sep 2020.

- [79] J. P. Archie, “A mathematical model for pulmonary mechanics: The alveolar surface contribution,” *International Journal of Engineering Science*, vol. 11, no. 6, pp. 659–671, jun 1973.
- [80] N. J. Douville, C. B. Douville, G. Mentz, M. R. Mathis, C. Pancaro, K. K. Tremper, and M. Engoren, “Clinically applicable approach for predicting mechanical ventilation in patients with COVID-19,” *British Journal of Anaesthesia*, vol. 126, no. 3, pp. 578–589, 2021. [Online]. Available: <https://doi.org/10.1016/j.bja.2020.11.034>
- [81] N. S. M. Sauki, N. S. Damanhuri, N. A. Othman, B. C. C. Meng, Y. S. Chiew, and M. B. M. Nor, “Assessing the asynchrony event based on the ventilation mode for mechanically ventilated patients in ICU,” *Bioengineering*, vol. 8, no. 12, 2021.
- [82] S. Perinel-Ragey, L. Baboi, and C. Guérin, “Variability of tidal volume in patient-triggered mechanical ventilation in ARDS,” *Respiratory Care*, vol. 62, no. 11, pp. 1437–1446, 2017.
- [83] A. M. Valencia, I. Ruiz, J. I. García, and A. Galvis, “Design of a patient simulator for clinicians training in mechanical ventilation: SimVep,” *Journal of Medical Engineering and Technology*, vol. 49, no. 3, pp. 79–92, 2025. [Online]. Available: <https://doi.org/10.1080/03091902.2025.2484672>
- [84] I. Ruiz, G. Jaramillo, J. I. García, A. Valencia, A. Segura, and A. F. Caballero-Lozada, “Modelling ventilation with spontaneous breaths: Improving accuracy with shape functions and slice method,” *Computer Methods and Programs in Biomedicine*, vol. 263, no. August 2024, pp. 1–13, 2025.