

Final Degree Project

**Biomedical Engineering Bachelor**

**“Predictive modelling of Loss Of Consciousness under general anaesthesia“**

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**Abstract**

The abstract is a very brief summary (up to 250 words) of the TFG contents. It should provide sufficient detail that someone unfamiliar with the project is able to understand the general content on the basis of the abstract alone and should therefore be written for a general audience.

Table of Contents

[1. Introduction 4](#_Toc92199629)

[1.1 Objectives 4](#_Toc92199630)

[1.2 Methodology and Structure 4](#_Toc92199631)

[1.3 Scope of the project and limitations 5](#_Toc92199632)

[2. Background 5](#_Toc92199633)

[2.1 Background 5](#_Toc92199634)

[2.1.1 General Anaesthesia 6](#_Toc92199635)

[2.1.1.1 States of anaesthesia 7](#_Toc92199636)

[2.1.1.2 Anaesthetic drugs 8](#_Toc92199637)

[2.1.2 Anaesthesia monitoring 13](#_Toc92199638)

[2.1.2.1 Basic anaesthesia monitoring 13](#_Toc92199639)

[2.1.2.2 Advanced monitoring systems 14](#_Toc92199640)

[Electroencephalogram 14](#_Toc92199641)

[2.1.3 Model theory 15](#_Toc92199642)

[2.1.3.1 Predictive modelling 16](#_Toc92199643)

[2.1.3.2 Model performance 18](#_Toc92199644)

[2.2 State of the art 18](#_Toc92199645)

[3. Market analysis 18](#_Toc92199646)

[4. Solution implementation 18](#_Toc92199647)

[4.1 Concept engineering 18](#_Toc92199648)

[4.1.1 Different solutions 18](#_Toc92199649)

[4.1.2 Proposed Solution 18](#_Toc92199650)

[4.2 Detail engineering 18](#_Toc92199651)

[4.2.1 Data processing 18](#_Toc92199652)

[4.2.2 Exploratory analysis 18](#_Toc92199653)

[4.2.3 Model training 18](#_Toc92199654)

[4.2.4 Model Validation 18](#_Toc92199655)

[5. Chronogram and execution 18](#_Toc92199656)

[6. Technical 19](#_Toc92199657)

[6.1 Specifications and technical characteristics 19](#_Toc92199658)

[6.2 DAFO 19](#_Toc92199659)

[7. Economic viability 19](#_Toc92199660)

[8. Legal aspects 19](#_Toc92199661)

[9. Results 19](#_Toc92199662)

[10. Discussion and Future Prospects 19](#_Toc92199663)

[11. Bibliography 19](#_Toc92199664)

[12. Annex 21](#_Toc92199665)

[Table 1 Systemic effects of i.v. agents. SVR, systemic vascular resistance; MAP, mean arterial pressure; CBF, cerebral blood flow (Khurram Saleem Khan, Sept. 2013, págs. 100-105) 6](#_Toc92130562)

[Table 2: Most used Total Intra Venous Anaesthetics (Roop Kaw, 2014). 10](#_Toc92130563)

[Table 3: Recorded variables in this project. Redundant variables have been excluded, and we the same variables recorded for propofol have been recorded for remifentanil. (Altès, 2020, pág. 26) 13](#_Toc92130564)

# Introduction

This project is implemented within the Systems Pharmacology Effect Control-Modelling (SPEC-M) Reserch Group from the Department of Anaesthesiology and reanimation of the Hospital Clinic of Barcelona. The field work takes place in the Operating Room (OR) number 4 of the Major Ambulatory Surgery department of the Hospital Clinic. The data used in the project has been collected inside this OR.

## Objectives

The objectives mentioned below are conceived around the expressed necessity of the anaesthesiology team to acknowledge the state of arousal of a patient rapidly and beforehand. Even though anaesthesiologists have great knowledge in this matter, no predicted parameter is now a days used to directly approach this state of arousal of stato. Of consciousness.

Therefore, the principal aims of this project is **to generate, train and validate a model in order to predict the level of Loss of Consciousness (LoC) of a newly given patient undergoing Propophol and Remiphentanil mediated general anaesthesia**.

In order to achieve the main goals of the project, several sub-goals are defined:

Firstly, it is crucial to **get deeply familiarized with the surgical environment, anaesthetic procedures, and recorded biological parameters**, which will be done through practical sessions in gynaecological surgical room 4 throughout of two whole months.

