UNIVERSITAT DE BARCELONA

Final Degree Project

Biomedical Engineering Degree

Study and prediction of time of recovery of consciousness after general anaesthesia

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ABSTRACT

Several studies address the process of loss of consciousness during the induction of general anaesthesia, but few of them discuss or study the process of recovery of consciousness once the of general anaesthesia has been administered successfully. The main objective of this project is to study and develop a predictive model of the duration of this process of consciousness recovery based on Machine Learning (ML) and the analysis of electroencephalographic (EEG) signals.

A dataset comprising 143 patients from the 4th operating room of the Hospital Clínic of Barcelona was analysed. The project involved data pre-processing, including the segmentation of EEG signals during the recovery process, feature extraction, and correlation analysis. Five ML regression algorithms, namely Linear, Lasso, and Ridge Regression, Support Vector Regression (SVR), and Random Forest (RF), were evaluated using a Cross-Validation pipeline. Model performance, feature selection, and hyperparameter optimization were assessed using the R-squared score criterion.

The best performing algorithm was the regularized linear regression model, Lasso, achieving an R-squared score of 0.74 ± 0.032 (mean and standard deviation). Through the correlation analysis and the feature selection performed by the algorithm, high predictive capabilities of consciousness recovery time were obtained for alpha and beta relative averaged band power in the first minute before stopping general anaesthesia administration. The findings demonstrate that EEG signals contain valuable information regarding the process of consciousness recovery, enabling the construction of ML predictive models.

However, further studies are required to enhance our understanding of the consciousness recovery process and to validate the predictive model in a clinical setting. Future investigations should focus on increasing data variability, addressing biases in validation techniques, exploring additional EEG channels to capture global brain activity, and considering regulatory considerations for Artificial Intelligence algorithms.

Keywords: General anaesthesia, Anaesthesia monitoring, Consciousness Recovery Process, Electroencephalogram, Predictive model, Machine Learning.

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LIST OF ABBREVIATIONS

AI	Artificial Intelligence
BIS	Bispectral Index
BP	Blood pressure
CE	Effect-Site Concentration
CEIC	Ethics and Clinical Research Committee
CMA	Major Ambulatory Surgery
CT	Target Concentration
DL	Deep Learning
DT	Decision Tree
ECG	Electrocardiography
EEG	Electroencephalography
EMG	Electromyography
FFT	Fast Fourier Transform
GB	Gradient Boosting
IQR	Interquartile Range
LMA	Laryngeal Mask Airway
LR	Linear Regression
MAE	Mean Absolute Error
ML	Machine Learning
MLR	Multiple Linear Regression
MSE	Mean Squared Error
NCC	Neural Correlates of Consciousness
NIBP	Non-invasive arterial blood pressure
NN	Neural Networks

PERT	Programme Evaluation and Review Technique
PiCCO	Pulse Contour Cardiac Output
PR	Polynomial Regression
RF	Random Forest
SaMD	Software as a Medical Device
SEF	Spectral Edge Frequency
SQI	Signal Quality Index
SPEC-M	Systems Pharmacology Effect Control and Modelling research group
SVD	Singular Value Decomposition
SVM	Support Vector Machine
SVR	Support Vector Regression
TCI	Target Controlled Infusion Systems
TEE	Transoesophageal Echocardiography
TIVA	Total Intravenous anaesthesia
XGBoost	Extreme Gradient Boosting
WBS	Work Breakdown Structure

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INTRODUCTION

Anaesthesia is a medical process that protects patients from the aggression that represents surgery including inducing unconsciousness and avoiding the perception of painful stimulation, during surgery or other kind of medical procedures. Large numbers of life-saving surgical procedures nowadays would not be possible without general anaesthesia (1). General anaesthesia is a reversible and controlled state of unconsciousness and analgesia (2).

Loss of consciousness is induced with specific drugs called hypnotics to diminish the awareness of the patient regarding the procedure and complements the absence of response to noxious (painful) stimulation induced by powerful analgesic drugs such as opioids. Although the drugs used are highly controllable and their effects are powerful but fast in both onset and offset, there is uncertainty regarding the process of loss and recovery of consciousness. To control the process, anaesthesiologists use the measurement of the activity of the brain through the electroencephalogram (EEG). Once the surgery is finished drug administration stops and the recovery process starts, although with a significant degree of uncertainty regarding recovery of consciousness because the mechanisms depend totally on the patient and the anaesthesiologist can only wait for signs of recovery.

This project has been developed in collaboration with the Systems Pharmacology Effect Control and Modelling (SPEC-M) research group at the Department of Anaesthesiology at Hospital Clínic de Barcelona. The objective of the present project is to define specific features in the continuum of EEG waves that could anticipate and predict that the patient is ready to recover consciousness: opening the eyes, able to breath (discontinuation of mechanical ventilation) and able to respond to simple verbal commands. To do so, the characterization of patterns of recovery of consciousness in the EEG will be studied and machine learning tools will be used to predict the time to recovery.

The study aims to characterise the patterns of recovery of consciousness after general anaesthesia in electroencephalographic signals and to predict this recovery time using machine learning (ML) tools.

Objective

The main objective is to **study and predict the time of recovery of consciousness once anaesthetic drugs have been stopped**. This study based on the analysis of EEG signals of different patients looks for certain characteristics or factors that alter or affect this time and ultimately allow the prediction of the consciousness recovery.

This project enables further knowledge to be gained about this transitional period in the recovery of consciousness. At the same time, it may also allow the understanding of the most determinant factors of such process. This study may contribute to improve the protocols of use for guiding the anaesthesia procedure, including recovery of consciousness and to understand how to improve the experience of the patient.

Both physiological knowledge of the state of consciousness and ML computer science will be applied to the development of this final degree project.

In order to achieve the main goal of this project, different tasks must be defined, and more specific objectives are required.

Regarding Biomedical Engineering research on the topic:

- Bibliographic research about general anaesthesia and the definition of consciousness from a clinical physiological and pharmaceutical point of view.

- Research will also be carried out about the current State of Art of patient monitoring during general anaesthesia

- Review and enhance knowledge of statistics, ML and data analysis. Being able to program ML predictive models in the present study based on my skills of gathering information on the basis of ML, statistics, data analysis and feature extraction behind these models.

Regarding data analysis and the development of the predictive model from an already existing database belonging to the SPEC-M group:

- Elaborate a program for adequate data processing, including EEG signals pre-processing.

- Data analysis and feature extraction to determine the most relevant parameters for conscious recovery prediction.

- Time of conscious recovery after general anaesthesia prediction program. Create various ML models to determine which is the most accurate, taking into account which one performs better.

- Ultimately, the selected prediction model has to be tested on a variety of patients in order to determine how it would behave and operate if tested on actual patients.

Methodology and Workflow

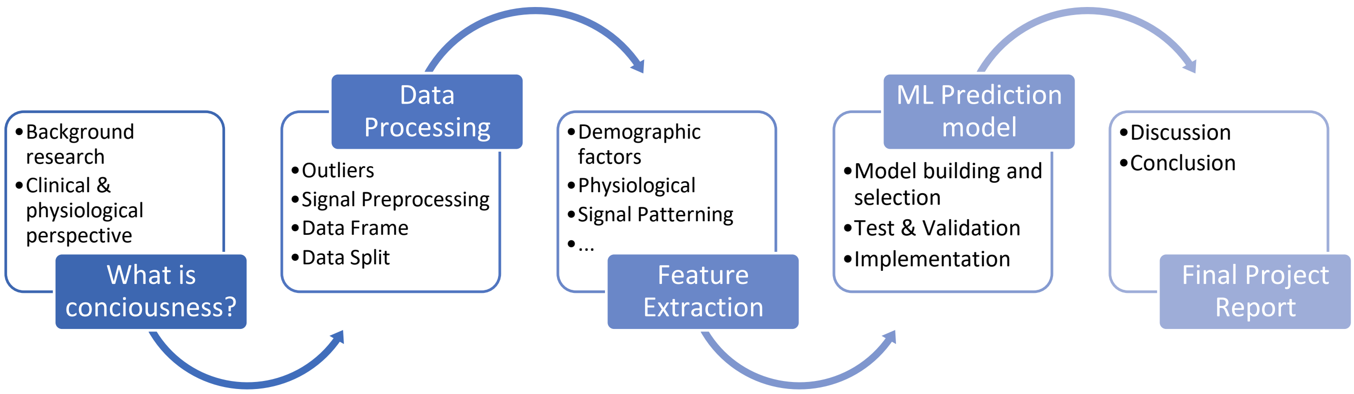


***Figure 1:** Methodology workflow of the overall Final Degree Project.*

The total duration of this Final Degree Project will be 4 months including all the preliminary stages of developing the first general idea, initial planning and extensive research in the field together with the subsequent stages of project implementation. The execution phase of the project is divided into several tasks, which in turn are grouped into different stages as described in **Figure 1**.

The first stage of the project has consisted in initial bibliographical research into general anaesthesia and the definition of consciousness from a clinical and physiological perspective. It has not only been important to perform bibliographic research about these topics, but also, into ML introduction basics and algorithms, as well as an extent market analysis of all these topics. This research has been combined with a weekly stay at the major ambulatory surgery (CMA) operating room. This preview has provided me with the essential knowledge for continuing with the study in the following stages.

In the second stage of the project, a processing of the database was performed in Python scripts using Anaconda's environment. Unrelated data of the database was removed, as well as analysed the characteristics and distribution of the extracted data. The program is also prepared to perform the pre-processing of the various EEG signals.

Subsequently, the third stage includes the extraction and selection of different features of the pre-processed EEG signals. All the data and features extracted from these signals are analysed and selected the most relevant ones for the study. The program is also able to structure all the parameters in a suitable way for the following stage.

The fourth stage involves the elaboration of the ML predictive models. A new Python script is developed in order to implement different ML models. An exhaustive analysis and comparison are performed with the aim of selecting the model presenting a better performance and accuracy. The chosen model is next tested and validated with a large number of patients to simulate its real-life behaviour. For further projects, the final goal will be implementing this model for clinical use.

Finally, the fifth stage consists in the evaluation and discussion of the results obtained during the project, the writing of the definitive draft and the conclusion of the Final Degree Project.

Scope and Span

From an initial idea to a final project, the most detailed and extensive definition as possible of the project is essential. A proper definition of the project is given by well-defined and clearly expressed objectives. Another key aspect in this process is to make extensive research of the current state of the art related to the prediction of the recovery of consciousness after the administration of general anaesthesia. In case related projects exist, it is important to review their characteristics, as well as their limitations and their current clinical use.

Following the market analysis, the draft project contains sections on how to manage the project. The project management consists of a detailed planning of the project execution to ensure maximum efficiency and optimal conditions. The execution is divided into different tasks, in which it is important to adequately define their completion times, costs and deadlines. With these tasks we can generate a GANTT diagram to visualise the time schedule of the project execution.

Once the planning process has been completed, the project background has been studied and the current state of the art in the area has been analysed, the different tasks defined involving the final goal of this final degree project can proceed. The execution process begins with the processing of the data obtained in the surgical room, and it is worth highlighting the performance of an appropriate pre-processing task for the electroencephalographic signals. Subsequently, a study of the characteristics of this type of signals will be conducted and the most relevant features of the signals will be selected to build different ML models. The performance of each one of the models will be evaluated according to its ability to determine the time of recovery of consciousness and an evidence-based selection will be made of the most favourable one. The resulting model will then be tested and validated with multiple patients.

Finally, the comparison of the resources and deadlines established in the planning with the actual performance allows us to evaluate the project as a whole and estimate its success.

BACKGROUND

General Anaesthesia

General Anaesthesia is a drug-induced reversible state which involves certain behavioural and physiological traits: unconsciousness, amnesia, analgesia and immobility (2). EEG signals show a variety of patterns associated with general anaesthesia, the most prevalent of which is a steady rise in low-frequency and high-amplitude activity as the depth of general anaesthesia increases (3).

This drug-induced reversible state must be regarded as a spectrum of independent pharmacological actions targeted to achieve multiple objectives. On one hand, patient immobility is desired by surgeons to improve exposure and precision and, on the other hand, the patient primarily desires oblivion, amnesia and loss of pain during surgery. The primary intended goal in this state of general anaesthesia is tolerance towards nociception [1] induced by surgery (4).

The desired effects upon central nervous system do not remain isolated. The anaesthetic drug administration might entail severe side effects, such as cardiovascular instability, respiratory depression, and an altered function of the thermoregulatory systems. These undesired effects of the drugs are generally enhanced both within the surgical procedure and less drastically throughout the recovery process further increasing concentrations of anaesthetics once the desired therapeutic effect is reached.(5) The anaesthesiologist must try to maintain the physiologic equilibrium of the patient to avoid adverse events and potential damage to the organs or consequence in different clinically relevant outcomes. For this reason, and besides monitoring other vital signs and organ changes, great interest exists in identifying and monitoring the relevant neurophysiological correlates of consciousness among multiple other physiological parameters during general anaesthesia, in order to adjust the dose precisely to the patient's needs.

ANAESTHESIA STATE

As stated above, the state of general anaesthesia is a combination of both physiological and behavioural traits combined to achieve the therapeutic effect necessary to start the intervention safely. The combination of different anaesthetic drugs can produce different patterns on the EEG accordingly to the different hypnotic, analgesic, amnesic and akinetic behavioural features stated and explained in **Table 1**.

