Using Machine Learning Models to Predict Oxygen Saturation Following Ventilator Support Adjustment in Critically Ill Children: A Single Center Pilot Study

by

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LIST OF SYMBOLS

δ	Random number in [0,1] used for creation of data points by SMOTE algorithm
$\boldsymbol{X}$	A given feature vector
x_i	Data point (observation) of row *i* of a feature vector $\boldsymbol{X}$ in dataset
x_{knn}	Nearest neighbor of data point x_i chosen during creation of synthetic data by SMOTE algorithm
x_{syn}	Synthetic data created by SMOTE algorithm
x_{min}	Lowest value in a given feature vector $\boldsymbol{X}$
x_{max}	Lowest value in a given feature vector $\boldsymbol{X}$
μ	Mean of a data distribution within a feature vector
σ	Standard deviation of a data distribution within a feature vector
E^t	Cross-entropy
$\{\boldsymbol{W}_i\}_i$	Weight matrix for ANN connections between neurons of layers *i* and *j*
η	Learning rate set for SGD
y_i	Output of a classifier for observation *i*
r_i	Target value for observation *i*
$\boldsymbol{T}$	Training set
$\{\boldsymbol{T^i}\}$	Replicate training sub-sets bootstrapped from training set $\boldsymbol{T}$
Κ	Cohen`s Kappa statistic
p_o	Relative observed agreement among raters
p_e	Hypothetical probability of chance agreement between two raters
n	Number of classes
N	Number of instances
n_{ki}	Number of times rater *i* predicted class label *k*
H	Harmonic mean

LIST OF ALGORITHMS

LIST OF ABBREVIATIONS

SpO_2	oxygen saturation
FiO_2	oxygen inspired fraction
CO_2	Carbon Dioxide
PEEP	Positive End-Expiratory Pressure
PaO_2	Arterial pressure in oxygen
PIP	Positive Inspiratory Pressure
CDSS	Clinical Decision Support System
AI	Artificial Intelligence
PICU	Pediatric Intensive Care Unit
ANN	Artificial Neural Network
MLP	Multi-Layer Perceptron
ARDS	Acute Respiratory Distress Syndrome
CDSS	Clinical Decision Support System
Bagging	Bootstrap Aggregating
SMOTE	Synthetic Minority Oversampling Technique
$EtPCO_2$	End tidal Partial pressure in CO_2
LSE	Least Square Error
SGD	Stochastic Gradient Descent
SVM	Support Vector Machine
RNN	Recurrent Neural Network
Bi-LSTM	Bi-Directional Long Short-Term Memory

INTRODUCTION

Mechanical ventilation assists or controls the inhalation of oxygen into the lungs and the exhalation of carbon dioxide. Many variables need to be monitored during mechanical ventilation. Some of these variables are: expiratory minute volume, expiratory tidal volume, mean airway pressure, peak airway pressure, measured frequency, level of dyspnea, respiratory rate, heart rate, blood pressure, patient-ventilator synchrony, arterial blood gas, oxygen saturation. One of the important variables that the clinician wishes to monitor and control during mechanical ventilation, to ensure it remains within an acceptable range, is the oxygen saturation (SpO_2). The SpO_2 variable should ideally be maintained between 92% and 97%, at all time, during mechanical ventilation. One of the ways to control the SpO_2 is by tweaking some setting variables during mechanical ventilation. The setting variables that we considered in this study, are: oxygen concentration (FiO_2) setting, Positive End-Expiratory Pressure (PEEP) setting and Tidal Volume setting. One of the challenges the clinician faces when it comes to monitoring and controlling the SpO_2 variable, is being able to forecast the effect that a change in one or more setting variable(s) will have on the SpO_2. Although the time for stabilization of SpO_2 following a setting change depends on the changes in setting variables, the SpO_2 is considered to reach steady state five (5) minutes after the setting change is made. Hence, given the values of measured variables, the setting variables, as well as any change(s) in the values of one or more setting variable(s), at a given time step during mechanical ventilation, the clinician would want to be able to predict the value of SpO_2, within a range of acceptable precision, five (5) minutes after the setting change(s) is/are made. At any given time during mechanical ventilation, the clinician may need to decide, based on various respiratory variables, the values by which to tweak the setting variables. These modifications in one or more of the setting variable(s) are intended to allow the SpO_2 variable to remain within its acceptable range (92-97%).

In the aim of developing a Clinical Decision Support System (CDSS) for the management of mechanical ventilation, we attempted to create a system that predicts SpO_2 when a modification in mechanical ventilation settings is performed. Therefore, the motivation of this research project is to propose a method which is intended to support the clinician in her/his decision-making process when it comes to the settings of FiO_2, PEEP and PIP/Tidal Volume variables. This is achieved via the use of a machine learning model (classifier) capable of successfully predicting values of SpO_2 based on values of other biological signals, combined with any changes in setting variables made by the clinician. The predictive model used would ideally make it possible for the clinician to have an accurate prediction of the effect any change in the setting variables would have on the SpO_2, five minutes after the change is made. As revealed in the previous paragraph, this five-minute duration was prescribed by the clinician as the minimal SpO_2 settling time, following a setting change.

The mechanical ventilation expert cannot reasonably be expected to always be present at the patient's bedside. The development of artificial intelligence (AI) in medicine provides caregivers with assistance in the management of mechanical ventilation variables. The use of AI is intended to improve patient management in intensive care, as well as mechanical ventilation teaching to respiratory therapists and physicians. Several expert systems have been developed based on medical knowledge to help clinicians in the management of mechanical ventilation. However, only a few of them are commercialized and none have been widely in use in intensive care. Another approach is to model patient reaction to mechanical ventilation settings modifications to predict its impact on oxygenation and on CO_2 removal, using physiological algorithms rather than supervised learning algorithms. Some physiological algorithms have been developed, but none has been validated for this indication. In the aim of developing a CDSS for the management of mechanical ventilation, we propose a method through which the SpO_2 variable can be classified within a predefined set of class labels, when any modification in mechanical ventilation settings is performed. The method we propose is based on machine learning algorithms to develop predictive models via the extraction of patterns from large amounts of available data.

To ensure the feasibility of this study, a large amount of data was required. Therefore, the data for 610 patients were extracted from the CHU Sainte-Justine research database, as per inclusion criteria specified by the clinician. The CHU Sainte-Justine research database contains mechanical ventilation data that were collected over a period of over 2 years. The data of all children (age under 18) admitted to the Pediatric Intensive Care Unit (PICU) of Sainte-Justine Hospital that were mechanically ventilated with an endotracheal tube (invasive ventilation) between May 2015 and April 2017 were included. Exclusion criteria were 2 or more vasoactive drugs (epinephrine, norepinephrine, dopamine or vasopressin) at the same time or an uncorrected cyanotic heart disease (defined by SpO_2 always below 97% during PICU stay). For each included patient, the vital signs and ventilatory data, collected every 5 and 30 seconds during PICU stay, were extracted from the CHU Sainte-Justine research database. The main elements of this study were: formatting and pre-processing the raw data obtained from the research database, training a machine learning predictive model through supervised learning, ie., using target variable class labels on a subset of the pre-processed data, and then using the trained model to make predictions on the values of SpO_2 five minutes after any setting change is performed by the clinician, on new data (test set). In summary, once the data are pre-processed, the machine learning model is trained and fitted on a portion of the data (the training set) and then tested on new data (test set).

Among the multiple classifiers we tested in throughout the study, the ones which yielded the most satisfactory classification performances were the Artificial Neural Network (ANN), also referred to as Multi-Layer Perceptron (MLP), and the Bootstrap Aggregation (short: “Bagging”) ensemble method applied to complex trees (will be referred to as complex tree “Bagging” or “Bagged” trees). The ability of the model to accurately represent data on which it has never been trained (generalization capability) is evaluated using the following metrics: confusion matrices, precision-recall (for classification precision of the different classes involved), f1-score, and the Cohen’s Kappa statistic.

This study was made up of three (3) main phases: data extraction and pre-processing, training and testing of machine learning classifiers using the available training and testing data, evaluation and comparison of the classifiers based on the classification results they yielded. In the data pre-processing phase, a major task consisted in formatting the data to prepare it to be used for classifier supervised training and testing. Once the data was formatted and cleaned up with the aim of being used for machine learning supervised training, all nineteen of the input variables (or features) which represent the respiratory signals, including the three setting signals, were normalized to values in the range [0, 1]. This was deemed necessary due to the high variability in the value ranges of the input variables. The pre-processing phase also included the definition as well as the data balancing. The necessity to attempt data balancing was made evident by the unsatisfactory results that were obtained, after a few training/testing cycles using a few different supervised learning models, including the ANN and the Ensemble of Bagged Complex Trees. The severe imbalance in the data is caused by the fact that more than 90% of the observations belonged to class-label "3". This imbalance in the data causes significant bias in the learning of the various class labels by the classifier. This means that a high classification accuracy would not necessarily be representative of the classification accuracy of any of the various class-labels. In simple terms, with such a high degree of data imbalance, the classifier can learn the majority class very well, but doesn't get enough samples of the other class-labels (minority classes) to be able to learn them well enough. The data balancing process used in this study, consisted in combinations of down-sampling and up-sampling techniques. A down-sampling of the majority class and an over-sampling using the S*ynthetic* M*inority* O*versampling* Te*chnique*, (SMOTE) of the minority classes were needed to balance the three (3) classes of the data involved.

The aim of this study was to find a way to use machine learning models, through supervised learning, to extract knowledge from research data to predict the effect any setting change made by the clinician would have on the SpO_2 signal five minutes later.

Some significant contributions were made throughout this research project, namely:

- Large amounts of data from an ICU research database were exploited for SpO_2 prediction via machine learning classification models, which, as per the literature reviewed, doesn't seem to have been done up to this date.

- To render the available ventilatory data compatible with machine learning supervised training methods, a data formatting process was proposed.
- To counter the imbalanced nature of the data, various combinations of different data balancing techniques were proposed.
- Supervised machine learning algorithms were proposed for attempting to extract knowledge from large amounts of patient mechanical ventilation data in the aim of predicting the behavior of SpO_2, based on values of other variables and those of any setting changes made by the clinician.