Last but not least, it is necessary **to properly use a control version software**, generating a commit every time an improvement has been made on the code until the final application is done, and correctly handling possible errors.

## Methodology and Structure

The structure of the project is divided in three differentiated temporal sections:

* Practical sessions in the operating room
* Working from home on the data and documents
* Document submission and personal presentation. (buscar algun gràfic rollo data rangling i tot això o ferlo jo...).

Firstly, practical sessions in OR take place, where data is collected from the surgical procedures in the operating room number four of the Major ambulatory Surgery department on Tuesdays and Thursdays from September until November. In this section, Dr. Pedro Gambús guides the gathering of the intraoperatory data and gives explanations around the activity undergone in the operating room and the parameters recorded.

Secondly, work from home takes place. In this section procedures like data analysis and document preparation are performed. Data preparation and model building, training and validation are performed using python language and Visual Studio Code user interphase. The packages used in the data analysis are a wide range, with special mention to scikit-learn. This package is a python package specifically designed for ML programming. In this section PhD undergraduate Joan Altés guides the programming process.

Finally, documents submission and presentation take place.

## Scope of the project and limitations

Table

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Limitacions:

1. Perdua de resposta verbal i no de LoC, que es un concepte vago.
2. Limitacions amb les dades, no son les que vam recollir nosaltres.
3. Buscar limitacions generiques de models de ML
4. Perquè ML i no estadidtica pura i dura

# Background

## Background

In interventions under general anaesthesia some methods are used by the anaesthesiologists in order to determine the state of consciousness of the patient. Typical examples of undertaken actions to determine LoC are palpebral reflex, corneal reflex, and verbal response. If the three of them are negative, the patient is considered to be unconscious, thus permitting further actions such as intubation. [podria haverhi referencia]

This clinical assessment has been frequently endorsed by the introduction of indexes, mostly extracted from EEG signal processing, that try to indicate the depth of unconsciousness of the patients. Bispectral Index (BIS) is an example of this approach, which gives a value between 0-100, being 0 completely unconscious and 100 completely conscious. Typical values of BIS under general anaesthesia go from 40-60 (Mathur S, 2021 Jan-. Available).

In the approach proposed, we pretend to generate an index not dependent on EEG but trained to identify at every second the state of consciousness of the patient through training with previous patients’ data.

### General Anaesthesia

General anaesthesia is a medically induced reversible loss of consciousness, with loss of both protective reflexes and the ability to acknowledge painful stimuli (Smith G, 2021). Depending on the anaesthetics administered and their effects in the brain and muscles the effects of the anaesthesia are discerned in four different parts: unconsciousness or hypnosis, amnesia, analgesia, skeletal muscle relaxation, and akinesia. (Siddiqui BA, 2021)

That general anaesthesia is a reversible coma state of the patient is a widely accepted statement in the clinical environment. Although the patterns of EEG activity observed in comatose patients depend on the extent of the brain injury, they frequently resemble the high–amplitude, low-frequency activity seen in patients under general anaesthesia, therefore supporting this analogy (Emery N. Brown, 2010). This comparative rises an immediate question: How much anaesthetics are enough for an intervention under general anaesthesia? The desired effects upon CNS does not remain isolated: when anaesthetic drugs are administered a wide range of other parameters such as HR, Contractility, SVM, MAP and respiratory functions are modulated. Once the desired therapeutic effect is achieved, further increasing concentrations of anaesthetics generally enhance these undesired effects of the drugs both within the surgical procedure and less drastically throughout the recuperation process. It is therefore accepted that the optimal concentrations of anaesthetics in a surgical procedure is the one that achieves the desired therapeutic effects and not more than that (Khurram Saleem Khan, Sept. 2013, págs. 100-105)[3].