[1] Nociception is the neural process of encoding and processing noxious stimuli.(94)

HYPNOSIS	Drug induced impairment of cognitive functions required for responding adequately to environmental stimuli regarding attention and perception.(6) The highest level of hypnosis is unconsciousness. $GABA_A$ receptor agonists, such as propofol, are the main hypnotic agents. Hypnosis state is monitored and analysed through EEG and EEG derived parameters.
ANALGESIA	Analgesia is the absence of sensibility to pain when receiving a noxious stimulus.(7)
AMNESIA	Amnesia is a profound loss of memory and impossibility to retain information or remember any event during the transient state. It can be induced during surgery to ameliorate the stress experienced by the patient during surgery.(8)
AKINESIA	Akinesia or immobility is the inability or suppression of movement in response noxious stimulus, such as surgical incision or tetanic electrical pulses, usually requires the administration of neuromuscular blocking agents.(9)

Table 1: *Definition of the different behavioural features characteristic of the state of general anaesthesia [Own elaboration]*

ANAESTHETIC DRUGS

Anaesthetic drugs are the chemical compounds administered to patients in order to achieve the different states of anaesthetic desired and can be classified according to its administration pathway; either inhalational or intravenous. Total intravenous anaesthesia (TIVA) refers to the exclusive use of the intravenous route for anaesthetic administration (10). Compared to inhalational anaesthesia, TIVA shows several benefits regarding better hemodynamic stability, better recovery conditions and reduced post-operative complications including nausea and vomiting(11). However, both techniques are long-established and different factors must be taken into account when selecting the most appropriate administration pathway type for each patient and procedure.

Although intravenous drugs can be administered manually through an initial bolus injection, target controlled infusion systems (TCI) are often preferred for TIVA drugs administration. TCI systems use integrated algorithms based on pharmacokinetic and pharmacodynamic models for calculating the amount of drug to be delivered every ten seconds to achieve, maintain and rapidly change anaesthetic effect in response to demands, as well as compensating for drug clearance and distribution from the blood to other tissues. In comparison with manual administration, TCI systems offer many benefits as they allow accurate control of the desired pharmacodynamic effect, along with short recovery time(12).

Anaesthetic drugs must be carefully selected and combined to produce the desired and most beneficial effect. TIVA requires the use of intravenous hypnotics and opioids. Hypnotics are used to achieve a state of unconsciousness, whereas opioids allow to achieve antinociception. Muscular relaxation state of the patient is achieved both by neuromuscular blocking drugs and by unconsciousness and antinociception (induced by other drugs)(13). The clinical outcome will depend on the drugs chosen, its dosage and pharmacological drug interactions. A synergistic combination of drugs often produces more intense effects than the drugs separately generating a reduction in the required doses, while, consequently, also reducing the potential side effects of the drugs by themselves(9).

In the operation room for major ambulatory surgery (CMA) at Hospital Clínic, TCI-TIVA induced general anaesthesia based on a synergy of propofol (hypnotic) and remifentanil (opioid) is used and occasionally combined with other drugs such as rocuronium (neuromuscular blocking agent) to warrant immobility. The synergistic effect of propofol and remifentanil has demonstrated to achieve the desired therapeutic effect with less concentration of both drugs required. In **Figure 2** we can observe the different characteristics of the main three anaesthetic drugs administered in Hospital Clínic CMA.

PROPOFOL

- Hypnotic and amnesia effect.
- Fast induction due to its lipophilic nature.
- Interaction with GABA receptor mediated ionic channels.
- It produces a drop in blood pressure as well as a reduction in heart rate.
- After anaesthesia, rapid recovery and low incidence of nausea and vomiting.

REMIFENTANIL

- Fast opioid analgesic agent.
- Short acting, nonspecific esterase metabolised, selective mu-opioid receptor agonist.
- It results in fewer responses to noxious stimuli and with a fast recovery time.
- Respiratory depression, bradycardia and hypotension.

ROCURONIUM

- Immobility and muscle relaxation agent.
- Amino steroid non-depolarizing neuromuscular blocker.
- Long action duration, rapid effect and reversibility.
- Commonly required for tracheal intubation.

Figure 2: *Explanatory table with the main characteristics reviewed of Propofol, Remifentanil and Rocuronium anaesthetic drugs* (14–16).

Anaesthesia Monitoring

During general anaesthesia the autonomous homeostatic control of the patient is lost. Therefore, it is fundamental to measure and evaluate the physiological signals and indicators in real time to assess how the patient is reacting to the surgical aggression and anaesthesia drugs. The monitoring of vital constants and drug doses is crucial for the maintenance of homeostatic equilibrium, as well as it assists the anaesthesiologist in the individualised administration of anaesthetic drugs.

Multiple monitoring systems are available and used in the operating room to measure, they display and record a physiological signal or a set of physiological signals. In the following sections, a briefly description of different commonly monitored physiological signals are stated.

ELECTROCARDIOGRAM

An electrocardiogram (ECG) is a recording of the electrical activity of the heart as a function of time through voltage detection by means of different skin electrodes placed in different derivations. It provides important information about various cardiac parameters such as pulse and heart rate as well as the ST-segment. Changes in the electrical activity of the heart may be related to alterations in the patient's homeostatic balance. Hypnotic effect and antinociception are determining factors of changes in heart rate variability during surgical anaesthesia (17).

ARTERIAL BLOOD PRESSURE

Blood pressure (BP) is the force exerted by circulating blood on the walls of the arteries. The BP value is a commonly used parameter for the assessment of cardiovascular function and, similar to the ECG, is sensitive to changes in the patient's homeostatic equilibrium.

Blood pressure can be measured by invasive or non-invasive methods. Invasively we can calculate blood pressure through an intra-arterial catheter that allows continuous monitoring. Although, non-invasive methods are commonly preferred. Non-invasive arterial blood pressure (NIBP) relies on automated cuffs that measure the arterial blood pressure every period of time (usually 3min) using the oscillometry principle(18).

PULSE OXIMETRY

Pulse oximetry is a non-invasive measurement of blood’s oxygen saturation. It quantifies oxygen blood levels through a sensor placed in the fingertip of the patient which emit light at specific wavelength. Through spectrophotometric methods is able to estimate the saturation level (0 to 100%) from the absorbance values of deoxygenated and oxygenated haemoglobin (19).

CAPNOGRAPHY

Capnography is the concentration or partial pressure of carbon dioxide (CO_2) monitoring in the respiratory gases. It is used to assess the ventilatory function of the patient during anaesthesia. In particular, the monitoring helps to ensure CO_2 elimination and correct intubation during anaesthesia (20). It monitors also indirectly the production of CO_2 by tissues and the circulatory transport to the lungs.

ELECTROENCEPHALOGRAM

The electroencephalogram (EEG) is a non-invasive, continuous recording of electric activity, voltage, of the cortical area of the brain as a function of time (21). It is obtained through several electrodes placed on the forehead and it is one of the main monitoring systems used during general anaesthesia.

The EEG pattern of the waves are related with different behavioural and neurophysiological anaesthetic states, as described in **Figure 3** (22,23). During general anaesthesia, the EEG patterns are altered depending on drugs, dose and duration of infusion, with significant variance between subjects (24). Low frequency, high amplitude EEG profiles are enhanced as unconsciousness deepens (3).

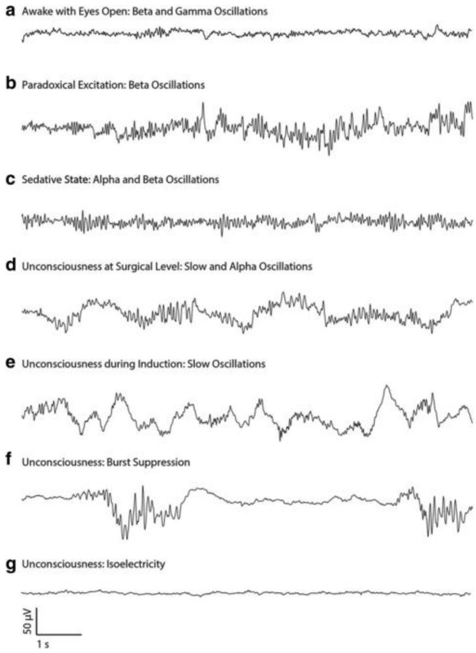


***Figure 3**: Raw EEG waveforms in time domain in different propofol-induced sedation and unconsciousness levels. (21, 22)*

It is usually difficult to visualize and detect changes of patterns in the raw EEG signal in real time. Not only that, but it is also difficult to extract signal characteristics. That is why several mathematical approaches have been developed and used to analyse EEG signals. Frequency domain methods are commonly used, such as Fourier analysis through Fast Fourier Transform (FFT) algorithms. Frequency decomposition of the signals can be performed to classify different waveforms and anaesthetic states according to their characteristic frequency (**Table 2**).

Waveform Name	Frequency range (Hz)	Brain Activity Interpretation
Beta (β)	12-30	Awake with brain activity, consciousness
Alpha (α)	8-13	Awake and relaxed, low-level excitement
Theta (θ)	4-7	Sleeping
Delta (δ)	<4	Deep sleep and unconsciousness

***Table 2:** Main Brain Waves sub-bands of diferent frequency associated to diferent mental states and activities.*(25,26)

Advanced signal processing algorithms are also used to compute parameters or indexes to help evaluate the EEG signals. Bispectral Index (BIS) is one of the most popular EEG derived parameters to assess the hypnotic effect of anaesthesia (27). It uses a proprietary algorithm that measures the pharmacodynamic anaesthetic effect by means of a dimensionless number from 0 to 100, being 0 complete absence of electric activity and 100 fully awake (28). For anaesthesiologist, BIS guided anaesthesia has reduced the risk of awareness, the requirement for propofol and has improved post operative recovery (29).

OTHER PHYSIOLOGICAL SIGNALS

We have reviewed the main monitored physiological signals during general anaesthesia and its key role to provide real-time information on the patient's physiological status in order to adjust anaesthesia and fluid management accordingly.

For monitoring the cardiac system during general anaesthesia, not only exists ECG or NIBP, but also, advanced monitoring systems such as Pulse Contour Cardiac Output (PiCCO) or Transoesophageal Echocardiography (TEE) are used in complicated and specific surgeries to assess hemodynamic monitoring. PiCCO system is used to monitor cardiac output and fluid status, while TEE system provides detailed images of the heart and its function (30). Photoplethysmography can also be used to detect changes in blood volume and it is indirectly obtained by the pulse oximeter.

However, there are also other advanced monitoring systems that provide information on the physiological state of other devices and systems in the human body. Electromyography (EMG) and Pupillometry are other examples of advanced monitoring systems. EMG is used in neuromuscular monitoring to assess immobility status (31). Pupillometry monitors the pupil diameter which increases in response to noxious stimuli and helps assess central opioid effects of the patient (32). Other advanced monitoring systems could be introduced to evaluate kidney damage and anticipate through urine output or proteins levels measurements such as creatinine or potassium.

Consciousness

Consciousness is a complex and multifaceted concept, and there are different approaches and theories about what it is and how it arises. There is ongoing research and debate in the fields of neuroscience, psychology, and philosophy about the nature of consciousness and how it can be studied and understood.

Dr. Ignacio Morgado in his new book defines consciousness as a state of the human mind in which we become aware of our own existence, the existence of others and the world around us.(33). Mental processes can occur in both conscious and unconscious states. For humans, consciousness is what disappears during dreamless sleep and returns upon waking up (34). More formally, consciousness for Seth, Anil K. et al. involves a continuous stream of conscious experiences, which form a subjective and private phenomenal world for the conscious organism. While this stream of experiences can be interrupted, it represents a fundamental aspect of conscious life(35).

Beyond these basic statements, opinions differ about how to characterize consciousness and the concept should be open to revision as further theories and experiments develop. Nowadays the main strategy within consciousness science lies in the connection between objective data about the brain and subjective data about the properties of conscious experiences (35). The Neural

Correlates of Consciousness (NCC) research strategy is achieving results in relating behavioural correlates of consciousness to the neural mechanisms underlying them(36).

This project aims to focus on consciousness at the clinical level and the recovery of this consciousness once the administration of anaesthetic drugs has been completed. As mentioned above, during general anaesthesia the patient loses consciousness, which impacts on mental processes and leads to a loss of the patient's homeostatic balance. At the end of the surgery, it is very important to accompany and assist the patient in this process of consciousness recovery in order to ensure that the patient is fully capable of self-regulating this physiological and homeostatic equilibrium. Nowadays, anaesthesiologists consider that the patient has fully regained consciousness when they are capable of opening their eyes and automatically responding to the intubation or laryngeal mask. Therefore, this study of consciousness will be based on a clinical perspective without taking into account subjective data from the patient.

Model Theory

The process of developing a simplified representation of a complicated system or phenomenon in order to better comprehend and analyse, it is known as modelling. Advances in technology have revolutionised the power of computer processing and data storage. Many different fields have been affected by this continuous technological advancement. Regarding modelling algorithms and techniques, they have changed and evolved to predictive advanced models with several approaches including Machine Learning (ML) and Deep Learning (DL), which have gained popularity in the recent years.

As a consequence of this growth, the term Artificial Intelligence (AI) is more and more prevalent in our daily lives. AI is defined as the ability of a digital computer or computer-controlled robot to perform tasks commonly associated with intelligent beings such as reasoning, learning, creativity and the ability to plan (37,38). ML and DL are branches if this AI broad term.

Regarding medical and clinical field, huge improvements are the result of combining medicine with computer sciences and engineering. Patients' diagnosis and health status predictions, as well as monitoring and categorization of biological signals, are crucial responsibilities of medical care with a single basic goal: anticipating the patient's medical conditions in order to foresee and avert potential unfavourable outcomes. As a result, predictive models have been built in order to accurately duplicate the patient's condition in order to make predictions (39). However, AI is struggling to realize its full potential in the medical field, owing to the high complexity of medical data (40).