CHAPTER 1

LITERATURE REVIEW

The development of machine learning algorithms in the field of AI presents countless promises to the medical field. A medical intervention during which data can be stored about the evolution of the intervention and of the patient's state, offers the possibility of the integration of machine learning algorithms which could assist the clinician(s) involved in the decision-making process throughout the intervention. The ICU mechanical ventilation is an area, among possibly many other areas of the medical field, to which AI could potentially contribute remarkable progress. However, based on the available information which we have reviewed from research papers, no study which addresses the possibility of SpO_2 prediction via machine learning has been undertaken by any research group, yet. Nonetheless, the following section presents a literature review, which includes a study in which an expert system was developed to assist in the mechanical ventilation weaning process. It also presents a review of studies that address topics regarding some data balancing methods used in this study, in the data pre-processing phase. The *general conclusion* section provides a review of the study by summarizing the essential elements of it and the results it yielded, as well as some recommendations for future work.

- Physiologic Cardiorespiratory Simulators, which can reproduce cardiorespiratory physiology and provide arterial blood gas values. An example is the MacPuf simulator developed by C.J Dickinson, 1977. The Dickinson model considers blood circulation, the gas exchange system, ventilation control, and tissue metabolism. It simulates gas exchange and respiratory mechanics according to the alveolar ventilation and gas-exchange time, as well as in terms of respiratory rate, compliance, lung capacity, and oxygen saturation. It requires the setting of 26 parameters to simulate the evolution of the state of the targeted sub-parts of the respiratory system. Another simulator is known as VentSim [22]. It includes a ventilator component, ie., a volume-cycled, constant-flow ventilator, an airway component, and a circulation component. This simulator includes arterial and venous blood gases. It has been validated on simulated patients and showed a good match between the blood gas it provided and that of clinical range. However, a comparative assessment with data from actual ventilated patients is missing, and the ability to simulate unstable patients, which are frequently encountered in ICU's has not sufficiently been evaluated. SOPAVent [23] developed a simulator based on a 3-compartment physiological model. A significant limitation of this model is that it presently only works with stable patients, which is not a realistic expectation given the reality of ICU's.

- Simulators for Ventilation Management Recommendations: A model that includes oxygen and carbon dioxide gas exchange and storage modelling and a linear model of lung mechanics, has been developed by Intelligent Ventilator: Rees et al. [19]. The model uses a decision theory approach for lung mechanics simulation. It is combined with penalty functions which allow it to line up with clinical preferences, given the goals and side effects of lung mechanics.

The above-mentioned models all share the limitation of not being suited to learn from ever-growing sets of clinical research data, and potentially improve their simulation performances. This is a major reason for which a machine learning approach to the problem of lung mechanics modeling should be given much attention, as it could prove to be a means by which a CDSS could be rendered reliable enough to provide significant support to ICU physicians. In this study, we propose a method for predicting SpO2 via a supervised machine learning algorithm, using patient data which we extracted from CHU Ste-Justine Hospital research database.

CHAPTER 2

USING MACHINE LEARNING MODELS TO PREDICT OXYGEN SATURATION FOLLOWING VENTILATOR SUPPORT ADJUSTMENT IN CRITICALLY ILL CHILDREN: A SINGLE CENTER PILOT STUDY

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ABSTRACT

Clinical experts in mechanical ventilation are not continuously at each patient's bedside in an intensive care unit to adjust mechanical ventilation settings and to analyze the impact of ventilator settings adjustments on gas exchange. The development of clinical decision support systems analyzing patients' data in real time offers an opportunity to fill this gap. The objective of this study was to determine whether a machine learning predictive model could be trained on a set of clinical data and used to predict hemoglobin oxygen saturation 5 min after a ventilator setting change. Data of mechanically ventilated children admitted between May 2015 and April 2017 were included and extracted from a high-resolution research database. More than 7.10^5 rows of data were obtained from 610 patients, discretized into 3 class labels. Due to data imbalance, four different data balancing process were applied and two machine learning models (artificial neural network and Bootstrap aggregation of complex decision trees) were trained and tested on these four different balanced datasets. The best model predicted SpO_2 with accuracies of 76%, 62% and 96% for the SpO_2 class "< 84%", "85 to 91%" and "> 92%", respectively. This pilot study using machine learning predictive model resulted in an algorithm with good accuracy. To obtain a robust algorithm, more data are needed, suggesting the need of multicenter pediatric intensive care high resolution databases.

2.1 Introduction

In case of respiratory failure, mechanical ventilation supports the oxygen (O_2) diffusion into the lungs and the carbon dioxide (CO_2) body removal. As an expert in mechanical ventilation cannot reasonably be expected to be continuously present at the patient's bedside, specific medical devices aimed to help in ventilator settings adjustments may help to improve the quality of care. Such devices are developed using either algorithms based on respiratory physiology/medical knowledge that adapt ventilator settings in real time based on patients' characteristics but are not accurate enough to be used widely in clinical practice, especially in children [1, 2]; or physiologic models that simulate cardiorespiratory responses to mechanical ventilation settings modifications but none was validated for this indication [3]. The above-mentioned models all share the limitation of not being suited to learn from ever-growing sets of clinical research data, and potentially improve their performances. To overcome this drawback, another avenue is the development of algorithms using artificial Intelligence to provide caregivers with support in their decision-making tasks. In this study, we assessed machine learning methods to predict transcutaneous hemoglobin saturation oxygen (SpO_2) of mechanically ventilated children after a ventilator setting change using a high-resolution research database.

2.2 Materials and Methods

This study was conducted at Sainte-Justine Hospital and included the data collected prospectively between May 2015 and April 2017 of all the children, age under 18 years old, admitted to the Pediatric Intensive Care Unit (PICU) who were mechanically ventilated with an endotracheal tube. Patients' data were excluded if the patient was hemodynamically unstable defined as 2 or more vasoactive drugs delivered at the same time (ie., epinephrine, norepinephrine, dopamine or vasopressin) or with an uncorrected cyanotic heart disease defined by no $SpO_2 > 97\%$ during all PICU stay. All the respiratory data from included patients were extracted from the PICU research database [4], after study approval by the ethical review board of Sainte-Justine hospital (number 2017 1480).

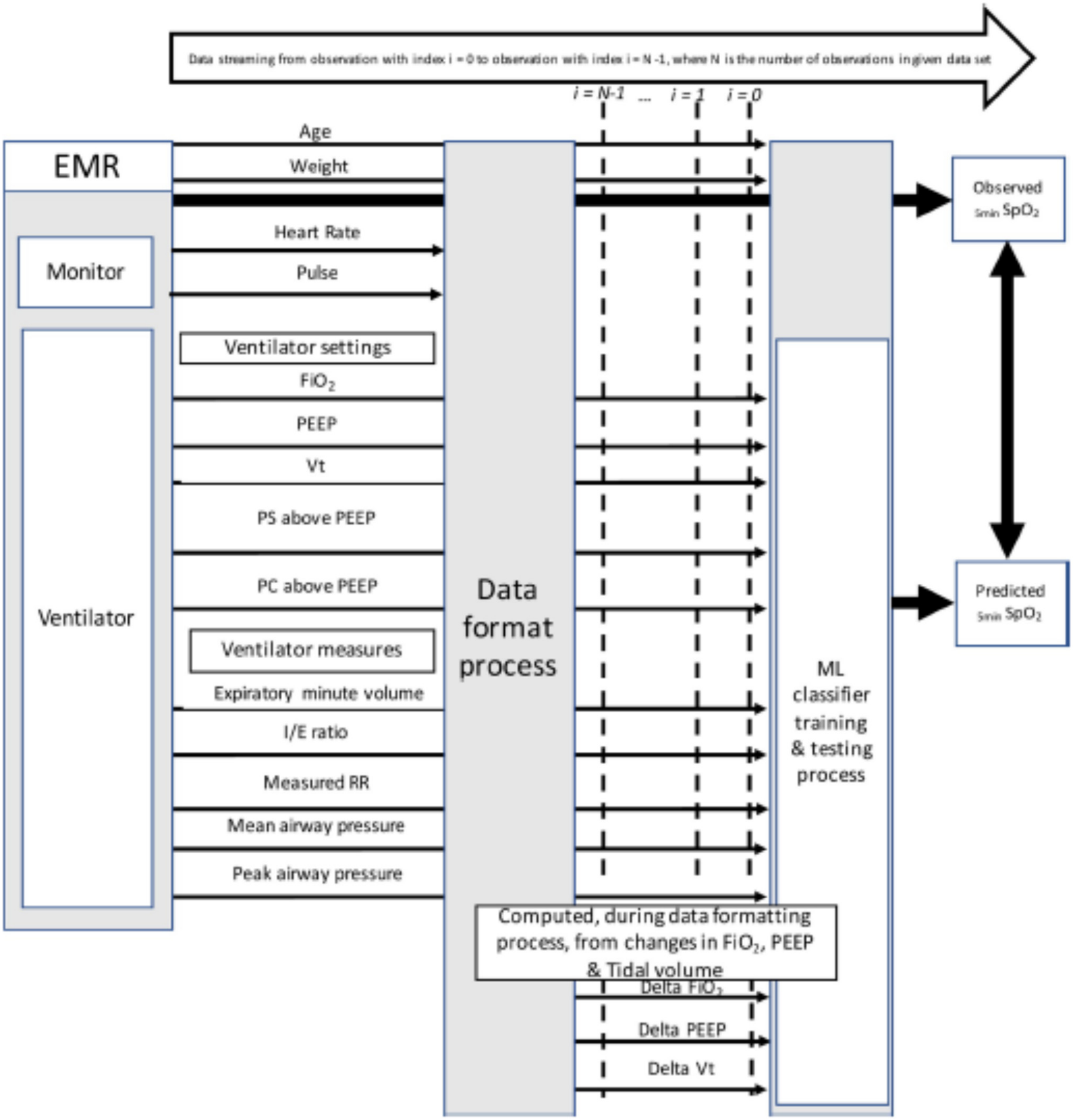


Figure 2.1 Schematic description of the analysis process and items involved

EMR: electronic Medical Record, FiO_2: inspired fraction of Oxygen, Vt: tidal volume, PEEP: Positive end expiratory pressure, PS above PEEP: pressure support level Above PEEP, PC above PEEP: pressure control level above PEEP, MVe: expiratory minute volume, I:E Ratio: inspiratory time over expiratory time, Measured RR: respiratory rate measured by the ventilator, PIP: positive inspiratory pressure ie maximal pressure measured during inspiration. ${}_{5min}SpO_2$: SpO_2 observed 5 min after PEEP, FiO_2, tidal volume, PS above PEEP, PC above PEEP change, ML: machine learning, ANN: artificial neural network, BACDT: Bootstrap aggregation complex decision trees.