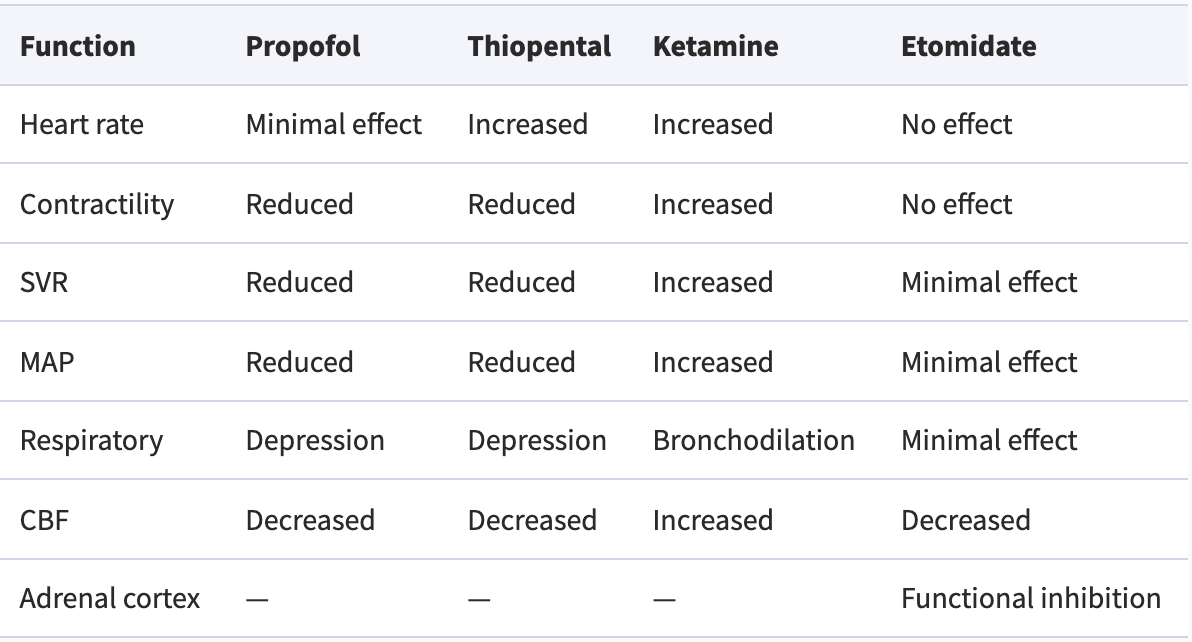


Table 1 Systemic effects of i.v. agents. SVR, systemic vascular resistance; MAP, mean arterial pressure; CBF, cerebral blood flow (Khurram Saleem Khan, Sept. 2013, págs. 100-105)

The final desired therapeutic effect when performing general anaesthesia is to achieve the LoC state of the patient, where the effect of the anaesthetics is strong enough to start with the surgical procedure without risk of awakening of the patient, but avoiding the undesired increased effect of administering too much anaesthetics as shown in Table 1.

Several pharmacological models and approaches such as Target Controlled infusion (TCI), EEG suppression analysis and BIS analysis have been implemented to achieve the goal of infusing minimal necessary anaesthetic drugs (Guarracino F, 2005) and will be further discussed in the Anaesthetic drugs and Anaesthesia monitoring chapters respectively.

Indicacions i contraindicacions

#### States of anaesthesia

As stated in the previous section, the states of anaesthesia are not part of a continuous process towards being under general. Anaesthesia, but the different effects expected from anaesthetic drugs which might be necessary to combine to achieve the therapeutic effect necessary to start the intervention safely. This state are unconsciousness, which refers to patients’ unawareness state; analgesia, which refers to patients’ incapacity of feeling painful stimuli; amnesia, which refers to patients’ inability to remember; and akinesia, which refers to patients immobility.

**Hipnosis and unconsciousness**

The state of hypnosis, which is analogous to unconsciousness, is typically defined as an state of impairment of cognitive functions in the patients’ brain that blocks patients’ adequate response to external stimuli, regarding attention and perception (Jason A. Campagna, 2003)]. Hypnosis is induced by hypnotic agents such as propofol, and there are several levels of hypnosis: drowsy, sedated and unconscious.

The mechanisms of action involved in the process of hypnosis have not yet been determined accurately as a whole. Nevertheless, in the last decades it has been shown that different molecular targets in various regions of the nervous system are involved in the multiple components of anaesthetic action, and these targets can vary between specific anaesthetics. When talking about unconsciousness induction the main inhibitory neurotransmitter involver is Gamma-aminobutyric acid (GABA). This neurotransmitter acts selectively modulating GABAA receptors (Hemmings HC Jr, (2005), págs. 503-510), which are ligand-gated ion channels, persistently opening the channels and therefore inhibiting synapses in big areas of the brain (Hemmings HC Jr, 2005).