Predictive models use mathematical models and processes to predict outcomes or behaviours through data or information patterns. ML is a branch of artificial intelligence that focuses on the learning component of AI by constructing algorithms that best represent a set of data. It uses subsets of data to build an algorithm that may use different combinations of features and weights than can be determined from basic principles (41). DL algorithms are ML class of techniques based on artificial neural networks used commonly for unstructured and complex non-linear data (41,42).

There are other ML methodologies available, however supervised learning is the most commonly used in predictive models. In supervised learning, the model is trained using a set of labelled data, with prior knowledge of what the data's output values should be (43). This method is applicable to both regression and classification tasks.

LINEAR REGRESSION (LR)

Linear regression (LR) is one of the simplest ML algorithms. The main basis of this type of predictive models consists of a regression analysis in order to specify relationships between one or more numerical features and a unique numerical target value using a linear model to describe the dataset.

The regression problem can be simplified to a univariate model in which a single feature is used for the predictive model, or we can generate a predictive model with multiple features. Multiple linear regression algorithms generate a lineal model from as many weights as features describing the dataset.

$$y = \beta_0 + \sum_{i=1}^{N}(\beta_i * x_i) + \epsilon \qquad (1)$$

Each of the weights (β_i) describes to what degree each feature (x_i) influences the target (y). The β_0 value is a constant term representing the intersection with the target axis and ϵ is the model error term. The goal is to minimize the cost function, derived from distances between predicted and intended values, to find the best-fit model, but, at the same time, dealing with overfitting issues.

In addition to standard LR, there are two regularization techniques that can help address overfitting issues and improve the performance and generalization capabilities of LR predictive models: Lasso and Ridge regression. Both regularization techniques offer a trade-off between model complexity and simplicity by the adjustment of a regularisation hyperparameter (λ) that prevents excessively large weights (44).

Lasso regression, also referred to as L1 regularization, incorporates a penalty term into the cost function with the objective of minimizing it while simultaneously forcing for some of the weights to become zero (45). Conversely, Ridge regression employs L2 regularization, which likewise seeks to minimize the cost function while reducing the magnitude of the weights, but it does not impose a requirement for them to reach zero (46).

SUPPORT VECTOR REGRESSION (SVR)

Support Vector Regression (SVR) is a predictive regression model based on Support Vector Machines (SVM). SVM algorithms determine the optimum N-1 dimensional hyperplane for separating and classifying observations, where N is the number of features in the dataset. The observations that are closest to the hyperplane and determine its position and direction are known as support vectors (47).

The hyperplane basis of SVM can also be used for regression tasks by finding the linear functional hyperplane that transfers variables from the input space to variables from the output space (48). The main advantage of SVR compared to multiple linear regression is that it gives higher flexibility to define the acceptable error in the model as it fits the best line within a range of values, frequently referred to as the epsilon-insensitive tube(49,50).

RANDOM FOREST (RF)

Random Forest (RF) is an ensemble learning technique used for classification and regression tasks, based on Decision Trees. An ensemble learning method such as RF combines predictions from multiple machine learning algorithms, in this case Decision Trees, to make a more accurate prediction (51). The model's final class prediction is based on the majority vote among the different decision trees.

A Decision Tree (DT) is a tree-like structure in which each node represents a decision or test on a feature and each branch represents the test's conclusion. The tree's leaves symbolize the final prediction. The algorithm recursively divides the data into progressively smaller groups depending on feature values until a stopping criterion is reached. The goal is to build a tree that can forecast new information effectively.

DTs are probably the closest to having the desired combination of features. Not only it handles well high-dimensional data, but also has the ability to ignore irrelevant descriptors (52). In RF the different decision trees are independently trained.

XGBoost, which stands for extreme gradient boosted trees, consists in training the ML algorithm in an additive manner to minimize the loss function. Which means that each decision tree is trained in order to improve the performance from the previous one (53). The performance of the model is evaluated by a loss function which describes the difference between actual and predicted values (54). The gradient boosted regression tree is an open-source package, and it has also been widely recognized in a number of machine learning and data mining challenges (53).

MODEL PERFORMANCE

Once ML models have been constructed and integrated into systems, it is critical to effectively evaluate their performance. This ensures that the models behave precisely, reliably, and faithfully to the actual data. To accomplish this, the models must be tested on datasets that are distinct from those used for training. If the same data is used for training and testing, the model may overfit, which means that it will predict outcomes that exactly match the expected results but only for the training data. Because no predictive model is perfect, this can lead to incorrect conclusions. An underfit model, on the other hand, performs badly on both training and test datasets, as it has not learned the training dataset, and is still not generalizable.

To confirm generalization of the developed model to new data, it is essential to test the model using a distinct test dataset. A supervised learning model's performance can be measured in a variety of ways, although it is most typically measured in terms of prediction accuracy (classification) or error and residuals (regression) (41).

The main performance evaluation model's metrics for regression are based on how close the predictions are against the real outcome. The main metrics for model evaluation in regression are R square (R^2), average mean squared error (MSE) and mean absolute error (MAE).

R^2 measures the variability of the dependent variable that can be explained by the model, which means that it can be a good measure to determine how well the model fits the dependent variables. It is the square of the correlation coefficient (55). The main disadvantage of this metric is that it does not take into consideration overfitting, therefore it is introduced Adjusted R Square to penalise and adjust with the addition of new independent variables to the model (55).

$$R^2 = 1 - \frac{\sum_i (y_i - \hat{y}_i)^2}{\sum_i (y_i - \bar{y}_i)^2} \tag{2}$$

The MSE is an average measure of how close a predicted value of the model is to the intended outcome value. It is estimated by the sum of all these squared differences and dividing it by the total number of instances (N). It is interesting for comparing results with different models (41).

$$MSE = \frac{1}{N} \sum_{i=1}^{N} (y_i - \hat{y}_i)^2 \tag{3}$$

Finally, MAE metric, which is very similar to MSE, takes the sum of the absolute error values instead of the squared error. The main disadvantage is that a good MAE is relative to the specific dataset (56).

State of the Art

General anaesthesia is one of the most common surgical practices in modern medicine, allowing for much safer and more effective surgical procedures. The use of anaesthetic drugs to induce a reversible state of unconsciousness, amnesia, analgesia and akinesia disrupts the patient's homeostatic balance (3). This is the reason why most studies related to general anaesthesia are focused on monitoring vital functions to keep the patient within normal safety ranges (57,58), studying the state of awareness depth during the surgical procedure (59–61), predicting possible adverse effects during the administration (62–64), among many other aspects. As a result, the administration of general anaesthesia has become a much safer, effective and trustworthy procedure in clinical practice.

However, there is still very little knowledge about this intermediate state of the patient's recovery of consciousness, cognition and vital functions. According to G. Mashour et al. (65), this cognitive emergence and recovery occurs through a process and not at a single point. Consequently, at the end of surgery, it is very important to accompany and assist the patient in this process of recovery of consciousness to ensure the patient's full capacity to self-regulate his physiological and homeostatic balance. In the operating room, great variability has been observed in this time of recovery of consciousness according to each patient. Therefore, it would be essential in order to better accompany, not only the patient but also the anaesthesiologist, during this process is to have a better study of this process as a whole.

At present, there are some comparative studies of the recovery time of consciousness between different anaesthetic drugs (66), studies of external variables such as caffeine and its effect on the recovery time of cognition (67), among other studies that explore the cortical dynamics and the sequence of events during this process (65). Most of the studies seek as a clinical goal to reduce the recovery time of consciousness as this allows for improved efficiency in busy operating areas. However, no external studies have been found to be related to predictive models of cognitive or conscious recovery time after full completion of general anaesthesia administration.

On the other side, the SPEC-M research group has already carried out multiple studies based on ML algorithms to construct predictive models based on EEG analysis in the framework of Final Degree and Master Projects.

In this direction, I consider it of great relevance to conduct a first study of the recovery time of consciousness based on the analysis of EEG signals and to build the first predictive regression model on this topic. This study will not only allow to deepen the knowledge of this cognitive recovery process, but also in clinical practice will help in the management of patients in a crowded environment such as the operating room.

MARKET ANALYSIS

This project is focused on the study of the time and process of consciousness recovery in order to not only extend the knowledge of the process of consciousness recovery from EEG signals' analysis, but also to cover the need for a system capable of predicting the time of recovery of the patient's consciousness once the administration of general anaesthesia has been successfully completed.

Based on this goal, in this section we will analyse the possible applications and potential users of the conscious recovery time predictive model, as well as its future prospects.

Potential Users

The developed predictive model in this project aims to forecast the duration until the patient opens their eyes, indicating the eventual recovery of consciousness or cognitive function after the administration of general anaesthesia. This prediction is derived from the analysis of the patient's EEG signals during the anaesthesia emergence process. The model uses advanced analytical techniques to identify EEG patterns that correspond to the transition from unconsciousness to consciousness, thereby enabling accurate prediction of the time of emergence.

This approach has the potential to enhance patient care and facilitate more efficient use of healthcare resources by enabling clinicians to better anticipate emergence times and tailor postoperative management accordingly. This will provide, as well, a much more efficient management of patients, medical staff and resources in post-anaesthesia care units. Therefore, this tool can be very powerful in surgical environments and operating rooms where surgeries requiring general anaesthesia are common. Furthermore, the findings of this study may be of interest to researchers exploring factors that influence the rate of emergence from anaesthesia, which could inform the development of novel strategies to expedite the recovery of consciousness.

It is worth noting that the predictive model has been developed based on data solely from surgical procedures performed under general anaesthesia induced by propofol-remifentanil. Consequently, the applicability of the model is limited to situations with similar anaesthetic conditions. Moreover, as the model has been trained solely on data from female patients, it is expected to provide more accurate predictions for patients with similar characteristics. Nonetheless, this fact does not prevent it from being used with caution in different scenarios.

It is essential to emphasize that successful implementation of this predictive system in operating rooms requires the integration of an EEG monitoring system, which provides the primary source of data for prediction. In addition to EEG signals, the model requires access to certain information regarding Propofol and Remifentanil effect-site concentrations (CE) in order to accurately predict consciousness recovery times. Therefore, adequate measures must be taken to ensure that the necessary information and monitoring systems are in place prior to integrating the predictive model in clinical environment.

MARKET EVOLUTION

ML predictive algorithms have been increasingly adopted in the healthcare industry in recent years. Significant potential exists to enhance patient outcomes and lower costs thanks to the ability of ML algorithms to learn from sizable and complex datasets and make precise predictions. As a result, the market for ML prediction algorithms in healthcare has been developing quickly.

At first, academic institutions and researchers produced ML algorithms for particular use cases, which led to a slightly tiny market for such products. However, as the value of ML algorithms in healthcare became more widely recognized, the market for these products grew exponentially(68). Nowadays, Clinical decision support, diagnostic imaging, and personalised medicine are just a few of the healthcare applications where ML prediction algorithms are currently applied(69,70).

In the upcoming years, it is anticipated that the market for these products would continue to expand quickly due to factors like rising interest for personalised treatment, expanding access to healthcare data, and rising uptake of digital health technology. Nonetheless, maintaining the precision and dependability of these algorithms as well as protecting the confidentiality and privacy of patient data are major challenges for the market.

FUTURE PROSPECTS

The future prospects for a ML predictive algorithm for consciousness recovery time once general anaesthesia has been successfully withdrawn are promising. Not only because of the increasing traction of predictive ML algorithms in healthcare, but also the valuable tool it provides for optimizing patient care, resources and staff management, as well as it could help identify factors that influence recovery time and inform the development of interventions to speed up the recovery process.

Nonetheless, for this system additional data collection is required to enable the implementation of the established predictive model in various clinical contexts because recovery of consciousness following general anaesthesia is not restricted to women or propofol-remifentanil induced anaesthesia. To increase the generalizability of the model, it is necessary to collect a large and diverse dataset that includes male patients and a range of other widely used anaesthetics. The database for the present model could then be enlarged to accommodate such information, or different models could be created using the same methodology as the current model. As a result, the model's clinical applicability would be increased, and patient outcomes would be improved across a larger range of clinical settings and patient populations.

CONCEPT ENGINEERING

In order to build a predictive model to predict the recovery time of consciousness of the patient once general anaesthesia has been successfully withdrawn, multiple development options are available, each one with its own advantages and disadvantages. In this section, we will explore and discuss the possible available predictive model development options and justify the selected approach. In this way, we can ensure that the resulting model can be accurate, reliable and clinically relevant.

Options Description

When building a predictive ML model, there are two main aspects to consider. On one hand, there is the environment or programming language of the algorithm with which you will work with the data, train, test and validate the algorithm constructed. On the other hand, there also exist multiple different ML algorithms that will build a better or worse models for the desired system. For each of the above-mentioned aspects, we will discuss and show both the advantages and disadvantages of the different alternatives.

PROGRAMMING LANGUAGE

Taking into consideration my programming skills and knowledge on different programming languages, we will consider the following programming languages for data processing and ML model building.

- MATLAB:

MathWorks' MATLAB is a numerical computing and programming language. It's popular in engineering and scientific research, as well as data analysis and visualisation. MATLAB has a number of built-in functions and toolboxes for data processing, statistical analysis, and the creation of machine learning models. It also includes an easy-to-use interface and allows you to create interactive visualisations and graphs. One of MATLAB's strengths is its performance and efficiency, which makes it suited for large-scale data processing and modelling (71). However, MATLAB is proprietary software that can be rather costly.

- R:

R is a statistical computing and graphics programming language and environment. It is open-source and freely available, with a significant developer and user community contributing to its development. R is a popular choice for data scientists and researchers because it offers a diverse set of tools and libraries for data processing, visualisation, and statistical analysis (72). R also offers considerable support for creating machine learning models, with packages such as *caret*, *mlr*, and *tensorflow* (73,74). However, one disadvantage of R is its slower performance in comparison to languages such as MATLAB and Python, which may be a limiting issue for larger datasets and models.