2.3 Methodology

2.3.1 Data extraction

To determine the data that will be extracted for each child, an item generation was conducted by three physicians (PJ, MS, DB). The resulting items are presented in Fig 2.1 within their sources, means of extraction and a schematic of the main components of the study. The predictive SpO_2 value was the SpO_2 5 minutes after a change of a ventilator setting. The delay of 5 min corresponded to the shortest period of time to reach a steady state after modification of a ventilator setting [5].

2.3.2 Data Categorization

SpO2 levels at 5min were classified into three categories (Table 2.1). The thresholds were selected according to clinical value: a SpO2 < 92% is a target to increase oxygenation in mechanically ventilated children [6]. The critical level of 85% SpO2 is used as an alarm of severe hypoxemia in intensive care [7].

The SpO_2 variable (target) has been classified in three categories to correspond to clinically relevant values.

Table 2.1: Definition of SpO_2 class labels specifications

SpO_2 classification	SpO_2 range (%)	Rows number (n)
1	< 84	17,112
2	85 to 91	29,869
3	92 to 100	729,746

2.3.3 Data formatting

The extraction of data from the patient database produces data files with a format which does not allow for classifier training. This is mainly because, in these initial data files, the respiratory variables are not separated in columns, which would become the input and output vectors during model training. Moreover, a significant proportion of rows in the initial files do not represent data which are measured within mechanical ventilation time intervals. Thus, it is necessary for the formatted files which are to be used for classifier training to be rid of any unnecessary rows, which do not contain mechanical ventilation readings.

The classifiers used to predict (classify) the SpO_2 values are built when mathematical models are trained on a set of data which displays the relevant variables in a table format. The table must be arranged as follows: the respiratory signals (variables) represent the labels of the various columns and the data storing times and patient codes represent the rows. The data formatting process described herein consists basically in making the data format machine learning friendly. Below are the steps taken to format and pre-process the raw data to make it suitable for classifier training. Many of the data pre-processing criteria have been established by the clinicians involved in this study.

- **Read content of initial data file into a Python (Pandas library) data frame:** The data contained in the initial files are stored into data frames which are used to manipulate and preprocess the data.

- **Strip away the microseconds part from the data storing times in the initial files, as it is not contextually relevant:** Following this step, the storing times are represented in the following form: *"year:month:day:hours:minutes:seconds"*
- **Pivot the data that were stored in the data frames:** This step transforms the data from the linear format in the initial files into a table, where the biological variables are the column labels and the patient codes and storing times are the row labels.
- **Align the data of the variables in the pivoted table within mechanical ventilation time slots:** Since the readings for the various variables involved are not all set at the same frequency, the data for the different variables are not aligned along the rows (time-steps). Therefore, it is necessary to align the data readings for the various variables (along any given row within a mechanical ventilation interval), to prepare the data to be used for classifier training. This data formatting step ensures the alignment of the data for "FC", "SpO_2", "Pulse", "Pressure Support Level Above PEEP" and "Pressure Control Level Above PEEP" variables with the data of the other variables, for any given time-step within mechanical ventilation time-slots.
- **Fill cells of "Tidal Volume Setting" variable with the values given by *"Expiratory Minute Volume" / "Measured Frequency" x 1000,* as per clinician`s requirement.**
- **Drop rows with any empty cell(s):** Once alignment of the data is completed, all rows containing empty readings are to be dropped to ensure that only time-slots of mechanical ventilation readings are preserved.
- **Create 3 new variables which represent the changes made to the setting variables (one for each setting variable):** Run through all the rows in the data frame, and for any of the 3 setting variables (FiO_2, PEEP, Tidal Volume), if the value at any time-step is NOT EQUAL to the value at the previous time-step, then calculate the difference between the values at both time-steps and place the results in new columns, called "Delta FiO_2 Setting", "Delta PEEP Setting" and "Delta Tidal Volume Setting". This step allows the creation of three (3) new variables: "Delta FiO_2 Setting", "Delta PEEP Setting" and "Delta Tidal Volume Setting" which are deemed very significant for the prediction of SpO_2 (5 min. following the change in at least one of the setting variables). For each patient section (as per the patient code), whenever the readings show that at least one of the three (3) setting variables (FiO_2, PEEP, Tidal Volume) is modified from one row (time-step) to the next,

the values of the differences are stored in the new columns created ("Delta FiO_2 Setting", "Delta PEEP Setting" and "Delta Tidal Volume Setting"). This means that only the time-steps at which at least one of the setting variables is modified are to be preserved in the data file to be used for classifier training.

There are two main conditions for this step:

1) To verify that the data of different patients are treated separately, as per the patient codes which these data are grouped by. This ensures that the readings for different patients are not mixed up. In other words, the various sections of rows which are grouped by the patient codes are to be treated separately.
2) To verify that the change in "FiO_2 Setting" does not exceed 20%, as per clinician's requirement.

Copy the value of "SpO_2" at the row 5 minutes following the current examined row, into the current row, in a column assigned to this variable: "SpO_2 in 5 min.".

- **Create a new column called "Binned SpO_2" in the data frame and fill it with values as per the binning criteria in table 1. This variable is to be used as the target variable:** The target variable is created by binning the data of variable "SpO_2 in 5 min." into three classes (see table 2.1). The binning of the target variable data into three classes allows for better classification performance, since it reduces the size of the range of values that the trained model would have to predict from. This naturally implies that it increases the amount of observations per target class label, which allows the classification model to extract more information per class label, during the training process.
- **For all time-steps, verify the accuracy of "FC" readings by making sure that they are within ± 10 of "Pulse":** All rows containing "FC" readings which do not respect this condition are dropped.
- **All rows in data frame where "Peak Airway Pressure" ≤ 5 are dropped.**

- **Add “Age” and “Weight” data of all patients to the data frame:** Using the Patient-specific data file and the data frame which represents the data file which is used to train the predictive model, the age and the weight of every patient are added to the data frame in which the data is being formatted. The weight and the age of each patient, at the time of undergoing mechanical ventilation, are inserted in their newly created columns, at the appropriate rows, in the data frame. The data frame containing the formatted data is copied into a comma-separated file (csv) file.

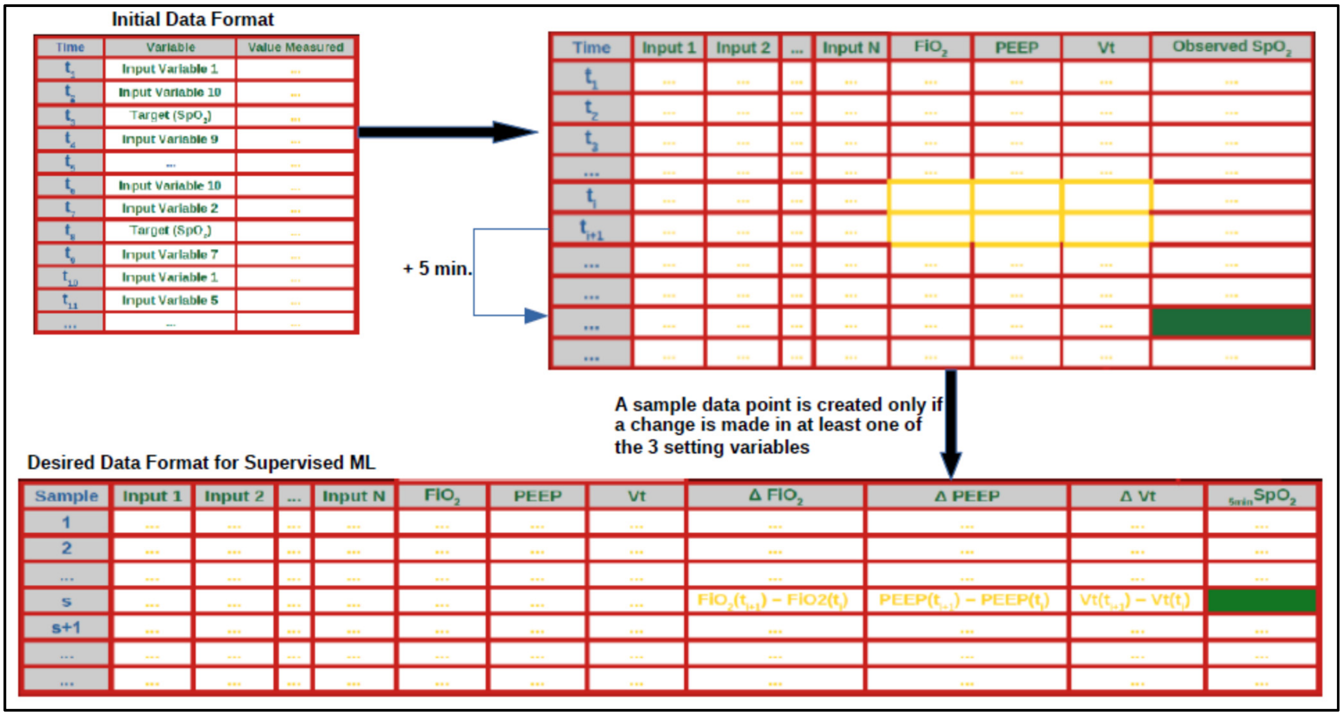


Figure 2.2 Data cleaning and formatting for supervised ML

Figure 2.2 presents a visual overview of how we performed cleaning and formatting of the data to prepare it for supervised learning.