Even though several indexes mostly related to EEG have been used lately to acknowledge the level of hypnosis of patients under general anaesthesia, our intraoperative ability to evaluate levels of consciousness still remains limited. An example of this approach is Bispectral index (BIS), but further research in this field is still necessary to construct deterministic models involving hypnosis induction and its effects upon patients.

**Analgesia**

In 2020 the International Association for the Study of Pain proposed a review of the definition of pain. This definition stated that pain was "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Srinivasa N Raja, 2020). Therefore, analgesia could be defined as the state of mind that permits the inhibition of painful sensations in situations where it would be expected.

**Amnesia**

The term amnesia refers to the impossibility of a patient to remember or recall any moment or event that they perceived during the transient state. Hypnotic agents cause unconsciousness by suppressing neural mechanisms mediating arousal and awareness, but they can also cause amnesia by disrupting mechanisms of memory consolidation.

When a high enough dose of a hypnotic agent is administered, information from the outside world is not processed by the patient and, thus, no conscious memories are formed. In this sense, all hypnotic agents are amnesic at a certain dose (Robert A. Veselis, 2009, pág. 2). Furthermore, hypnotic agents acting on GABA receptors such as propofol might have amnesic effect even at lower sedative doses (Robert A. Veselis, 2009, pág. 1).

**Akinesia**

The term akinesia refers to the inability to perform a clinically perceivable movement. It can present as a delayed response, freezing mid-action, or finally total abolition of movement (Ramakrishnan S, 2021). In general anaesthesia akinesia is typically achieved by means of hypnotic and analgesic agent combination, but in some cases it is necessary to administer a neuromuscular blocker, like Rocuronium, to achieve muscle relaxation and guarantee the intervention security.

#### Anaesthetic drugs

Anaesthetic drugs are the chemical compounds administered to patients in order to achieve anaesthetic effects. Depending on if the desired effect is local anaesthesia, sedation, general anaesthesia, or others the anaesthetic drugs, their quantities and the way of administration are chosen.

Anaesthesia drugs can either be inhalational or intravenous. Total intravenous anaesthetics (TIVA) refers to the administration of anaesthetic agents via intravenous route. Compared to inhalational anaesthesia, TIVA shows several benefits including better hemodynamic stability and reduced post-operative incidence of nausea and vomiting (Total Intravenous Anesthesia (Tiva)- A Brief Review., 2018).

The infusion of TIVA can either be administered manually through an initial bolus injection, or through the usage of algorithm-mediated infusion pumps, such as TCI.

**TCI**

Progress in computing technology has allowed the development of target controlled infusion devices, with drugs delivered to achieve specific predicted target site blood drug concentrations. Target controlled infusion (TCI) system has been developed as a standardised infusion system for the administration of opioids, propofol and other anaesthetics by target controlled infusion. A set of pharmacokinetic parameters has been selected using computer simulation of a known infusion scheme. The selected model is incorporated into a computer-compatible infusion pump. Clinical trials with such systems have provided appropriate target concentrations for the administration of TCI of anaesthetic drugs (Guarracino F, Target controlled infusion: TCI., 2005).

In the figure below we can see the comparison of a bolus injection (right) versus target controlled infusion (left). The Blue line is the plasmatic concentration of propofol, the red line is the effect site concentration, and the green line is the effect. Here we can observe that through TCI systems we achieve a stable and controlled effect of the anaesthetic agent, propofol in this specific case.

Chart, line chart

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Figure 1: Bolus vs TCI anaesthetic infusion (Brian J.Anderson, 2019, págs. 177-198)

Anaesthetic drugs are divided depending on their effect first and later on their type. Most common drug types used in TIVA are hypnotic and analgesic drugs, as seen in the figure below, sometimes combined with other drugs if necessary, such as Rocuronium for muscle relaxation. In the Hospital Clinic a mixture of propofol and Remifentanil is used, as this hypnotic and analgesic altogether have demonstrated to create a synergic effect, achieving the desired therapeutic effect with less concentration of both drugs (Mertens MJ, 2003).

Table

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Table 2: Most used Total Intra Venous Anaesthetics (Roop Kaw, 2014).

**Propofol**

Propofol is an intravenous hypnotic agent used for procedural sedation, during monitored anaesthesia care, or as an induction agent for general anaesthesia. It may be administered as a bolus or an infusion, or some combination of the two. Propofol is prepared in a lipid emulsion which gives it the characteristic milky white appearance. Strict aseptic technique must be used when drawing up propofol as the emulsion can support microbial growth (Folino TB, 2021).