- Python:

Python is a general-purpose programming language that has grown in popularity in recent years for data analysis and machine learning. It features a significant user and developer community, as well as a diverse set of tools and packages for data processing, visualisation, statistical analysis, and machine learning (75). Python is an open-source language; thus it is free to use and modify. It also has a simple syntax and is simple to learn for beginners. Python has become one of the most popular machine learning languages, thanks to libraries such as *scikit-learn*, *Keras*, and *TensorFlow* (76,77). Python's adaptability, which allows it to be used for tasks beyond than data analysis and machine learning, is one of its key merits. However, for some processes, Python's speed may be slower than that of MATLAB, and its syntax may be more complex than that of R.

In terms of designing, testing, and implementing predictive models, the three programming languages have similar characteristics and usages; consequently, all three may be regarded valid for the purposes of this study.

MACHINE LEARNING ALGORITHM

ML models have the capability to analyse large amounts of data and make predictions based on patterns and trends in the system or its data. ML models use algorithms to learn from data, allowing them to make predictions and decisions with increasing accuracy over time.

There are two main broad categories of ML algorithms depending on the approach for learning from the data. Supervised algorithms predict known outcomes from labelled input data based on relationships between input and output data. In comparison, unsupervised models find patterns or structures within the unlabelled input data. They are therefore able, for example, to cluster similar data points or identify anomalous data points.

Because of the particular characteristics of our study and data, we will work with supervised ML models. In particular, as the prediction of the recovery time of consciousness is a continuous variable, we will rely on the use of algorithms capable of performing regression tasks. The main algorithms used for regression tasks are the following:

- Linear Regression (LR)
- Multiple Linear Regression (MLR)
- Polynomial Regression (PR)
- Decision Trees (DT)
- Random Forest (RF)
- Gradient Boosting (GB)
- Extreme Gradient Boosting (XGBoost)
- Support Vector Regression (SVR)
- Neural Networks (NN)

All of the algorithms mentioned above have the capability to predict with varying degrees of accuracy the recovery time of consciousness once the administration of general anaesthesia has been completed.

Proposed Solution

For the implementation of our project, in order to study and predict the time of recovery of consciousness after the administration of general anaesthesia, one of the options described and discussed in the previous section will be used.

With regard to the programming language, since all options are optimal, suitable and none of them offer major advantages or disadvantages for the building of the model and the analysis of the data. The decision criterion for the programming language is based on personal reasons in relation to my own experience. Therefore, I will be using mainly the Python language for the programming of the code, although in some cases I will use R for the visualisation of the data and results obtained.

The ML predictive models used for the regression task will be selected according to the software developer's criteria, as well as, taking into consideration the most commonly used models. First, we will try to find a predictive multiple linear regression model between various EEG signal's features and the consciousness recovery time. Then, in order to compare their performance, we will employ algorithms such as SVR, RF, and XGBoost to develop new separate models.

To summarise, a Python script will be developed to analyse EEG signals, extract a set of features from these signals and, finally, build four predictive models of the conscious recovery time. The models will be developed using the supervised regression algorithms LR, Lasso and Ridge Regression, SVR, RF and RF-XGBoost. Once all the predictive models have been trained, they will be tested, compared and evaluated to finally select the most accurate and best performing model, based on R^2 criterion.

DETAILED ENGINEERING

This section contains a detailed explanation of the methodology implemented during the development of the project. It includes a first subsection with an explanation of the used data and the data collection protocol in the operating room. Followed by the subsections on data processing, pre-processing of the raw EEG signals and the extraction of selected features. Finally, the section concludes with a detailed explanation of the pipeline of the different ML models implemented.

Dataset

PATIENT AND POPULATION CHARACTERISTICS

Under the approval of the Institutional Review Board and Ethics in Clinical Research Committee (Hospital Clínic de Barcelona, registration nºHCB/2016/0318), and in accordance with the principles of informed consent, a total of 143 female patients scheduled for ambulatory gynaecologic surgical procedures under general anaesthesia were recruited in this study from the Ambulatory Surgery facility at Hospital Clínic de Barcelona, Spain.

The characteristics of the studied patient population is detailed in the following **Table 3**.

Subjects (N)	143		
Female	143		
	Mean	**Min**	**Max**
Age (years)	49	16	84
Height (cm)	161	145	180
Weight (kg)	65.2	43	105
Body Mass Index	25.2	16.8	34.93

Table 3: *Patient Population characteristics.*

STUDY PROTOCOL

Upon the patient entering the operation room, standard monitoring devices were promptly applied, including continuous EEG, ECG, pulse-oximetry, and non-invasive blood pressure. All the recorded data from these instruments were stored in the local computer. General anaesthesia was achieved and maintained with propofol and remifentanil administered using TCI-TIVA Orchestra® Base Primea and two Module DPS from Fresenius Kabi, Homburg, Germany. Manual entry of some demographic parameters such as age, sex, weight and height are required for this system.

In addition to the continuous monitoring of the different physiological parameters, throughout the surgery, the succession of relevant events such as the insertion and removal of Laryngeal Masks Airway (LMA), presence of movements, opening of the eyes, among many other possible events, were also recorded.

At the conclusion of the surgical procedures, the administration of general anaesthesia using propofol, and remifentanil was completed. Using the aforementioned monitoring devices, the complete process of patient's recovery of consciousness was closely monitored. The duration of this process may vary, ranging from less than one minute to over 10 minutes, depending on the individual patient.

Using the event logging keyboard, the patient's eye opening was recorded, and the appropriate action of either extubating or removal of the LMA was also documented. Once the patient regained consciousness and demonstrated the ability to independently open their eyes, as well as recover their vital physiological and homeostatic functions, the continuous monitoring devices were disconnected. Subsequently, the patient was transferred to the post-anaesthesia care unit.

The entirety of the collected data from each patient is stored within the database of the SPEC-M research group, distributed across three distinct CSV files. Specifically, the monitored EEG and ECG signals are stored in two of these files, respectively. The remaining CSV file consolidates all other recorded physiological parameters, events, and TCI parameters.

Data Processing

Upon completion of data acquisition, an exhaustive data processing phase becomes essential to extract the recovery time of consciousness from the recorded events. This also involves analysing the recovery times values, performing data quality filtering, and subsequently undertaking pre-processing of the raw EEG signals. The signals are then segmented to enhance the interpretability of the results. Python 3.8.3 with the NumPy 1.23.5 (78), Pandas 1.5.2 (79) and SciPy 1.9.3 Signal Processing (80) packages will be the main ones used for the processing of the data.

CONSCIOUSNESS RECOVERY TIME ASSESSMENT

The initial step entails assessing the time it takes for each patient in the database to regain consciousness. This requires identifying specific timestamps from a CSV file containing event, physiological, and TCI parameter information. The initial time (t_0) of the consciousness recovery process is identified when the total concentration administered to the patient reaches zero, indicating the end of general anaesthesia administration. Similarly, the final time (t_f) of the process when the patient opens their eyes is determined based on the event column in the CSV file.

The consciousness recovery time for the patient is then estimated as the difference between the final time (t_f) and the initial time (t_0).

Before conducting this assessment, it is essential to visually analyse the events recorded in the CSV file. During this inspection, we will encounter various codes representing the eye-opening event, and we will also come across patients who lack any of these records, which should be excluded from further analysis.

Once we have evaluated the total time it takes for patients to regain consciousness, it is worthwhile to examine the distribution of these values across different patients using visual inspection.

OUTLIERS ANALYSIS and QUALITY ASSESSMENT

After estimating the recovery time of consciousness, we conducted an analysis to identify any potential unusual observations within the distribution of values. Simultaneously, a data filtering process was also applied based on the signal quality index (SQI) provided by the EEG and ECG system algorithm. Only patients with an SQI index higher than 50 were considered for inclusion in this study.

With regard to the analysis of the outliers, we have considered discarding by visual analysis certain patients with unusually long recovery times of consciousness. It is important to emphasize that all patients discarded for abnormal recovery times of consciousness exhibit values that exceed 1.5 times the interquartile range (IQR) of the variable's distribution.

EEG PREPROCESSING

Frontal raw EEG signals were acquired and recorded using the BIS VISTA™ Bilateral Monitoring System from two left-side channels, with a sample rate of 128 Hz. Prior to feature extraction, these 2-channel raw EEG signals underwent minimal pre-processing. A ninth-order zero-phase Butterworth low-pass filter was applied in order to remove components above 45 Hz. This step was necessary as valuable information is typically found at lower frequencies, while higher frequencies are often affected by mains (powerline) interferences (81,82). Alternatively, lower threshold values could have been chosen.

Since the EEG channels were closely located on the scalp during the surgery, it was expected that the recorded information would be similar. Therefore, to minimize abrupt artifacts and discrepancies between the two channels, the mean of the two raw channels was subtracted from each point of the EEG filtered signals, resulting in a smoothing effect.

DATA SEGMENTATION

Based on the assessment of the initial and final times of the conscious recovery process of individual patients, the EEG signal related to this process was extracted from the complete 2-channel EEG recordings. Additionally, a one-minute signal previous to the finalization of the general anaesthesia administration was also taken into consideration for the feature extraction.

As each EEG recording had a different duration because the time of consciousness recovery varies widely between patients, a three-period segmentation approach was adopted for feature extraction. The first period (T1) designated as the minute before the initiation of the conscious recovery process was divided in epochs of 5-seconds duration. An analogous approach was also performed for the second period (T2), from which the 30-seconds after the finalization of general anaesthesia were also divided in 5-seconds epochs. Lastly, the rest of the EEG signal for each patient constituted the third period (T3). This last period was divided into 5 epochs of variable duration based on its proportion to the overall signal duration. Both 2-channel raw EEG pre-processed were segmented as described and used to extract the features in the following section.

Feature Extraction

For each epoch from each period, feature extraction has been conducted. These features have demonstrated their usefulness in various EEG classification tasks and have exhibited improved performance when used in combination (83,84). The analysis undertaken in this project involves extracting features from both the time and frequency domains, along with incorporating entropic and fractal dimension parameters of the signal. All the specific features used are listed in the **Table 4** below.

TIME DOMAIN:
Non-linear Energy Operator, Activity (1st Hjorth parameter), Mobility (2nd Hjorth parameter), Complexity (3rd Hjorth parameter), Root Mean Square Amplitude, Kurtosis, Skewness, Mean, Standard Deviation, Peak-to-Peak Amplitude, Maximum Peak, Minimum Peak and Normality Test.
FREQUENCY DOMAIN:
Absolute and Relative Mean Power in Delta, Theta, Alpha and Beta band, Total Spectral Power, Spectral Edge Frequency, 1st Peak Frequency and 2nd Peak Frequency of the Power Spectrum.
ENTROPY:
Singular Value Decomposition Entropy, Spectral Entropy, Sample Entropy, Rényi entropy, Shannon Entropy, Permutation Entropy, Petrosian Fractal Dimension and Katz Fractal Dimension

Table 4: *List of all Extracted Features in the analysis.*

Time and frequency domain features were extracted using SciPy 1.9.3. (80) and NumPy 1.23.5. (78). Entropy and Fractal Dimension characteristics were extracted using Antropy 0.1.5. (85). Power spectral density (PSD) computed using Welch's method.

The ultimate objective of this analysis is to derive tabular data from the different time series. To accomplish this, the characteristic value for each period has been estimated as the mean of that particular characteristic across all epochs. By computing the mean value, we aim to obtain a representative measure of the characteristic for each period. This approach allows for a comprehensive understanding of the temporal dynamics within the time series and facilitates further research on the relationship between the most correlated characteristics of each period with the conscious recovery time. The different features extracted from the three periods were used as inputs for training the different ML models.

Exploratory Data Analysis

Before proceeding with the implementation of the ML training algorithms, it is crucial to conduct a comprehensive exploratory study of the data and features that will be used. This extensive study entails analysing the correlations among various features extracted from the raw EEG signals, both with each other and with the prediction factor of recovery time for regaining consciousness. By thoroughly examining these correlations, we aim to gain deeper insights into the underlying patterns and relationships within the dataset.

The exploratory analysis delved into the rich landscape of features extracted from the EEG signals. These features encompass a wide range of characteristics, from averaged spectral power to fractal dimension measures, and include diverse temporal, frequential, and entropic aspects of brain activity. Understanding the interplay between these features is crucial for developing accurate and robust ML models that can effectively predict the time of recovery of consciousness.

Statistical and visualization techniques were performed in order to find meaningful associations and dependencies within the dataset. Correlation analyses aimed to identify the relationships between changes in one feature and those in others, offering important information about potential dependencies and interactions among the EEG-derived features. In addition, further detailed analysis was performed to examine the correlations between specific characteristics and the duration of consciousness recovery. This study helped identify potential markers or predictors that could be used to estimate the time required for consciousness to be restored.

ML Pipeline Implementation

In the implementation of the pipeline for this project, not only different ML regression models have been considered, but also a previous feature selection have been performed according to two different techniques. The feature selection on the training split has been performed either by embedded, lasso regression, and filter methods, selecting the k features with highest F-values scores between label and feature. At the same time, the regressor to be used has been also built along with the specific combination or set of hyperparameters. The scaling of the features has been performed for some specific models, such as Ridge Regression and SVR, in order to standardize the data and to make it comparable for the algorithm.