2.3.4 Feature standardizing and scaling

The predictive model's training/testing trials have been carried out both on standardized and on scaled input data. These data pre-processing steps were deemed necessary, since the input variables have ranges of values which are very dissimilar.

The standardization (z-score normalization) transforms the various data vectors (variables) in such a way that they'll have the properties of a standard normal distribution with $\mu = 0$ and $\sigma = 1$. Standardizing the variables so that they are centered around zero with a standard deviation of 1 is not only important when measurements that have different units are compared, but it is also a general requirement for many machine-learning algorithms, including ANNs. The standardization is performed (ie., the z-score is computed) for every observation $\boldsymbol{x_i}$ of a variable $\boldsymbol{X}$, using the mean $\mu(\boldsymbol{X})$ of the variable and its standard deviation $\sigma(\boldsymbol{X})$.

The data rescaling, on the other, allows for the conversion of the different input variable ranges to a common range, namely [0,1]. Feature data rescaling is performed as follows:

$$x_i = \frac{x_i - x_{min}}{x_{max} - x_{min}} \tag{2.1}$$

In equation 2.1, x_i is the feature value at observation i, x_{min} and x_{max} are the minimum and maximum values of feature $\boldsymbol{X}$, respectively.

For the data involved in this study, feature rescaling yielded better results than feature standardizing on model training and testing performances. Therefore, all the results presented in this paper are the ones obtained via training and testing of the classifiers on the rescaled data (eq. 2.1).

2.3.5 Data Balancing

The data analysis showed a severe imbalance with most SpO_2 at 5min above 92%. This is logical as caregivers want to maintain SpO_2 in normal range during child PICU stay. In such condition, the classifier learns the majority class label (class 3) (Table 2.1) but doesn't learn the minority class labels (classes 1 and 2) [8]. The data balancing process aims to allow the classifier to learn from all class equally. The data balancing process used in this study included a combination of down-sampling and up-sampling techniques: to balance the three classes of the data involved, a down-sampling of the SpO_2 class 3 using TOMEK algorithm [9] and an over-sampling of SpO_2 class 1 and 2 using Synthetic Minority Oversampling Technique (SMOTE) [10] were performed.

The very imbalanced nature of the studied data presented a significant challenge. A data balancing process was required prior to training and classification. As previously mentioned, the range of values of the target variable is binned into three class labels (table 2.1). The severe imbalance in the data is caused by the fact that most observations belonged to the class labelled "3", since most SpO_2 readings happen to be 92% or above. This imbalance in the data causes significant bias in the learning of the various class labels by the classifier. This means that a high classification accuracy would not necessarily be representative of the classification accuracy of any of the various class labels. In simple terms, with such a high degree of data imbalance, the classifier can learn the majority class very well. However, it doesn't get enough samples of the minority class labels to be able to learn them well enough. The data balancing process used in this study included a combination of down-sampling and up-sampling techniques. To balance the three classes of the data involved, a down-sampling of the majority class and an over-sampling of the minority classes were performed.

The down-sampling process was made up of the following steps:

1) TOMEK algorithm used to detect TOMEK links throughout the whole dataset, for all three classes, and remove them. TOMEK links are the links between any two observations considered nearest neighbors, but which belong to different classes, ie., have different class- labels [17]
2) Remainder of points to be removed are selected at random.

The oversampling process consisted of using the Synthetic Minority Oversampling Technique (SMOTE). The SMOTE algorithm, as its name indicates, creates synthetic points between a point and its nearest neighbors (the number of nearest neighbors used for each observation depends on the proportion by which the cardinality of the minority class is to be increased). These synthetic points replace the original points (observations) that belonged to the minority class being oversampled. The fact that the points created by SMOTE are synthetic does not necessarily hinder the generalization capability of the classifier, because all the synthetic points are placed between the original observation and a number k of its nearest neighbors [10]. The creation of synthetic data points by SMOTE can be formulated as follows:

$$x_{syn} = x_i + (x_{knn} - x_i) \times \delta \qquad (2.2)$$

In equation (2.2), x_{syn} represents the synthetic data point, x_i represents the original instance, x_{knn} represents the nearest neighbor data point which is randomly picked among the k nearest neighbors, and δ is a random number in [0,1] which determines the position of the created synthetic data point along a straight line joining the original data point x_i and its chosen nearest neighbor x_{knn}.

Sections 2.3.6 presents the two mathematical models that have yielded the most satisfying results in SpO_2 value predictions, five minutes following any change in at least one of the setting variables.

2.3.6 SpO2 Classification

To identify the best machine learning classification method, we tested various classification models on the four balanced datasets, of which the two (2) that yielded the best results were considered: artificial neural network and bagged complex decision trees.

2.3.6.1 Artificial Neural Network (ANN) Training and Testing

Once the data has been formatted and pre-processed, a machine learning predictive model can be trained on a sub-set of labeled training data. The model is then used to predict the target variable values on a testing subset where the class labels are hidden. We used Artificial Neural Networks (ANN) to make predictions of the SpO_2 variable, based on the values of other variables of interest. The values of the three setting variables and the changes applied to them were also used by the model as predictor variables. Through the function approximation that the ANN performs, it is possible to make predictions of SpO_2 variable, based on the input data.

For SpO_2 classification categories, please refer to table 2.1.

The ANN is trained on a set of training data, using the backpropagation algorithm, as follows:

- It takes in the values of all input variables of interest.
- It tunes its weights and creates a non-linear decision boundary to classify the response. A non-linear decision boundary is necessary to classify a target variable that varies in a non-linear fashion with respect to its explanatory variables, the input variables. In other terms, a non-linear decision boundary is required when the output cannot be reproduced from a linear combination of the inputs, which is very often the case. An activation function, such as the sigmoid, allows to model this nonlinear relationship between the input variables and the target variable. Without an activation function, an ANN only provides a linear transformation, ie., the outputs of a layer multiplied by the weights of their connections with the next layer [3].
- The output (SpO_2) is predicted based on the series of linear transformations followed by the creation of a non-linear decision boundary via the combinations of these transformations with the activation function(s) used.

  The learning algorithm runs through all the rows of data in the training data set and compares the predicted outputs with the target outputs found in the training data set.
- The weights are adjusted via supervised learning, in a manner to minimize the error of predicted SpO_2 vs target SpO_2.
- The process is repeated until the error is minimized.

The training of the ANN is carried out using a portion of the data available (ie., a training set). Once the training is completed, the model is tested on a test set, which is the data that was excluded during the training phase. The test set serves to validate the generalization of the model, meaning its ability to accurately predict output data based on new input data. The results obtained by this method of training/testing are presented in table 2.2.

The ANN classifier was implemented through cycles of forward propagation followed by backward propagation through the network's layers. The backpropagation algorithm is used for performance optimization. It fine-tunes the weights which, initially, are randomly set, so that the error function is minimized. The error function computes the difference between the ANN's output and its expected output, after an input example has been propagated through it. For instance, when the normalized data is presented to the ANN, the 18 inputs whose values are in [0, 1] are presented to the ANN, through the input units. These values, along with a bias value inserted into the ANN as input, are processed through the units with the sigmoid activation function, making up the middle layers of the ANN. Then, an output is produced representing the estimation, or prediction in the set {"1", "2", "3"}, of the SpO_2 value five minutes after the change in settings. The weights of the ANN are modified at each run through the training data, in the aim of minimizing the classification error. The loss function used for classification by the MLP is cross-entropy.

For a given number of classes K > 2, the cross-entropy error can be formulated as shown in eq. 2.3, where $\{\boldsymbol{W}_i\}_i$ is the matrix of weights between the neuron layers, r_i is the target value. y_i is the value generated by the ANN, ie., its output.

$$E^t(\{\boldsymbol{W}_i\}_i|x^t, r^t) = - \sum_i r_i^t \, log \, y_i^t \tag{2.3}$$

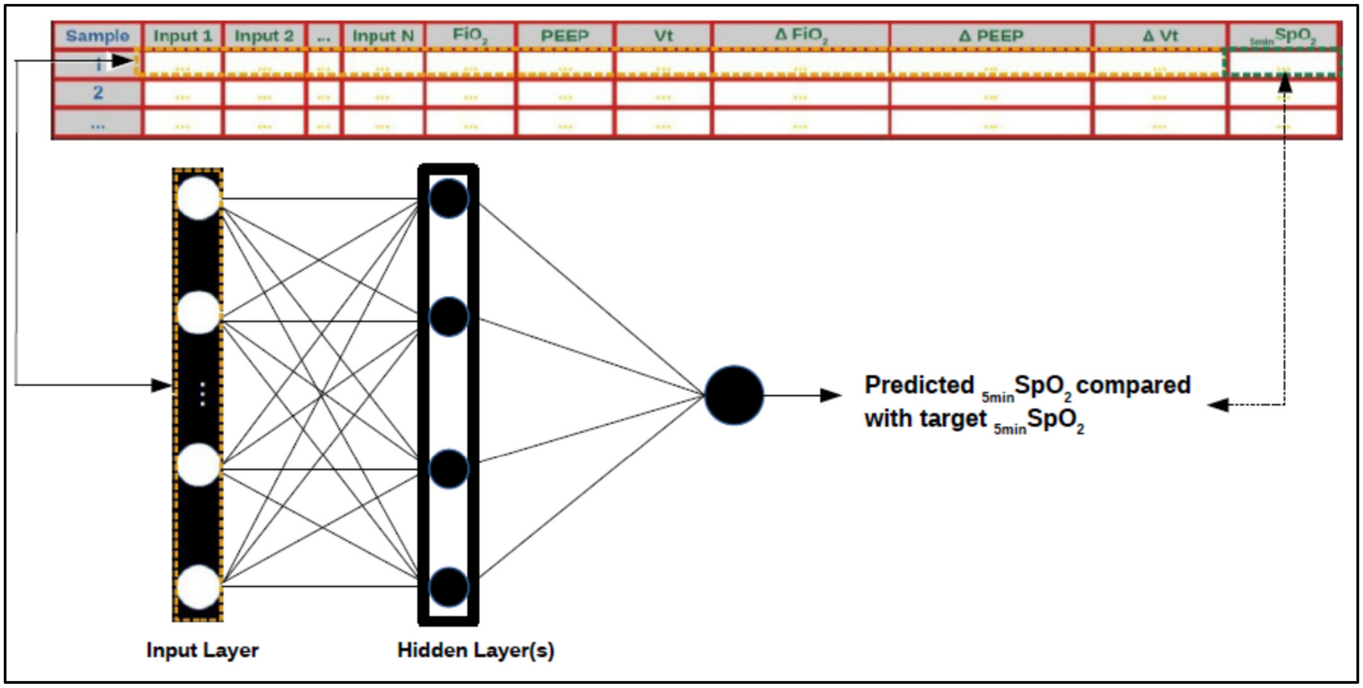
The outputs of the ANN are:

$$y_i^t = \frac{exp\, w_i^t x^i}{\sum_k exp\, w_k^t x^t} \tag{2.4}$$

Using stochastic gradient-descent (SGD) for error minimization, the update rule for the ANN weights, is:

$$\Delta w_{ij}^t = n(r_i^t - y_i^t)x_j^t \tag{2.5}$$

In equation 2.5, η is the learning rate which, when SGD is used, decreases as the error is minimized. During ANN training, each observation, comprised of an input vector and a target output, is denoted ($\boldsymbol{x}^t, \boldsymbol{r}^t$), with $\boldsymbol{r}^t \in$ {"1", "2", "3"}. The reason why the cross-entropy (eq. 2.3) is used instead of the Least Square Error (LSE) is to avoid long periods of training, due to the ANN going through stages of slow error reduction, ie., SGD local minima. The MLP classifiers were implemented with the use of the Scikit-Learn package within the Python programming language [http://scikit-learn.org].



Sample	Input 1	Input 2	...	Input N	FiO_2	PEEP	Vt	Δ FiO_2	Δ PEEP	Δ Vt	$_{5min}SpO_2$
1	...	...	...	...	...	...	...	...	...	...	...
2	...	...	...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...	...	...	...

Predicted $_{5min}SpO_2$ compared with target $_{5min}SpO_2$
Input Layer
Hidden Layer(s)

Figure 2.3 Schematic representation of ANN supervised training

2.3.6.2 Bootstrap Aggregation of complex decision trees training and testing

Bootstrap aggregating (acronym: bagging) was proposed by Leo Breiman in 1994 to improve classification by combining classifications of randomly generated training sets [8]. "Bagging" allows for the creation of an aggregated predictor via the use of multiple training sub-sets taken from the same training set, hence the term "bootstrapping". In other words, multiple versions of a predictor are created through the bootstrapping of the various training subsets. This aggregation of predictors generally allows for more accurate predictions (or classifications) than can be obtained through a single predictor. Thus, it can be considered as a wonderful technique used for improving a classifier's performance. It is noteworthy to mention that this method (bootstrap aggregation or "bagging") doesn't always improve the given classifier's performance, but it does most of the time.

Let $\{\boldsymbol{T^i}\}$ denote the replicate training sub-sets bootstrapped from the training set $\boldsymbol{T}$. These replicate sub-sets each contain N observations, drawn at random and with replacement from $\boldsymbol{T}$. For each of these sub-sets of N observations, a prediction model (classifier) is created. The computational model used for “bagging” was “complex decision trees”. This means that, for each bootstrapped sub-set of training data, a complex decision tree is trained and thus a classifier is created. If $i = 1, \ldots, n$, then n classifiers are created through the “bagging” process.

A decision tree is a flowchart computational model which can be used for both regression and classification problems. Paths from the root of the tree to its various leaf nodes go through decision nodes in which decision rules are applied in a recursive manner, based on values of input variables. Each path represents an observation $(\boldsymbol{X}, y) = (x_1, x_2, x_3, \ldots, x_n, y)$, where the label assigned to the target y is given in the leaf node, at the end of the path (ie., classification).

In the aim of maximizing the model’s generalization capability during the training process, the Bagged Complex Trees’ performance is tested via k-fold cross-validation. A value k = 10, which is common practice, was used in this study. The training using k-fold cross-validation is carried out as described in algorithm 2.1:

Algorithm 2.1 *k*-fold cross-validation

- The data set is first divided into two parts; the training-set and the test-set.
- The training of the “Bagged” Complex Trees includes a *k*-fold cross-validation, which is performed as follows:
  - ➢ Randomly partition the data-set into *k* equal-sized subsets (folds).
  - ➢ For each of the *k* equal-sized subsets:
    - ✓ Train/fit the model on the elements contained in the other (*k*-1) subsets.
    - ✓ Test the model’s accuracy on the given subset.
  - ➢ Iterate over the *k* subsets, until each one has been used once for testing the model’s performance during its training.
  - ➢ The training validation score consists of the average score obtained by validating the model on all *k* subsets.

The mathworks Matlab R2016b Machine Learning toolbox was used for the creation of the ensemble of “Bagged” complex trees model.

2.4 Assessment of performances of classifiers

We evaluated the performances of the classifiers based on the metrics including testing confusion matrix, average accuracy, precision, recall and F score [14] with a $_{5\text{min}}SpO_2$ prediction expected above 0.9 for each class.

- *Test confusion matrix :*

In a confusion matrix, the diagonal made up of the intersections of target and predicted SpO_2 is where the rates of correct classifications are provided.

- *Cohen’s Kappa* (eq. 2.6)

$$K = \frac{p_o - p_e}{1 - p_e} \qquad (2.6)$$

In labeling problems involving a number of class-labels $n > 2$, it is generally appropriate to estimate the agreement between the classifier and ground truth using a statistic known as Cohen’s Kappa (κ), which is in [0, 1], with 1 being perfect agreement and 0, no agreement whatsoever b. In equation 2.6, p_o is the observed agreement and p_e (eq. 2.7) is the hypothetical probability of agreement by chance, based on the distribution of the data among the n classes. In other words, p_e is the agreement expected by chance. In equation 2.7, N is the number of observations, with n_{k1} as the number of times class-label k appears in ground truth, and n_{k2} as the number of times the classifier predicted class-label k, with $k = 1,\ldots,n$.

$$p_e = \frac{1}{N^2} \sum_{k=1}^{n} n_{k1}\, n_{k2} \qquad (2.7)$$

- *Accuracy* (eq. 2.8):

$$Accuracy = \frac{\#\ Correct\ classifications}{Total\ \#\ observations\ in\ dataset} \tag{2.8}$$

- *Precision* (eq. 2.9):

$$Precision\ = \frac{\#\ True\ positives\ class\ i}{Total\ \#\ classifications\ for\ class\ i} \tag{2.9}$$

The *Precision* (eq. 2.9) is the ratio of all correct classifications for class *i* to all instances labeled as class label *i* by the model. In a non-normalized confusion matrix, this would mean dividing the number of instances classified in class label *i* by the total of instances in column *i.*

- *Recall* (eq. 2.10):

$$Recall\ = \frac{\#\ True\ positives\ class\ i}{Total\ \#\ observations\ class\ i} \tag{2.10}$$

Recall (eq. 2.10) is the ratio of the number of instances classified in class label *i* to the number of true class *i* labels. Again, in a non-normalized matrix, this would require dividing the number of instances classified in class label *i* by the total of row *i.*

F1-score (eq. 2.11) :

$$F1 - score = \frac{2}{\frac{1}{recall} + \frac{1}{precision}} \tag{2.11}$$

The *F1-score* (eq. 2.11) provides a single measure of classification performance of the model used. In the case of class-imbalanced datasets, the *F1-score* is better than the accuracy metric, which is simply the ratio of correctly predicted observations to the total number of observations. Mathematically, it is the harmonic mean *H*, computed using *Precision* and *Recall* (eq. 2.12). In equation 2.12, x_1 to x_n represent *n* positive real numbers. For the *F1-score* (eq. 2.11), $n = 2$, x_1 and x_2 are the values of *Precision* and *Recall*.

$$H = \frac{n}{\sum_{i=1}^{n} \frac{1}{x_i}},\ 1 < i < n \tag{2.12}$$

The values of these performance metrics for our eight experiments are presented in table 2.2.

DATASET 1	DATASET 2	DATASET 3	DATASET 4
Training set: 975,036 samples **Test set:** 193,528 samples **Class Balancing:** TOMEK applied to dataset (before dataset has been split into training & test set) to remove tomek links, random undersampling applied to class 3 once dataset is split into training and testing sub-sets, then SMOTE applied to classes 1 and 2 to make their cardinalities equal to that of class 3 (325,012).	**Training set**: 2,293,119 samples **Test set:** 201,926 samples **Class Balancing:** SMOTE applied to classes 1 & 2 to make their cardinalities equal to that of class 3 (764,373).	**Training set**: 487,464 samples **Test set:** 106,028 samples **Class Balancing:** TOMEK applied to dataset (before dataset has been split into training & test set) to remove tomek links, random undersampling applied to class 3 once dataset is split into training and testing sub-sets, then SMOTE applied to classes 1 and 2 to make their cardinalities equal to that of class 3 (162,488).	**Training set**: 1,462,503 samples **Test set:** 281,028 samples **Class Balancing** TOMEK applied to dataset (before dataset has been split into training & test set) to remove tomek links, random undersampling applied to class 3 once dataset is split into training and testing sub-sets, then SMOTE applied to classes 1 and 2 to make their cardinalities equal to that of class 3 (487,501).

Figure 2.4 Details on balancing procedures

Table 2.2 Classification performance metrics results for MLP and bagged tree classifiers

Dataset (figure 2.5) 2.		MLP				Bagged Trees			
		precision	recall	f1-score	Cohen's Kappa	precision	recall	f1-score	Cohen's Kappa
Dataset 1	Label 1	0.12	0.70	0.21	0.16	0.80	0.76	0.78	0.68
	Label 2	0.16	0.43	0.23		0.61	0.56	0.59	
	Label 3	0.96	0.67	0.79		0.97	0.98	0.97	
	Avg/total	0.88	0.65	0.73		0.94	0.94	0.94	
Dataset 2	Label 1	0.09	0.72	0.16	0.13	0.77	0.72	0.74	0.66
	Label 2	0.09	0.47	0.16		0.57	0.53	0.55	
	Label 3	0.98	0.70	0.81		0.98	0.99	0.98	
	Avg/total	0.93	0.69	0.78		0.96	0.97	0.97	
Dataset 3	Label 1	0.16	0.68	0.25	0.20	0.80	0.76	0.78	0.70
	Label 2	0.26	0.42	0.33		0.67	0.62	0.65	
	Label 3	0.92	0.60	0.72		0.95	0.96	0.96	
	Avg/total	0.80	0.58	0.65		0.91	0.91	0.91	
Dataset 4	Label 1	0.09	0.69	0.16	0.13	0.80	0.74	0.77	0.66
	Label 2	0.12	0.47	0.19		0.58	0.54	0.56	
	Label 3	0.97	0.68	0.80		0.98	0.98	0.98	
	Avg/total	0.92	0.67	0.76		0.96	0.96	0.96	

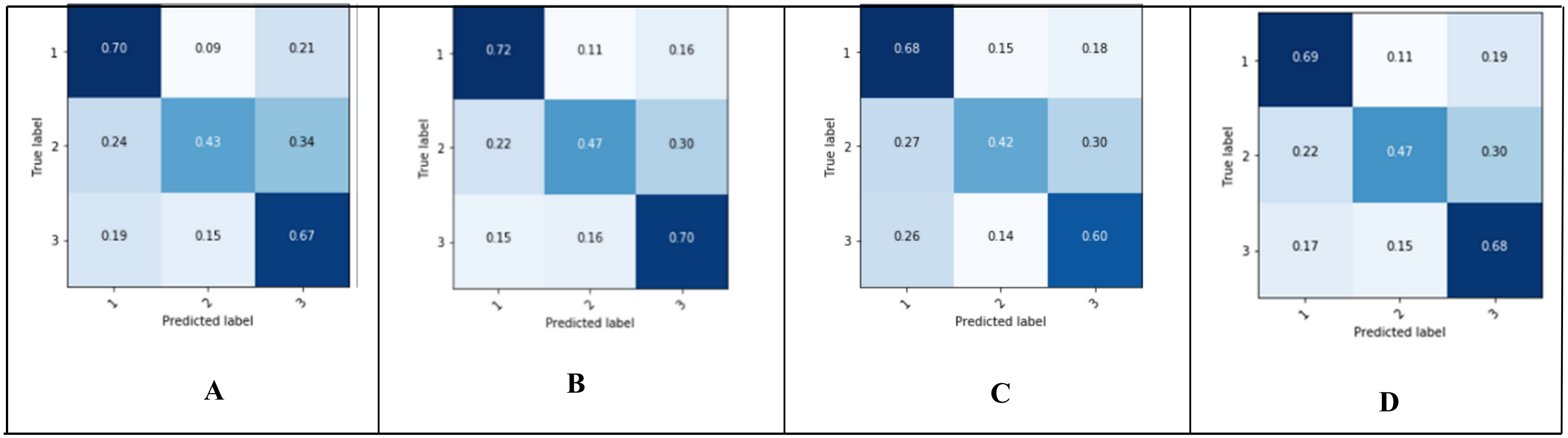


Figure 2.5 MLP test confusion matrices from training/testing (**A**: dataset 1, **B**: dataset 2, **C**: dataset 3, **D**: dataset 4)

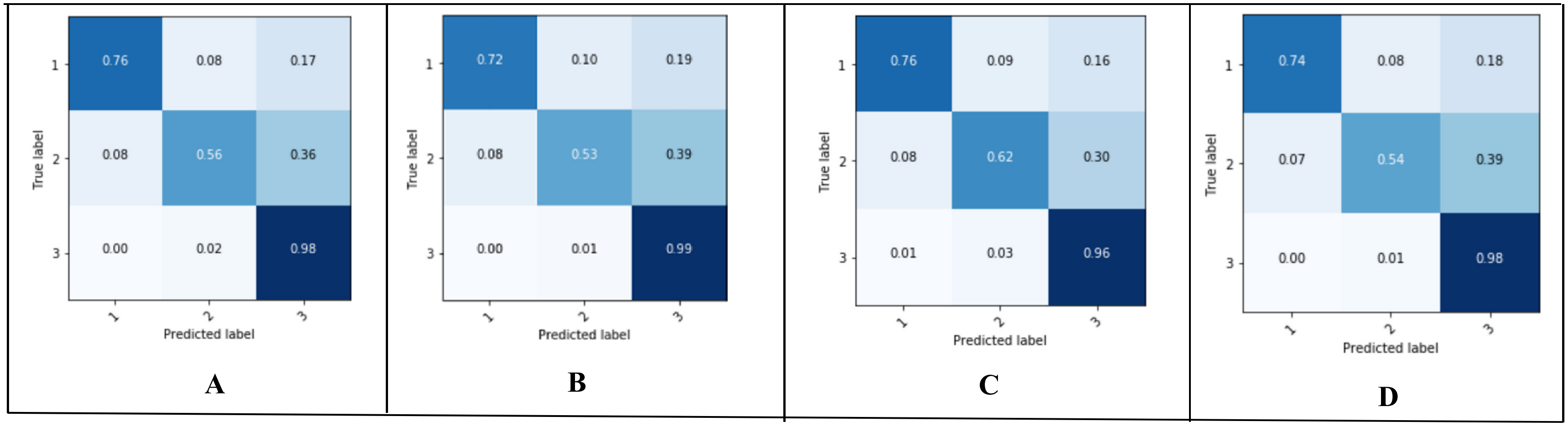


Figure 2.6 Bagged trees test confusion matrices from training/testing (**A**: dataset 1, **B**: dataset 2, **C**: dataset 3, **D**: dataset 4)

For the ANN, or MLP, the variation of the number of hidden layers and number of neurons per hidden layer did not seem to have a significant effect on the model's classification performance. As for the Bagged complex trees, the variation of the number of complex trees did not yield significant changes in classification performance. However, the experiments revealed that the data balancing processes had significant influence on SpO_2 classification accuracy.

As the classification metrics and the confusion matrices presented in table 2.2 and figures 2.5 and 2.6 reveal, the ensemble of bagged complex trees model has performed significantly better than the ANN. The darker colors in a confusion matrix represent the higher levels of accuracy obtained. According to what has been previously mentioned in the "related work" section regarding Bagging being generally a successful technique for medical data classification [8], it is not surprising that tree Bagging fared better than the other classifiers used in this study. It is noteworthy however to mention that the gaps in performance results between the training and testing confusion matrices are relatively higher in the case of bagged trees model than in that of the MLP. This seems to indicate that, although the bagged trees model was capable of learning very well from the data, there's still room for improvement in the generalization, especially for class-label "2" data.

The classification performance metrics (table 2.2) show that the bagged trees classifier trained on dataset #3 has yielded the best classification performance on the test sets. The interpretation of the results of this training/testing is provided in the following paragraphs.

In equation 2.6, p_o is the relative observed agreement among raters, or the ground truth labels and the classifier's labels, and p_e (eq. 2.7) is the hypothetical probability of chance agreement, using the observed data to calculate the probabilities of each observer randomly picking each class. If the raters are in complete agreement, then $\kappa = 1$. If there is no agreement among the raters other than what would be expected by chance, as given by p_e, $\kappa \approx 0$. This would simply mean that the classifier being tested is useless for classifying the given data. A value of **0.70** for the Cohen's Kappa statistic was obtained by the bagged trees model trained on training set #3. This is representative of the rate of agreement between the two raters, or between ground truth labels and a machine learning predictive model. In equation 2.7, n is the number of classes, N is the number of instances classified by each rater which, in our case, is ground truth vs classifier, and n_{ki} represents the number of times rater i predicted class label k. The confusion matrix of the ensemble of bagged trees shows that it could correctly classify **76%** of class- label "1" data, **62%** of class-label "2", and **96%** of class-label "3". This considerable variation in classification performances of the three class labels can be explained by the huge variation in the numbers of observations available for each of the class labels in the data used in this study. Refer to section *A* for details on patient sub- population studied.

The SMOTE algorithm is designed in such a way that should theoretically not affect the generalization of the trained model. In cases of extreme data imbalance, however, as is the case in this study, the over-sampling within the data space of a given minority class label, used for increasing the cardinality of the class label's set, is also likely to be extreme. This may render the data space of this class relatively dense with respect to the rest of the data, made up of real data points of the studied patient sub-population. This may potentially explain the classification model's relatively poor generalization for class-labels "1" and "2" with respect to the generalization for class-label "3". Another important consideration to make, in an attempt to explain the hindering effect that the over-sampling seems to have on the generalization of the classifier, is the following: since SMOTE generates synthetic data points by interpolating between existing minority class instances, it can obviously increase the risk of over-fitting when classifying minority class labels, since it may duplicate minority class instances, ie., data points. The fact that the training confusion matrix shows extremely high classification performances for the minority class labels "1" and "2", as opposed to those shown in the testing confusion matrix, suggests that the over-sampling of the minority class labels using SMOTE could have caused some overfitting for these classes, but this would have to be further investigated.

The *accuracy* (eq. 2.8) of the ensemble of bagged complex trees in classifying SpO_2 for dataset #3 is **91%**. This metric is very misleading, as it does not consider the imbalance in the numbers of instances of each of the three (3) class labels. This high accuracy (**91%**) can be, in a considerable part, explained by the fact that class-label "3" makes up **83%** of all instances in the testing dataset, and that **96%** of class-label "3" data are correctly classified. In other terms, there are **84,171** correct classifications for class-label "3" alone, out of **106,028** observations in the test set. The total number of correct classifications for all 3 class-labels is **96,667** out of a total number of observations of **106,028**, ie., an accuracy of **91%**. It is thus easy to see why this percentage of correct classifications is not representative of the model's accuracy in classifying the data of the three (3) classes involved. Clearly, the *accuracy* metric is not reliable for the evaluation of the performance of our model, hence the importance of the other metrics presented herein.

The *F1-score* for our model reveals that the model performed very well when predicting class-label "3". Although the model also performed significantly well for class-label "1", some over-fitting seems to have occurred for classes "1" and "2", the minority classes, during the training phase. Therefore, some recommendations for improvement in classification accuracy for the minority classes will be provided in the following section.