Model	Hyperparameters	Combinations
LR	-	-
Lasso Regression	Lambda (λ)	40-value sequence in the interval [0.1, 2]
Ridge Regression	Lambda (λ)	30-value sequence in the interval [0, 1]
SVR	Kernel C Gamma (ϒ)	('linear', 'rbf', 'poly') [20, 30, 50] [0.2, 0.1, 0.05]
RF-XGBoost	max_depth n_estimators	[2, 3, 5, 7, 10] [25, 50, 100, 500, 700, 1000]
RF	max_depth n_estimators Criterion	[3, 5, 7] [100, 200, 500] ("squared_error", "absolute_error", "friedman_mse", "poisson")

Table 5: *Set of models and the different hyperparameters optimized in the ML pipeline implementation of the project. All ML algorithms were extracted from Scikit-Learn 1.2.2.* (86)

In every instance, we implemented a nested cross-validation methodology to thoroughly explore all feasible combinations of hyperparameters and select the best model (**Table 5**). This approach ensured that the optimal set of parameters was selected based on a specific scoring criterion, in this case the R-squared score. For each regressor and feature selection method, a train-test splitting of the data was performed establishing as a reasonable partition a 0.7-0.3 proportion. This procedure was repetitively executed over multiple iterations, each time altering the random state to facilitate a fresh splitting of the data into training and testing subsets, which consequently yielded new outcomes. The models were evaluated taking into consideration the median results for the multiple iterations of each regressor.

RESULTS

Exploratory Data Analysis

The different results obtained for this comprehensive exploratory analysis provides a foundation for subsequent machine learning model development in the following section. By understanding the relationships among the EEG-derived features and their correlation to recovery time, informed decisions regarding feature selection, data pre-processing, and model architecture can be done.

CONSCIOUSNESS RECOVERY TIME

After assessing the recovery time of consciousness, a subsequent study was conducted to visually examine the distribution of this parameter within the dataset. Through visual inspection, it was determined that a total of 7 patients exhibited anomalous values for the recovery time of consciousness. Consequently, these patients were excluded from the analysis, resulting in a more homogeneous distribution of recovery time across the remaining dataset. The evaluation of signal quality by SQI, in conjunction with outlier detection, led to the inclusion of a final cohort comprising 112 patients in the study.

Figure 5.A illustrates the distribution of time required for recovery of consciousness among the 112 patients included in the study. The mean recovery time is estimated to be 6 minutes and 6 seconds, with a standard deviation of 2 minutes and 16 seconds. The analysis reveals that the minimum recorded recovery time is 52 seconds, whereas the maximum recorded recovery time is 11 minutes and 19 seconds. These extreme values provide insights into the range of recovery times observed within the patient cohort.

As mentioned in *Exploratory Data Analysis* section, the study into the process and duration of patients' recovery of consciousness entailed an analysis of correlations between various characteristics derived from the raw EEG signals and the corresponding recovery time. This exploratory study serves as a foundation for identifying the EEG-derived factors that exhibit the greatest influence on the duration of the consciousness recovery process. By comprehending these patterns, we can establish a robust selection of features for the implementation of ML algorithms. **Figure 4** below showcases the correlation coefficients between each extracted feature from the EEG signals of each individual patients and their respective recovery time during each period.

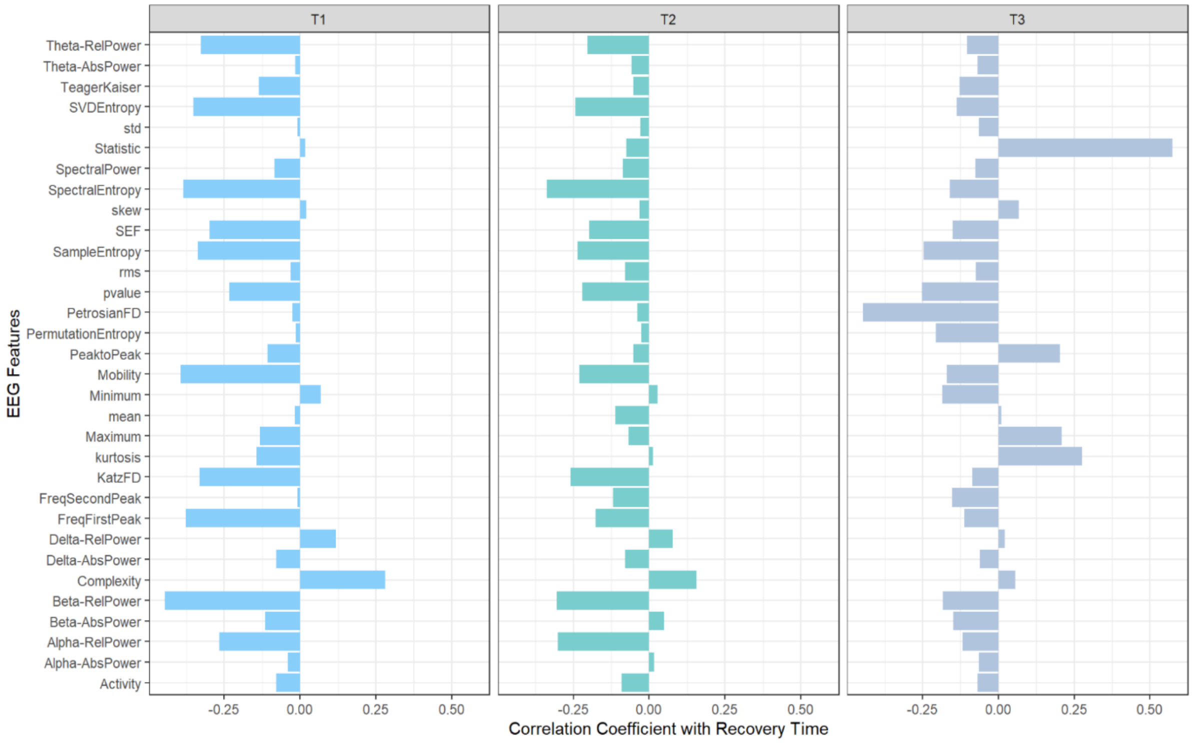


Figure 4: *Correlation Analysis for each feature extracted from raw EEG with Consciousness Recovery Time for the three different segmented periods.*

Amongst all the characteristics derived from the raw EEG, the parameter displaying the strongest positive correlation with the time to recovery of consciousness is the normality test statistic for the third period. This statistic assesses the adherence of the signal data to a normal distribution. It is also noteworthy to mention the significant positive correlation observed between the recovery time of consciousness and the mean effect-site concentration (CE) of both Propofol and Remifentanil during the last minute preceding the completion of general anaesthesia drug administration.

Conversely, one of the characteristics exhibiting the strongest negative correlation with the duration of the recovery of consciousness is the mean relative spectral power value in the Beta band in the first period, followed by the mean relative spectral power in Alpha band in first and second periods. To gain further insights into the role of mean relative spectral power values in the Alpha and Beta bands during the recovery process, **Figure 5.B** displays the dynamics of these frequency ranges in the EEG spectrum. P. Purdon et al.(87), in their article on EEG signatures marking the process of consciousness recovery, describe the reduction of low-frequency power and the loss of coherent frontal alpha oscillations. The dynamics shown in **Figure 5.B** align with the reported effects in the literature, where an increase in relative mean spectral power of the Beta band is observed throughout the recovery of consciousness, while a decrease is noted in the Alpha band. These bands have been associated to different clinical and consciousness states, as summarized in **Table 2**. Therefore, the observed correlations between these EEG bands and the recovery time of consciousness highlight the relevance of these neural oscillations in elucidating the dynamics and mechanisms underlying the consciousness recovery process.

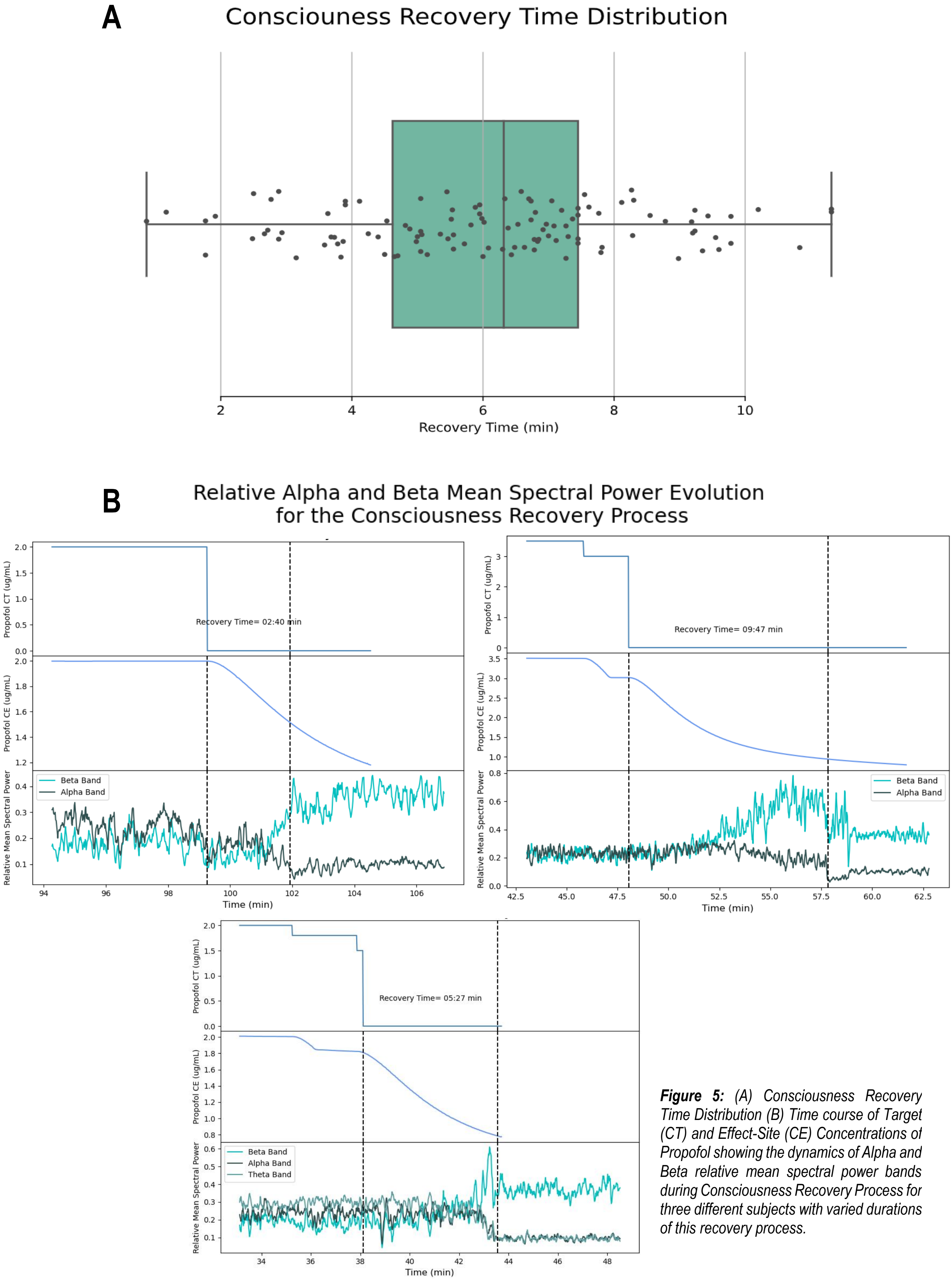


Figure 5: *(A) Consciousness Recovery Time Distribution (B) Time course of Target (CT) and Effect-Site (CE) Concentrations of Propofol showing the dynamics of Alpha and Beta relative mean spectral power bands during Consciousness Recovery Process for three different subjects with varied durations of this recovery process.*

FEATURE ANALYSIS CORRELATION

In addition to examining the correlation between the derived characteristics from the raw EEG data and the recovery time of consciousness, it is also of interest to explore and analyse the relationships among all the features in the dataset. **Figure 6** presents the correlation matrix representing these features. The primary objective of this correlation analysis is to enhance our understanding and identify the interdependencies between the various extracted features.

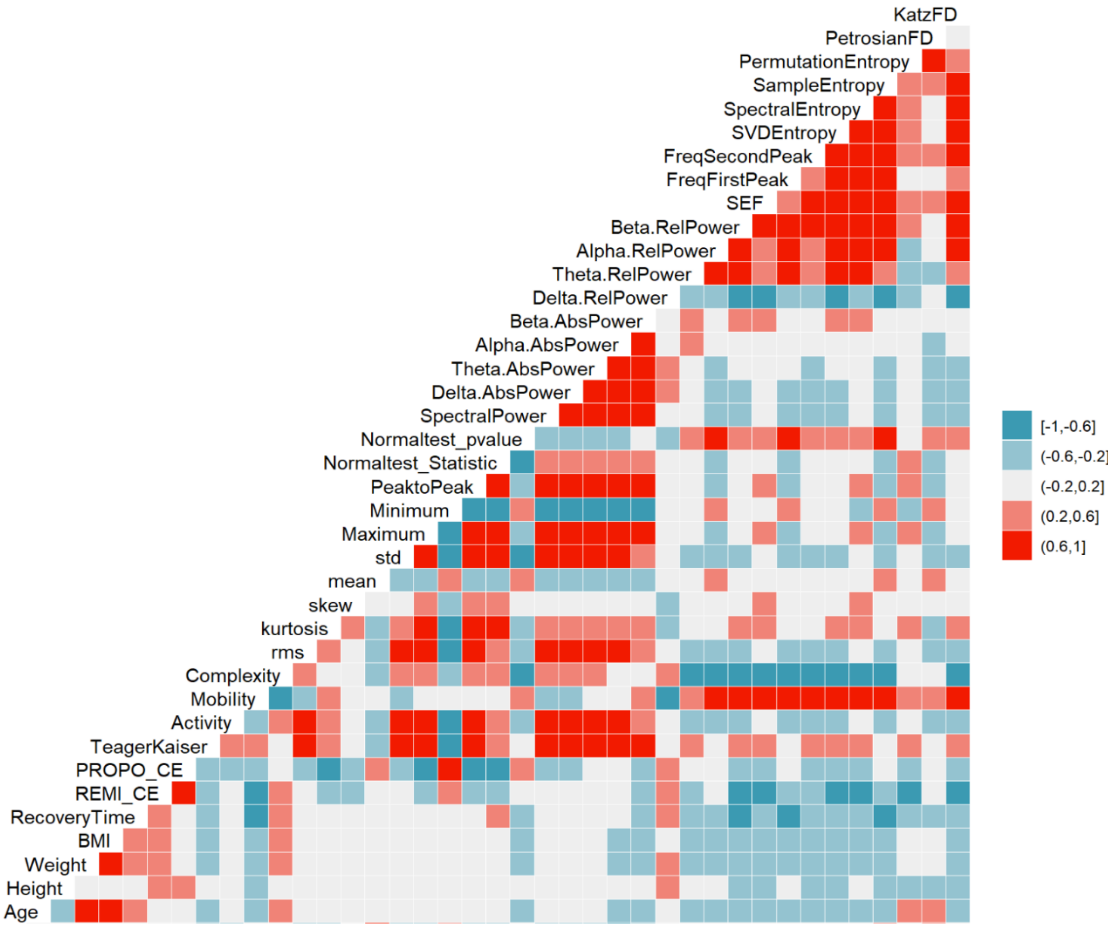


Figure 6: *Correlation Matrix for all the features in the data set.*

The correlation plot in **Figure 6** illustrates three prominent regions exhibiting strong correlations among their respective features, notably the entropic features. However, our primary focus lies in investigating the relationship between the features that have been found to exhibit high correlation with the consciousness recovery time and the remaining extracted EEG features.