2.5 Results and Discussion

We developed and assessed the performances of two machine learning classifiers on four different balanced datasets to predict SpO_2 at 5 min after a ventilator setting change (*ie* FiO_2, PEEP, Vt/Pressure), in 610 mechanically ventilated children. In Fig 4 and Table 2.2, we report the performances of these two classifiers. Using the classification performance metrics, the bagged trees classifier trained on dataset #3 (see Fig 2.2) has yielded the best classification performance on the test sets (Table 2.2). The confusion matrix of the whole bagged trees shows that SpO_2 at 5 min could correctly predict in 76% of class "1" data, 62% of class "2", and 96% of class "3" (Fig 2.4). This huge variation in classification performances of the three class labels can be explained by the large variation in the numbers of observations available for each of the class-labels in the initial dataset that has limited the machine learning (Table 2.1).

Table 2.3 Absence of impact on performance of the increase of neurons and hidden layers for artificial neural network (ANN). Example of the performance assessed by the F score on the balanced dataset 3 (see fig 2.2)

ANN										
Hidden layers (n)		1			2			3		
Neurons/hidden layer (n)		10	50	100	10	50	100	10	50	100
F-score	$_{5min}SpO_2$ class 1	25	25	25	25	25	25	22	22	19
	$_{5min}SpO_2$ class 2	33	33	33	33	33	33	33	33	32
	$_{5min}SpO_2$ class 3	72	72	72	72	72	72	69	69	69

Table 2.4 Absence of impact on performance of the number of complex trees for bootstrap aggregation of complex decision trees (BACDT). Example of the performance assessed by the F score on the balanced dataset 3 (see Fig 2.2)

		BACDT	
		n = 30	n=50
F-score	$_{5min}SpO_2$ class 1	78	78
	$_{5min}SpO_2$ class 2	65	65
	$_{5min}SpO_2$ class 3	96	96

In agreement with previous studies regarding bagging being a better method for medical data classification, tree Bagging fared better than the artificial neural network used in this study [12]. It is noteworthy however that the gaps in performance results between the training and testing confusion matrices are relatively higher in the case of bagged trees model than in that of the artificial neural network (Fig 2.5). This seems to indicate that, although the bagged trees model was capable of learning very well from the data, there's still room for improvement in the generalization. The SMOTE algorithm is designed in such a way that should theoretically not affect the generalization of the trained model. In cases of extreme data imbalance, however, as is the case in this study, the over-sampling within the data space of a given minority class label, used for increasing the cardinality of the class label's set, is also likely to be extreme. This may render the data space of this class relatively dense with respect to the rest of the data, made up of real data points of the studied patient sub-population. This may potentially explain the classification model's relatively poor generalization for ${}_{5min}SpO_2$ class "1" and "2" with respect to the generalization for ${}_{5min}SpO_2$ class "3". Also, since SMOTE generates synthetic data points by interpolating between existing minority class instances, it can obviously increase the risk of over-fitting when classifying minority class labels, since it may duplicate minority class instances. The fact that the training confusion matrix shows extremely high classification performances for the minority ${}_{5min}SpO_2$ class "1" and "2", as opposed to those shown in the testing confusion matrix, suggests that the over-sampling of the minority ${}_{5min}SpO_2$ class using SMOTE could have caused some overfitting for these classes, but this would have to be further investigated.

The strengths of this study include a large clinical database of mechanically ventilated children used with more than 7.10^5 rows. In a recent similar study in PICU, 200 patients were included with $1.15.10^3$ rows [15]. However, the volume of data is clearly insufficient. To use such machine learning predictive models, the pediatric intensive care community needs to combine multicenter high-resolution database. In addition, children data could be pooled to neonatal and adult intensive care data, when possible, such as MIMIC III database [16]. The other strength is the process used to transform the data into a usable format and to correct a variety of artifacts. In health care, there is a significant interest in using clinical databases including dynamic and patient-specific information into clinical decision support algorithms. The ubiquitous monitoring of critical care units' patients has generated a wealth of data which presents many opportunities in this domain. However, when developing algorithms domains, such as transport or finance, data are specifically collected for research purposes. This is not the case in healthcare where the primary objective of data collection systems is to document clinical activity, resulting in several issues to address in data collection, data validation and complex data analysis [17]. A significant amount of effort is needed, when data have been successfully archived and retrieved, to transform the data into a usable format for research.

This study has several limitations. The limited row number reduced the SpO_2 classification for machine learning predictive model to three clinically relevant classes. SpO_2 is a continuous variable and the use of three class is probably insufficient, especially when high SpO_2 range is suggested as potentially harmful [18, 19]. Instead of the classification model, the next step could be to test regression models' performance. SpO_2 was predicted at 5min after ventilator setting change, a clinically relevant delay. However, the delay between ventilator setting change and oxygenation steady state is not well defined and vary from 1 to 71 minutes according to the parameter set (FiO_2, PEEP or other parameters that change mean airway pressure) and clinical conditions studied [15, 20, 21]. This needs further research and probably more sophisticated clinical decision support systems using machine learning predictive models should consider these factors. Finally, we excluded hemodynamic unstable patients using a treatment criteria (≥ 2 vasoactive drugs infused) because this condition decreases pulse oximeter reliability [22, 23]. The validation and electronic availability of reliable markers of hemodynamic instability in children such as plethysmographic variability indices could be helpful [24].

2.6 Conclusion

This pilot study using machine learning predictive model resulted in an algorithm with good accuracy. To obtain a robust algorithm with such a method, more data rows are needed, suggesting the need of multicenter pediatric intensive care high-resolution databases.

2.7 Acknowledgment

We would like to thank Mr. Redha Eltaani for his support in all tasks related to data access at Ste-Justine Hospital. This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), by the Institut de Valorisation des Données (IVADO), by grants from the "Fonds de Recherche du Québec – Santé (FRQS)", the Quebec Ministry of Health and Sainte Justine Hospital.

CHAPTER 3
GENERAL CONCLUSION AND FUTURE WORK

The aim of this study was to create a model that would provide predictions of the SpO_2 variable, using the data of other biological variables as well as the changes in the setting variables (oxygen concentration (FiO_2) setting, Positive End-Expiratory Pressure (PEEP) setting and Tidal Volume setting). The ultimate objective of this undertaking was to find a way to exploit PICU mechanical ventilation research data via supervised machine learning to model SpO_2 behavior, based on other biological variables and any setting changes made by the clinician. Various supervised machine learning algorithms have been trained on the available data. The models built via the algorithm training process, were used to label (classify) the SpO_2 variable for all the observations (instances) provided in a test set made up of data which were not presented to the model during the supervised training. The target variable (SpO_2) was discretized (binned) into three (3) class-labels. The classifiers tested on the data, the Artificial Neural Network (ANN) and the Bootstrap Aggregation of complex decision trees ("Bagged" Trees) yielded the most satisfactory results. Of these two classifiers, the latter was the final choice, as it clearly outperformed the ANN.

The severe imbalance of the data required the incorporation of data balancing procedures in the study. The ANN and ensemble of Bagged trees were trained and tested, each on four different datasets, obtained from four different data balancing procedures. We used performance metrics which were deemed informative in the context of the study to evaluate and compare the SpO_2 classification performances of the various machine learning models tested. The results of this study have proven to be very promising and have thus revealed that supervised machine learning can effectively be used to provide the ICU medical practitioners with support in estimating SpO_2 reactions to setting changes, given the states of other biological data.

Some significant contributions were made throughout this research project, namely:

- To render the available ventilatory data compatible with machine learning supervised training methods, a data formatting process was proposed.
- Large amounts of data from an ICU research database were exploited for SpO_2 prediction via machine learning classification models, which, as per the literature reviewed, doesn't seem to have been done up to this date.
- To counter the imbalanced nature of the data, various combinations of different data balancing techniques were proposed.
- Supervised machine learning algorithms were proposed for attempting to extract knowledge from large amounts of patient mechanical ventilation data in the aim of predicting the behavior of SpO_2, based on values of other variables and those of any setting changes made by the clinician.

Considering that this was a first attempt to create a model for SpO_2 classification via machine learning supervised training, the results obtained can be deemed satisfactory from a perspective of providing some medical support in the decision-making process involved. However, a few different approaches to this problem could be considered in the aim of improving prediction performance.

Various approaches and methods may be considered, in the aim of improving SpO_2 classification, or prediction in the case of regression models. The undertaking which seems the least challenging would be to attempt reducing the over-fitting, which is potentially the cause for classification performances which can be considered relatively poor for class-labels "1" and "2", with respect to that of class-label "3". This could be achieved by one or more approaches.

One approach would be to try different class balancing algorithms and combinations of algorithms, from those applied and presented in this study. Instead of class balancing, some class-weighted training models can be tested. These are called *cost-sensitive classifiers*.

Examples of such classifiers are the *cost-sensitive decision tree and cost-sensitive Support Vector Machine (SVM)*. Bootstrap-based SVM aggregation could also be a viable option.

Any ML model which would increase or, at the very least, maintain the classification performance presented in this document, while also allowing a number of class-labels greater than three (3) for the SpO_2 variable, would be worth implementing. With what has just been said in mind, we propose that Deep Learning (DL) models which can create abstract representations of the patient's respiratory state through time are to be prioritized for future work. DL models would very likely yield greater predictions and eliminate one of the main challenges that our approach brought with it, namely the data class-imbalance as well as the need for class-labelling. For this purpose, we specifically propose the use of DL models designed to be trained on sequences of data which are represented through time. Intuitively, DL architectures that can create a representation of the context within which a data point at a given time-step t_i seem to make the most sense. For instance, Recurrent Neural Networks (RNN) with Bi-Directional Long Short-Term Memory (Bi-LSTM) would take into account historical data at time-steps t_{i-n}, …, t_{i-n} with respect to any time-step t_i as well as data at t_{i-n}, …, t_{i+n}.

This allows it to render representations of underlying spatial variable relations through time, which makes sense for biomedical data.

The RNN/LSTM approach would make it possible to predict future values of the setting variables instead of the effect of setting change on SpO_2. With the implementation of a CDSS in mind, this approach seems very appropriate.

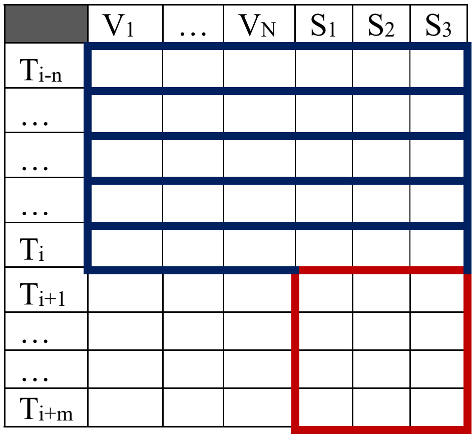
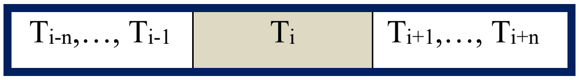


Figure 3.1 Data arrangement for RNN/Bi-LSTM sequence generation for setting variables; prediction of *m* time-steps for setting variables, given *n* past time-steps of all input variables, which include the setting variables

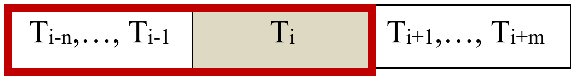
As shown in figure 3.1 above, the goal would be for the model to be able to predict *m* time-steps of S_1, S_2, S_3, the setting variables, given the data points for time-steps T_{i-n} to T_i. Every data point would include all variables available, including SpO_2 as well as all setting variables. This is important because any variable, however unimportant it may be deemed by any expert, may in reality contribute valuable information in high-dimensional space and through time, which cannot be visualized by the human mind.

The training of the RNN/Bi-LSTM neural network would likely allow for significantly better spatial representation of the data than a feedforward ANN or any classifier incapable of representational learning due to absence of memory units. The Bi-LSTM allows the model to create abstract representations of the data, preserving a memory of a representation for a given number of past time-steps. Moreover, the Bi-directional property allows the model to learn a data point at time-steps T_i, considering past and future data points. This means that for every training epoch, a sliding window trains the ANN on a data point, considering given number of past time-steps as well as future ones (see fig. 3.2)



$T_{i-n},\ldots, T_{i-1}$	T_i	$T_{i+1},\ldots, T_{i+n}$

Figure 3.2 Sliding window for RNN/Bi-LSTM; learning data point at time-step T_i based on past as well as future data



$T_{i-n},\ldots, T_{i-1}$	T_i	$T_{i+1},\ldots, T_{i+m}$

Figure 3.3 Prediction of a sequence of *m* data points by RNN/Bi-LSTM given data point at time-step T_i and its *n* past data points

Figure 3.4 below shows a simple representation of how an RNN/Bi-LSTM model would be used for the considered application.

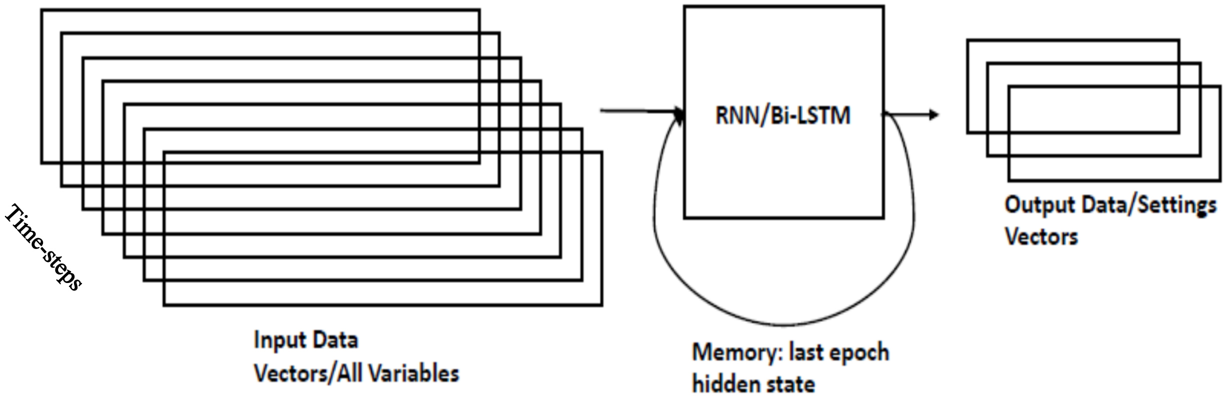


Figure 3.4 RNN/Bi-LSTM for setting variable sequence predictions

LIST OF BIBLIOGRAPHICAL REFERENCES

1. Rose L, Schultz M, Cardwell C, Jouvet P, McAuley D, Blackwood B. Automated versus non-automated weaning for reducing the duration of mechanical ventilation for critically ill adults and children: a cochrane systematic review and meta-analysis. Crit Care. 2015;19:48. doi: 10.1186/s13054-015-0755-6.

2. Jouvet P, Eddington A, Payen V, Bordessoule A, Emeriaud G, Gasco R, et al. A pilot prospective study on closed loop controlled ventilation and oxygenation in ventilated children during the weaning phase. Crit Care. 2012;16(3):R85. doi: 10.1186/cc11343.

3. Flechelles O, Ho A, Hernert P, Emeriaud G, Zaglam N, Cheriet F, et al. Simulations for mechanical ventilation in children: review and future prospects. Crit Care Res Pract. 2013;2013:943281. doi: 10.1155/2013/943281.

4. Brossier D, El Taani R, Sauthier M, Roumeliotis N, Emeriaud G, Jouvet P. Creating a High-Frequency Electronic Database in the PICU: The Perpetual Patient. Pediatr Crit Care Med. 2018;19(4):e189-e98. doi: 10.1097/PCC.0000000000001460.

5. Cakar N, Tuŏrul M, Demirarslan A, Nahum A, Adams A, Akýncý O, et al. Time required for partial pressure of arterial oxygen equilibration during mechanical ventilation after a step change in fractional inspired oxygen concentration. Intens Care Med 2001;27(4):655-9.

6. Pediatric Acute Lung Injury Consensus Conference G. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16(5):428-39. doi: 10.1097/PCC.0000000000000350.

7. Les recommendations des experts de la SRLF. Le monitorage et les alarmes ventilatoires des malades ventilés artificiellement. Réanim Urgences. 2000;9:407-12.

8. Chawla N, Japkowicz N, A. Kotcz A. Editorial: special issue on learning from imbalanced data sets. ACM SIGKDD Explorations Newsletter. 2004;6:1-6.

9. Elhassan T, Aljurf M, Al-Mohanna F, Shoukri M. Classification of Imbalance Data using Tomek Link (T-Link) Combined with Random Under-sampling (RUS) as a Data Reduction Method. Journal of Informatics and Data Mining. 2016;1:1-12.

10. Chawla N, Bowyer K, Hall L, Kegelmeyer W. SMOTE: Synthetic Minority Over-sampling Technique. Journal of Artificial Intelligence Research. 2002;16:321-57. doi: 10.1613/jair.953.

11. Gnana Sheela K, Deepa S. Review on methods to fix number of hidden neurons in neural networks. Mathematical Problems in Engineering. 2013;2013:11. doi: 10.1155/2013/425740.425740.

12. Breiman L. Bagging predictors. Berkeley: University of California, Statistics Do; 1994 421.

13. Safavian S, Landgrebe D. A survey of decision tree classifier methodology. IEEE Transactions on Systems, Man, and Cybernetics. 1991;21(3):660-74. doi: 10.1109/21.97458.

14. Sokolova M, Lapalme G. A systematic analysis of performance measures for classification tasks. Information Processing & Management. 2009;45(4):427-37. doi: 10.1016/j.ipm.2009.03.002.

15. Smallwood CD, Walsh BK, Arnold JH, Gouldstone A. Equilibration Time Required for Respiratory System Compliance and Oxygenation Response Following Changes in Positive End-Expiratory Pressure in Mechanically Ventilated Children. Crit Care Med. 2018;46(5):e375-e9. doi: 10.1097/CCM.0000000000003001.

16. Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, et al. MIMIC-III, a freely accessible critical care database. Sci Data. 2016;3:160035. doi: 10.1038/sdata.2016.35.

17. Johnson AE, Ghassemi MM, Nemati S, Niehaus KE, Clifton DA, Clifford GD. Machine Learning and Decision Support in Critical Care. Proceedings of the IEEE Institute of Electrical and Electronics Engineers. 2016;104(2):444-66. doi: 10.1109/JPROC.2015.2501978.

18. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial. JAMA. 2016;316(15):1583-9. doi: 10.1001/jama.2016.11993.

19. Pannu SR, Dziadzko MA, Gajic O. How Much Oxygen? Oxygen Titration Goals during Mechanical Ventilation. Am J Respir Crit Care Med. 2016;193(1):4-5. doi: 10.1164/rccm.201509-1810ED.

20. Tugrul S, Cakar N, Akinci O, Ozcan PE, Disci R, Esen F, et al. Time required for equilibration of arterial oxygen pressure after setting optimal positive end-expiratory pressure in acute respiratory distress syndrome. Crit Care Med. 2005;33(5):995-1000.

21. Fildissis G, Katostaras T, Moles A, Katsaros A, Myrianthefs P, Brokalaki H, et al. Oxygenation equilibration time after alteration of inspired oxygen in critically ill patients. Heart Lung. 2010;39(2):147-52. doi: 10.1016/j.hrtlng.2009.06.009.

22. Salyer J. Neonatal and pediatric pulse oximetry. Respir care. 2003;48(4):386-96.

23. Fouzas S, Priftis KN, Anthracopoulos MB. Pulse oximetry in pediatric practice. Pediatrics. 2011;128(4):740-52. doi: 10.1542/peds.2011-0271.

24. Chandler JR, Cooke E, Petersen C, Karlen W, Froese N, Lim J, et al. Pulse oximeter plethysmograph variation and its relationship to the arterial waveform in mechanically ventilated children. J Clin Monit Comput. 2012;26(3):145-51. doi: 10.1007/s10877-012-9347-z.