Firstly, the correlation coefficients of the normality statistic with the other characteristics were examined observing relatively elevated values in comparison to the surrounding coefficients, but all of them with coefficients lower than 0.6. Nonetheless, it is worth remarking, the positive correlation it exists between the normality test statistic and the total EEG spectral power, as well as the mean absolute spectral powers for each frequency band.

Furthermore, the study revealed a substantial degree of correlation between the average relative spectral powers observed in the Alpha and Beta frequency bands and the majority of entropic and fractal dimension features extracted from the raw EEG signal. Specifically, strong correlations were identified with Sample Entropy, Spectral Entropy, and Singular Value Decomposition (SVD) Entropy. Additionally, noteworthy associations were observed between the average relative spectral powers and other significant measures, including the frequency value exhibiting the highest spectral power and the Spectral Edge Frequency (SEF). Moreover, it is worth mentioning the high correlation observed among the mean spectral powers of the Alpha and Beta bands.

Lastly, acknowledge the correlation existing between the effect-site concentration of Propofol and the absolute minimum data value of the EEG in millivolts (mV), suggesting the potential influence of Propofol on the overall electrical activity of the brain as reflected in the EEG measurements.

ML Model Performances

Following the completion of the exploratory data analysis, we proceeded with the implementation of the Nested Cross Validation pipeline, incorporating the feature selection approach outlined in ML Pipeline Implementation Section. Regrettably, the obtained results were not promising, prompting us to conduct a preliminary manual feature selection based on a correlation study. The 9 selected features in each period for the execution of the Nested Cross Validation pipeline are presented in the **Table 6** below. It is important to note that the pipeline was implemented independently for both EEG channels.

Feature Name	Feature Abbreviation
Total Absolute Spectral Power	SpectralPower
Alpha Relative Average Bandpower	Alpha.RelPower
Alpha Absolute Average Bandpower	Alpha.AbsPower
Beta Relative Average Bandpower	Beta.RelPower
Beta Absolute Average Bandpower	Beta.AbsPower
Delta Relative Average Bandpower	Delta.RelPower
Delta Absolute Average Bandpower	Delta.AbsPower
Effect-Site Propofol Concentration	PROPO_CE
Effect-Site Remifentanil Concentration	REMI_CE

Table 6: *Name and abbreviations of the manually selected features for the ML implementation Pipeline*

The obtained results are collected in the subsequent **Table 7** showcasing the performance of various linear, SVR, and RF algorithms. Furthermore, two distinct feature selection approaches were considered: employing the Lasso regressor and selecting the top k features based on their F-values.

CH1:	R^2 SCORES	FEATURE SELECTION	
	CV=5	Lasso	SelectKBest
ML MODELS	LR-RIDGE	0.67±0.18	0.68±0.092
	LR-LASSO	0.7±0.15	0.7±0.088
	LR	0.66±0.22	0.68±0.1
	SVR	0.69±0.13	0.68±0.075
	RF-XGBOOST	0.24±0.074	0.24±0.091
	RF	0.33±0.022	0.29±0.076

CH2:	R^2 SCORES	FEATURE SELECTION	
	CV=5	Lasso	SelectKBest
ML MODELS	LR-RIDGE	0.69±0.04	0.54±0.17
	LR-LASSO	0.74±0.032	0.71±0.04
	LR	0.68±0.058	0.57±0.26
	SVR	0.68±0.089	0.69±0.11
	RF-XGBOOST	0.37±0.15	0.39±0.1
	RF	0.39±0.1	0.38±0.084

Table 7: *R^2 score (mean ± standard deviation) obtained results of the different ML models: Linear, SVR and RF for the implemented Nested Cross Validation Pipeline algorithm.*

Among the evaluated models, the linear models demonstrated the most favourable performance results for this particular database, as determined by the R-squared score criterion. Specifically, the linear regression model with L1 regularization, known as Lasso, exhibited superior performance by effectively mitigating data overfitting. For this reason, the following performance studies will be based on the Lasso linear regression model. It is important also to note that in all cases, hyperparameter optimization for the SVR algorithm favoured the selection of the linear kernel.

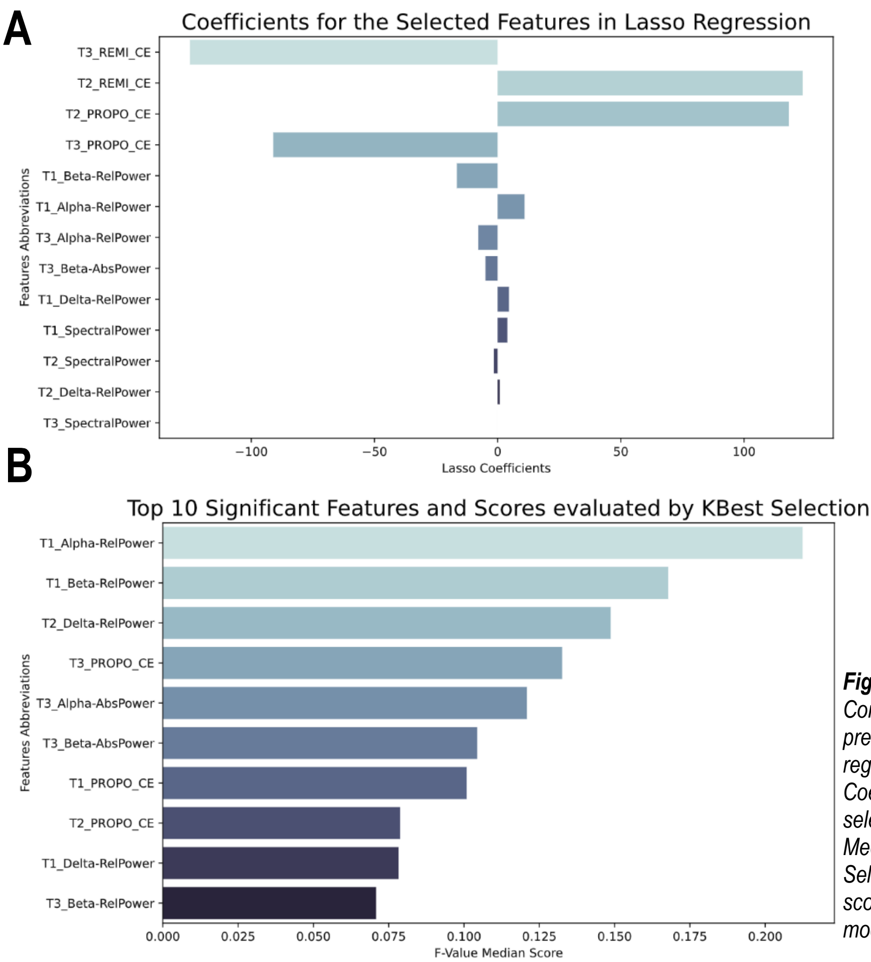
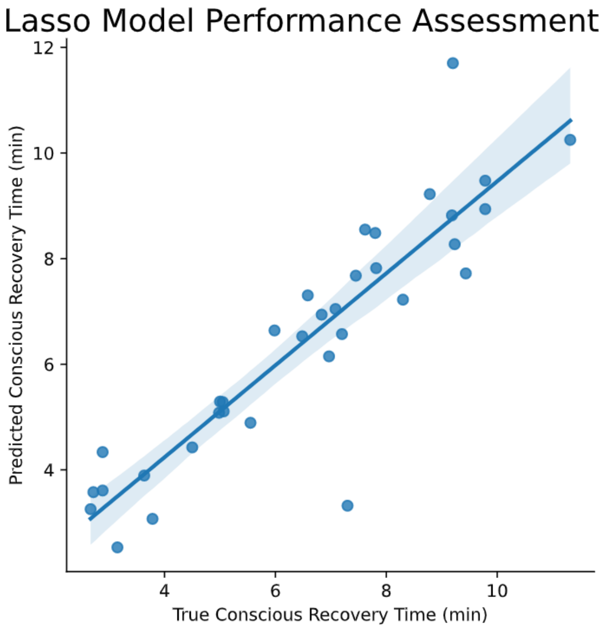


Figure 7: *Features Importance in Consciousness Recovery Time prediction with Lasso model regressor. (A) Median Lasso Coefficient values for each selected feature. (B) F-Value Median Scores for the Feature Selection based on K-best highest score optimizing Lasso regression model performance.*

Figure 7 illustrates the features selected by the two feature selection methodologies based on Lasso linear model regressor, which proved to be the most successful in modelling the time to recovery of consciousness in this study. The characteristics selected by the models with the greatest predictive power are the effect-site concentrations of Propofol and remifentanil throughout the process of recovery of consciousness. Significantly, the mean relative spectral power in the alpha band during the minute preceding the end of administration, period T1, exhibited a significant predictive capability, consistently appearing in the majority of models with high predictive power. Similar characteristics were observed for the mean relative spectral power in the beta band during the same timeframe, which also played a prominent predictive role in some models.



Finally, **Figure 8** presents a visual representation of the predictions made by the model with the highest performance on the test data. This model, after optimizing the penalty regularization parameter, λ, to 2, achieves a R-squared score value of 0.8 and mean squared error equal to 4031.43.

Figure 8: *Performance assessment for the Lasso Model regressor with test set data. Predicted time values in function of true consciousness recovery time values.*

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EXECUTION SCHEDULE

This section acts as a crucial framework, outlining the necessary tasks and phases, to ensure a systematic and effective approach towards achieving the study's initial objectives. It acts as a guide for the study development by providing a well-organized plan for organising, prioritising, and optimising all execution processes. Additionally, it provides insightful information regarding the time available for each task, enabling efficient scheduling and resource management. With this detailed and complete perspective, the study may move forward with focus and direction, increasing its chances of favourable results.

Task Definition

To ensure adherence to the project's timeline and meet the established deadline, a meticulous decomposition of the entire project into smaller tasks was conducted. In this section, the project has been divided into phases and individual tasks. In the following breakdown tables a brief description and the estimated duration for each task has been performed. In the following **Figure 9** a schematic of the detailed work breakdown structure is presented.

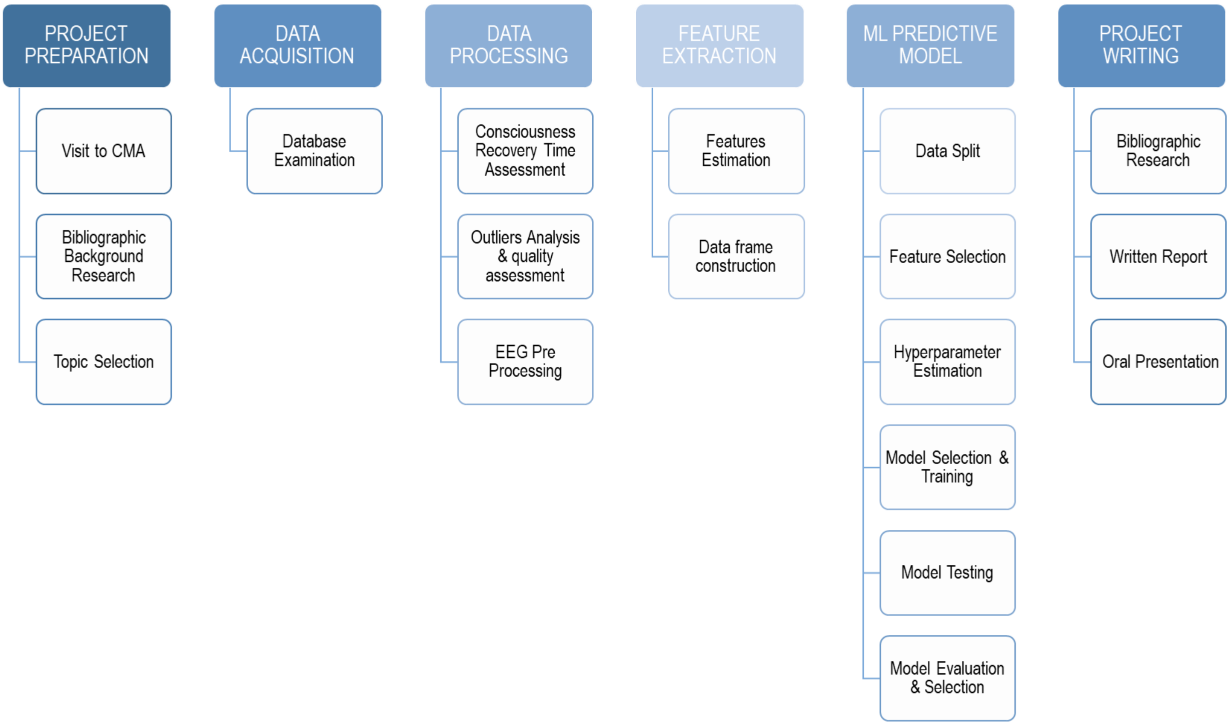

Figure 9: *Work Breakdown Structure (WBS) schematics for the project.*

Through this approach, a clear understanding of the time allocation for each task is provided, facilitating effective project management and ensuring that deadlines are met successfully.

1. Project Preparation

1.1.	Visit to CMA and Operating Rooms in Hospital Clínic	*Estimated duration 3 days*
Visit and 2 days stay in CMA in order to see the workspace environment, the monitoring devices, the anaesthesia control tower and familiarize with data collection procedures from patients undergoing propofol-remifentanil induced general anaesthesia.		

1.2.	Bibliographic Background research	*Estimated duration 3 days*
Introduction to the topic, reading of prior research from the study group, and exploration of personal interests		

1.3.	Topic Selection	*Estimated duration 1 day*
Analysis of the research group's interests, consideration of various topic suggestions, and selection of the final topic.		

2. Data Acquisition

2.1.	Database Examination	*Estimated duration 2 days*
Familiarisation with the database and extensive inspection of its structure, the collected data and the parameters compiled.		

3. Data Processing

3.1.	Recovery Time Assessment	*Estimated duration 3 days*
Assessment and estimation of the consciousness recovery time of each patient.		

3.2.	Outliers Removal and Quality assessment	*Estimated duration 3 days*
Analysis of the statistical distribution of the time of recovery of consciousness, identifying outliers and discarding them. At the same time, quality filtering of EEG samples is also required.		

3.3.	EEG Pre-Processing	*Estimated duration 14 days*

Application of some EEG pre-processing techniques and methods to clean, enhance and prepare the raw EEG data for subsequent analysis.

4. Feature Extraction

4.1.	Features' values estimation	*Estimated duration 7 days*
Evaluation, estimation, and extraction of a set of EEG signal features in the time, frequency and entropy domain for each patient.		

4.2.	Dataframe Construction	*Estimated duration 7 days*
Data manipulation in order to obtain a final matrix with all available data and features after processing to meet the requirements of the ML predictive models. This phase includes obtaining labels, a prior selection of features and observations, and an exploratory and analytical study of the features and distributions.		

5. ML Predictive Model Building: Nested Cross Validation

5.1.	Data Split into train and test set	*Estimated duration 1 day*
The patients will be divided into two datasets, with 70% of the patients assigned to the training dataset and the remaining 30% allocated to the test dataset.		

5.2.	Feature Selection	*Estimated duration 5 days*
Identifying and selecting a specified number of most informative and relevant features from the given training dataset based on statistical measures or scoring methods.		

5.3.	Hyperparameter Optimization	*Estimated duration 6 days*
Optimize the best combination of hyperparameters either for the feature selection and the model selection.		

5.4.	Model Selection and Training	*Estimated duration 3 days*
Train for different ML algorithms with the training dataset of patients. Including some pre-processing steps if considered, such as data scaling.		

5.5.	Model Testing	*Estimated duration 1 day*
Test the different constructed models with the test dataset split.		

5.6.	Model Evaluation and Selection	*Estimated duration 4 days*
Assessment of the results obatined by different metrics to select the most optimal model.		

6. Project Writing

6.1.	Bibliographic Research	*Estimated duration 20 days*
Gathering, evaluating, and documenting bibliographic information relevant to each topic of the final project.		

6.2.	Written Report	*Estimated duration 30 days*
Writing of the final report of the project.		

6.3.	Presentation	*Estimated duration 7 days*
Preparation and realisation of the 10-minute Final Degree Project presentation.		

PERT Diagram

Planning, scheduling, and coordinating tasks within a project can all be done using the effective project management tool known as a Programme Evaluation and Review Technique (PERT) diagram. A PERT diagram serves as a visual depiction of the project's activities and their interdependencies in the context of a project that is concerned with studying and predicting consciousness recovery time. It allows to identify critical paths, estimate timeframes, and allocate resources effectively. Specifically, this project has a very lineal execution timeline with an overall duration of 100 days. The PERT diagram is represented in **Figure 10** with the main critical path of the project outlined in blue. A PERT legend has been added with the identification and duration of each activity and their respective precedents, collected all in **Table 8**.

IDENTIFICATION	ACTIVITIES	PRECEDENT	DURATION (days)
A	Visit to CMA in Hospital	-	3
B	Bibliographic Background selection	A	3
C	Topic Selection	B	1
D	Database Examination	C	2
E	Recovery Time Assessment	D	3
F	Outliers analysis and quality assessment.	E	3
G	EEG Pre Processing	F	14
H	Features Extraction	G	7
I	Data frame Construction	H	7
J	Data split into train and test	I	1
K	Feature Selection	J	5
L	Hyperparameter Optimization	K	6
M	Model Selection and Training	L	3
N	Model Testing	M	1
O	Model Evaluation and Selection	N	4
P	Bibliographic Research	C	20
Q	Written Report	P, N	30
R	Presentation	Q	7

Table 8: *PERT Legend for the project with the duration of each activity and its respective precedent.*

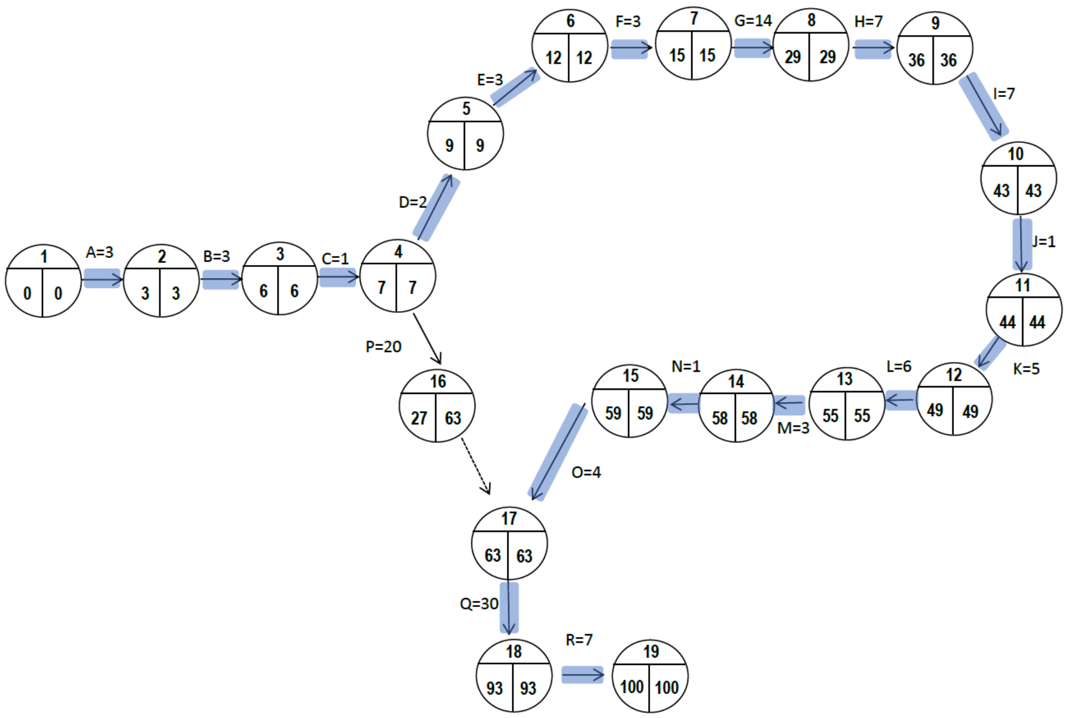

Figure 10: *PERT Diagram for the Project. Highlighted in blue the critical path.*

GANTT Diagram

Once all the phases and necessary tasks to achieve the initial goals have been established, it is crucial to create a schedule that outlines the completion dates for each task. This schedule ensures that the entire project is completed within the overall timeframe. To accomplish this, a GANTT diagram has been included in **Figure 11** of this subsection, along with the corresponding GANTT legend presented in **Table 9**. This diagram provides a straightforward visualization of the tasks to be executed at each stage and identifies tasks that can be performed simultaneously. It simplifies project management by presenting a clear overview of the project's timeline and task dependencies.

	Start Date	Duration	End Date
PROJECT PREPARATION			
Visit to CMA in Hospital Clínic	15/02/2023	3	1/03/2023
Bibliographic Background Research	6/02/2023	3	12/02/2023
Topic Selection	15/02/2023	1	15/02/2023
DATA ACQUISITION			
Database Examination	15/02/2023	2	17/02/2023
DATA PROCESSING			
Consciousness Recovery Time Assessment	20/02/2023	3	23/02/2023
Outliers Analysis & Quality Assessment	24/02/2023	3	26/02/2023
EEG Pre Processing	27/02/2023	14	13/03/2023
FEATURE EXTRACTION			
Features Estimation	13/03/2023	7	20/03/2023
Data frame Construction	21/03/2023	7	2/04/2023
ML PREDICTIVE MODEL BUILDING			
Data Split	3/04/2023	1	3/04/2023
Feature Selection	4/04/2023	5	10/04/2023
Hyperparameter Optimization	11/04/2023	6	18/04/2023
Model Selection & Training	19/04/2023	3	25/04/2023
Model Testing	26/04/2023	1	27/04/2023
Model Evaluation & Selection	28/04/2023	4	3/05/2023
PROJECT WRITING			
Bibliographic Research	23/02/2023	20	6/06/2023
Written Report	20/06/2023	30	6/06/2023
Oral Presentation	7/06/2023	7	12/06/2023

Table 9: *GANTT legend of the project with specified duration, starting and ending dates for each task.*

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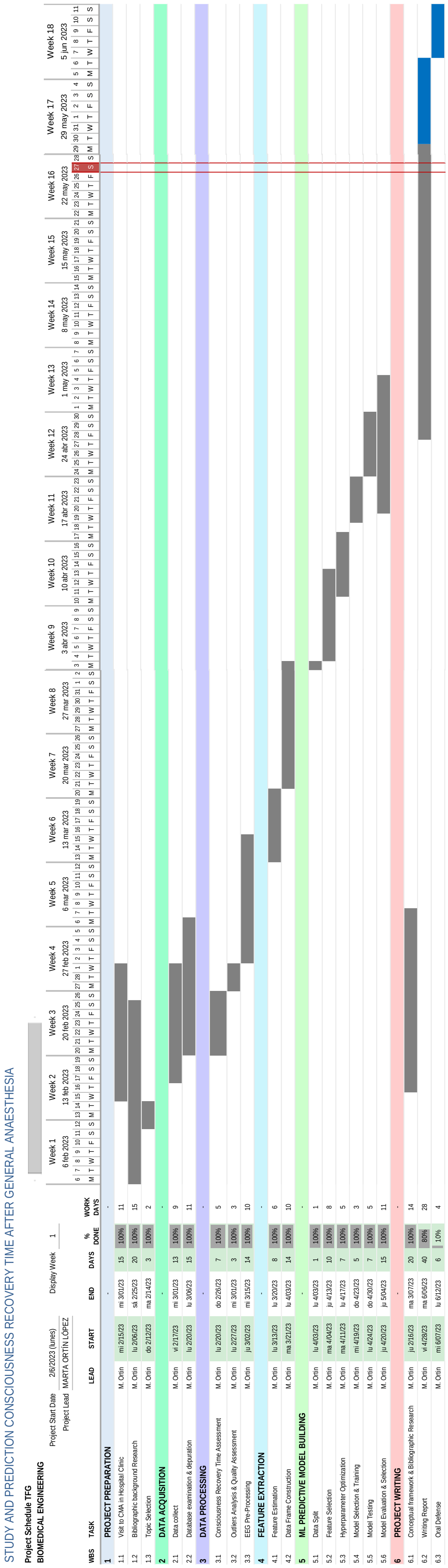

Figure 11: *GANTT Diagram for the Final Degree Project.*

TECHNICAL VIABILITY

In this particular section, it is intriguing to evaluate the development of the project from the perspective of acknowledging the potential for success of the proposed solution. A widely recognised project management tool for assessing the status of a proposed solution is the SWOT (Strengths, Weaknesses, Opportunities, Threats and Opportunities) diagram. This analytical tool provides a comprehensive assessment of both the internal attributes of the solution and the external environment within which it operates.

The trajectory and advancement of projects typically hinge upon a multitude of factors encompassing internal capabilities and the influence of external elements. Hence, conducting a thorough examination and analysis of internal strengths, weaknesses, external opportunities, and threats can help to anticipate and continuously assess the elements that can be improved.

STRENGTHS

- Data availability with an extensive already existing database.
- EEG signal analysis provides objective and standardized measurements as well as direct insights into brain activity.
- System without associated invasive techniques
- Help and guidance from professionals, master and doctoral students.
- Previous Python and ML model building experience and knowledge.
- Resulting model based on real patient data.

WEAKNESSES

- Limited prior knowledge on anesthesia monitoring.
- EEG data is complexity for analyzing and interpreting. It requires expertise in signal processing and neurophysiology.
- Conscious recovery time can vary significantly among individuals due to factors like age, health conditions, and anesthetics, making it challenging to build a generalized predictive model.
- Data acquisition and preprocessing: Collecting high-quality EEG data and removing artifacts can be time-consuming and technically demanding.
- Small demographic applicability.

S W

O T

OPPORTUNITIES

- Interest in individualized anaesthesia and Artificial Intelligence modelling is on the rise
- Hospital Clínic and the SPEC-M research group support the study
- Although ML models are currently not widely used in anaesthesia, they are becoming more and more acknowledged for enhancing patient care and optimizing anaesthesia management.
- No similar studies have been carried outside the SPEC-M research group
- Potentially integrable to an Operating Room
- Possibility to integrate the model with other predictors

THREATS

- No similar studies on the topic to compare and validate results.
- Monitoring devices required must be installed and incorporated in the operating room.
- Database expansion depends on the number of surgeries carried out.
- The predictive model may face challenges related to generalizability when applied to diverse patient populations or different clinical settings.
- Complex machine learning models may lack interpretability, making it challenging for clinicians to understand and trust the predictions.
- Ethical and regulatory considerations.

***Figure 12:** SWOT Diagram of the project.*

Taking into consideration all of the mentioned, the SWOT diagram made for this project can be seen in detail in the **Figure 12**. It highlights the advantages of the project, such as the availability of data and the support of the SPEC-M research group professionals, while at the same time it identifies the challenges, such as some limited prior knowledge and possible problems of generalisation and interpretability of the model. Related to the external factors, the growing opportunities stand out with the great interest in the applicability of ML predictive models in personalised medicine and anaesthesia, as well as the limited knowledge related to the process of recovery of consciousness after general anaesthesia and its potential advantages addressed in the **MARKET ANALYSIS**. However, the limitation of related external studies might also complicate the validation and comparison of results and also affect the generalisability of the model. In addition to other external ethical, regulatory and model-building factors that may pose threats to the project.

ECONOMIC VIABILITY

The following section aims to create an extensive accounting of all expenses incurred while developing the predictive model for conscious recovery time. To that purpose, a thorough cost and budget analysis has been carried out. This analysis includes both direct costs and indirect costs, covering for all project-related expenses. The costs, which are classified down into material and human resources, are further discussed in this section and are collected in **Table 10** for convenience.

Regarding the project's material costs, it is advisable to establish a secondary classification based on the hardware or software system utilized. In this particular project, a substantial portion of the hardware materials employed pertains to data acquisition, encompassing sensors, monitoring systems, computers, and dedicated professionals engaged in data acquisition. It is important to note that the hospital independently assumes the overall cost of data acquisition, irrespective of the project's development, and therefore, these expenses have not been considered in the cost analysis presented here. In other situations, these costs would otherwise be covered by the project. However, it is worth emphasizing the requirement of a powerful computer for which to perform the data processing and ML model building. This processing and training of ML predictive models often demands high computational costs and therefore a powerful and suitable computer is required. Given that the project development takes place in diverse locations rather than a fixed office setting, the use of a laptop is preferred.

Additionally, the use of open-source programming environments, wherein freely available packages are applied, effectively limits the costs associated with software. However, there are some unique circumstances in which using Microsoft® 365 services are recommended. Among other crucial functions, these services are used for communicating, conducting meetings, writing the final report, and examining patient data kept in files with the.xlsx extension.

Finally, during the development of the project with a duration of 100 days, a number of tasks detailed in **EXECUTION SCHEDULE** have been carried out by an undergraduate student. The research project has benefited from the oversight and contemporaneous guidance offered by both a professional anaesthesiologist and a PhD student. The number of hours devoted to the project's execution must be taken into account in order to assess the project's budget in its entirety. Based on various degrees of expertise and current cost of living standards, several salaries have been appraised.

	UNIT PRICE/ HOUR	UNITS/HOUR	TOTAL (€)
MATERIAL RESOURCES- HARDWARE			
Microsoft Surface Laptop i5-7200U		1	1179
Data Acquisition	-	143	-
SUBTOTAL			**1179**
MATERIAL RESOURCES- SOFTWARE			
Anaconda Environment	-	1	-
Google Colaboratory	-	1	-
Python programming & packages	-	7	-
Microsoft Office® 365	0,008	3	103,68
SUBTOTAL			**103,68**
HUMAN RESOURCES			
Undergraduate Student	10	350	3500
Undergraduate PhD Student	20	15	300
Professional Anaesthesiologist Supervisor	35	25	875
SUBTOTAL			**4675**
TOTAL			**5957,68**

Table 10: *Overall costs and budget for material and human resources for the entire project.*

REGULATORY and LEGAL ASPECTS

The development of a project like this one for the study and construction of a ML model for the prediction of consciousness requires careful consideration on regulatory and legal aspects. Special understanding and adherence to the aspects we are going to discuss in this section are crucial for ensuring safeguard patient privacy, comply with ethical guidelines, and meet the necessary regulatory requirements. In this section, we will address important aspects such as data privacy and protection, ethical considerations, regulatory compliance regarding AI, liability and risk management as well as medical device approvals regulation in case we wanted to integrate the system in a hospital environment.

The study and development of ML predictive systems requires access to sensitive patient data, in this case, access to raw EEG signals during general anaesthesia and other anaesthesia-related information. Considering that each expert involved in the surgical procedure has access to a patient's medical history upon entering the pre-operative room, it becomes crucial to implement stringent security measures. It is imperative, when dealing with personal data, to ensure an adequate and consistent level of protection for individuals in relation to this data, in accordance with the requirements outlined in the General Data Protection Regulation (2016/679) and the Organic Law 3/2018 of 5 December on data protection and the guarantee of digital rights (88,89). In order to adhere to their legal rights at all times and effectively handle such data, obtaining the patient's free, prior, and informed consent is mandatory. Furthermore, the collected data must be safeguarded through technical and organizational security measures.

However, the study and use of these data for scientific research also requires additional authorisation from the organisation's ethics committees. This project, which is part of the SPEC-M research group, works under the permission and approval of the Ethics and Clinical Research

Committee (CEIC) of the Hospital Clínic (Ref. nº. 2013/8356). The collection of physiological data during general anaesthesia in CMA operating room 4 occurs in a fully anonymous manner, exclusively for the purposes of research and validation of potential indicators of anaesthetic effects.

The exponential growth globally and high capacities of AI in such a short period of time has made it necessary for international organisations to create a regulatory and ethical framework for this type of system. Although regulatory measures specific to this domain are currently absent. At the European level, the European Commission aims to establish a horizontal and uniform legal framework for the development of inclusive, sustainable and citizen-centric AI through a regulatory Sandbox (90,91). The primary objective of this endeavour is to ensure that AI systems introduced in the European market and employed within the European Union adhere to principles of safety, legality, and the preservation of fundamental rights (92).

Softwares that are intended to process, analyse, create or modify medical information, either alone or in combination, may be qualified as a Software as a Medical Device (SaMD) if the creation or modification of that information is governed by a medical intended purpose. In the European context, this category of SaMD falls respectively under the scope of the Regulation (EU) 2017/745 – MDR (93). If the developed ML predictive software was intended to be used in operating rooms facilities across multiple hospitals, a comprehensive and detailed regulatory assessment must be conducted in accordance with the aforementioned regulations.

CONCLUSIONS and FUTURE OUTLOOK

The main objective of this final degree project, conducted in the second semester of Course 2022-23, is to study and develop a predictive model of anaesthesia recovery time based on ML and the analysis of patient EEG signals. This objective encompasses not only the in-depth analysis of the characteristics of the signals, but also the handling of ML tools and algorithms used to find certain characteristics or factors that alter or affect this time and that, ultimately, make it possible to predict the duration of the consciousness recovery process once anaesthetic drugs have been stopped.

In pursuit of this objective, motivation and personal goals as a student of Biomedical Engineering have played an important role in order to not only carry out an exhaustive study of current knowledge and theories on general anaesthesia and consciousness, but also to investigate and learn about the current state of patient monitoring during general anaesthesia. Furthermore, the development of the predictive model has provided me with the opportunity to engage in a thorough review, familiarization, and expansion of my knowledge in the domains of statistics, data analysis, feature extraction from EEG signals, and the current state of the art on ML model construction.

The data included in this study was obtained from operating room 4 of the CMA department at the Hospital Clínic of Barcelona. The data was collected by the SPEC-M research group and strictly adheres to regulatory standards concerning data confidentiality, anonymity, and informed consent. Prior to analysis, a comprehensive examination of the monitored data was conducted for ensuring that appropriate pre-processing techniques were applied to both the data included in the study and the raw EEG signals.

Several abilities of information gathering on the basis of ML, statistics, data analysis and feature extraction have contributed to an analysis of the raw EEG signals and the establishment of a database with information extracted from the characterisation of these signals. Correlation analyses have been conducted to detect how the Alpha and Beta frequency bands of the EEG are correlated with the time of recovery of consciousness. Ultimately, the construction of the ML predictive model, using the gathered information, has allowed us to validate the observed results in relation to its predictive power on the time of recovery of consciousness after the administration of general anaesthesia.

The implementation of a Cross Validation Pipeline has not only made possible to determine ML models with higher accuracy and better performance, but also to optimise the best combination of parameters for these models. Regarding the database generated, the regression model with the best predictive capacity for the selected characteristics is the linear model. Specifically, the L1 regularisation model, also known as Lasso, with the ability to effectively reduce the over-fitting effect of the data.

Lastly, a comprehensive discussion on the various implications and limitations of the generated predictive model will be undertaken in the subsequent sections.

Implications

The ML model generated demonstrates encouraging predictive outcomes concerning the duration of consciousness recovery following general anaesthesia administration. Although the Lasso model exhibited superior performance metrics according to the R-squared criterion, comparable results were achieved by alternative predictive models employing linear regression or kernel-based approaches. To summarize, linear models can prove to be valuable tools in conducting such investigations.

There are no significant discrepancies observed in the predictive outcomes between the two feature selection techniques. However, it is evident and noteworthy that there is a requirement for reducing feature dimensionality prior to model training. High data dimensionality results in poorer accuracy for the models. Hence, the inclusion of redundant data or features does not consistently enhance model performance.

Despite the dissimilarity in signal characteristics between the two EEG channels, their contribution to predicting the duration of consciousness recovery appears to be comparable. In certain scenarios, the use of both EEG channels may result in redundancy.

This project has substantiated the predictive capabilities of ML models in forecasting events or clinical decisions that enhance the treatment or diagnosis of various pathologies. Moreover, these models have also shown potential in assisting with patient management and optimizing hospital resources.

Limitations

Despite the excellent data quality achieved in terms of the extensive monitoring of numerous parameters and the inclusion of a large patient cohort, the data processing stage resulted in a significant reduction in the number of patients utilized, thereby diminishing the variability across certain parameters. It is worth noting that due to the geographical location of the operating room, the collected data exhibits a notable skew towards female patients, while also displaying an underrepresentation of diverse racial and ethnic groups. Consequently, there exists a possibility that the models have inherited this bias, potentially leading to performance discrepancies based on race or gender. This issue should be addressed in a prospective validation to detect and collect more data to overcome it, if it exists. It is also important to note that the data extracted are exclusively from surgical procedures performed under general anaesthesia induced by propofol-remifentanil.

The implementation of the models has solely focused on using intraoperative data pertaining to EEG signals and from surgical procedures performed under general anaesthesia induced by propofol-remifentanil. However, enhancing the model performance could be achieved by incorporating additional pre-existing conditions, such as medical history, or physiological intraoperative parameters, during the training and evaluation stages. This broader inclusion of patient-specific characteristics may yield improvements in the model's predictive capabilities.

As indicated in this study, it is noteworthy that information derived from two closely situated EEG channels has been incorporated. However, our observations suggest that this inclusion may introduce redundancy, without yielding substantial additional information to enhance predictive capacity. Future investigations could consider incorporating multiple channels distributed around the brain to comprehensively monitor its activity throughout general anaesthesia. This broader approach may potentially yield a more comprehensive understanding of neural dynamics during the anaesthetic state.

Discussion and future lines

In the forthcoming era, regulatory considerations within the legal framework will assume a pivotal role in the development and implementation of ML. It is imperative to acknowledge that the predictive model should be interpreted as an invaluable tool to guide the study of the process of recovery of consciousness and to assist in the management of patients in a surgical environment. However, it is crucial to note that the predictive model, as generated, is not yet prepared under no circumstances for immediate integration into such surgical environments.

Through diligent examination and experimentation, exceptional performance values may be achieved in future studies, thus warranting the potential integration of these models into operating room monitoring systems during general anaesthesia. However, it is vital to emphasize the need for further validation and generalization of these models before any such integration is considered.

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APPENDIX

APPENDIX 1: Data Processing and Feature Extraction

The full python code performed for the data processing and feature extraction tasks is available in the following QR code. In this there is the different functions used to import the data, data processing included raw EEG pre-processing, feature extraction of the different signals and data structuring of the different features in an excel file.

APPENDIX 2: Feature Analysis

In the following QR code there is access to the code and results for the performed Feature Analysis with R programming environment. Once imported the excel file with the extracted features, a first descriptive analysis is performed. Following with a correlation analysis for each extracted EEG feature and propofol effect-site concentrations.

APPENDIX 3: ML Pipeline Implementation

The following QR code gives access to the Google Python Collaboratory environment with the code implemented for the Cross-Validation ML Pipeline. Two feature selection methodologies were performed for six different regression algorithms: LR, Lasso, Ridge, SVR, RF and RF-XGBoost.