Propofol is a commonly used intravenous hypnotic agent, which also induces amnesia, as stated in States of anaesthesia chapter. This anaesthesia agent interacts with GABA receptor mediated ionic channels as shown in figure below.

Diagram

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Figure 2: Neurophysiological mechanisms of propofol’s actions in the brain. Propofol enhances γ-aminobutyric acid receptor type A (GABAA)-mediated inhibition in the cortex, thalamus, and brainstem. Shown are three major sites of action: postsynaptic connections between inhibitory interneurons and excitatory pyramidal neurons in the cortex; the GABAergic neurons in the thalamic reticular nucleus (TRN) of the thalamus; and postsynaptic connections between GABAergic and galanergic (Gal) projections from the preoptic area (POA) of the hypothalamus and the monoaminergic nuclei, which are the tuberomammillary nucleus (TMN) that releases histamine (His), the locus ceruleus (LC) that releases norepinephrine (NE), the dorsal raphe (DR) that releases serotonin (5HT); the ventral periacqueductal gray (vPAG) that releases dopamine (DA); and the cholinergic nuclei that are the basal forebrain (BF), pedunculopontine tegmental (PPT) nucleus, and the lateral dorsal tegmental (LDT) nucleus that release acetylcholine (ACh). Also shown is the lateral hypothalamus (LH) that releases orexin (Patrick L. Purdon, 2015, págs. 937–960).

Upper figure shows the inhibitory action of propofol in various sites of the brain, including cortical and subcortical structures. The disconnection between these two cerebral structures has been widely discussed to be the main component in loss of consciousness in patients anaesthetised with this drug (P. Guldenmund, 2015).

**Remifentanil**

Remifentanil, a fentanyl derivative, is a short acting, nonspecific esterase metabolised, selective mu-opioid receptor agonist, with a pharmacodynamic profile typical of opioid analgesic agents. Notably, the esterase linkage in remifentanil results in a unique and favourable pharmacokinetic profile for this class of agent. Adjunctive intravenous remifentanil during general anaesthesia is an effective and generally well tolerated opioid analgesic in a broad spectrum of patients, including adults and paediatric patients, undergoing several types of surgical procedures.

As mentioned in the section States of Anaesthesia, remifentanil is used as an intravenous analgesic and usually infused together with propofol, as they have presented a synergic combination achieving the same therapeutic effect with less concentration of both agents (Mertens MJ, 2003).

**Rocuronium**

Rocuronium bromide is an amino steroid [non-depolarizing](https://en.wikipedia.org/wiki/Neuromuscular-blocking_drug#Non-depolarizing_blocking_agents) [neuromuscular blocker](https://en.wikipedia.org/wiki/Neuromuscular-blocking_drugs) or [muscle relaxant](https://en.wikipedia.org/wiki/Muscle_relaxant) used in modern [anaesthesia](https://en.wikipedia.org/wiki/Anaesthesia) to facilitate [tracheal intubation](https://en.wikipedia.org/wiki/Tracheal_intubation) by providing [skeletal muscle](https://en.wikipedia.org/wiki/Skeletal_muscle) relaxation, most commonly required for [surgery](https://en.wikipedia.org/wiki/Surgery) or [mechanical ventilation](https://en.wikipedia.org/wiki/Mechanical_ventilation). Rocuronium is also commonly used to avoid unvoluntary hiccups while operating.

In general, neuromuscular blocking agents are divided between depolarizing and non-depolarizing. Depolarizing muscle relaxants act as acetylcholine (ACh) receptor agonists, whereas nondepolarizing muscle relaxants function as competitive antagonists as seen in figure below (Butterworth, 2013, pág. chapter 13).

Diagram

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Figure 3: Action of neuromuscular blockers on Acetylcholinergic ion channels (Marieke Kruidering-Hall, 2016)

When comparing, non-depolarizing blockers are reversed by [acetylcholinesterase inhibitor](https://en.wikipedia.org/wiki/Acetylcholinesterase_inhibitor) drugs since non-depolarizing blockers are competitive antagonists at the ACh receptor so can be reversed by increases in ACh. On the other hand, the depolarizing blockers already have ACh-like actions, so these agents have prolonged effect under the influence of acetylcholinesterase inhibitors. Administration of depolarizing blockers initially produces fasciculations (a sudden twitch just before paralysis occurs). This is due to depolarization of the muscle. Also, post-operative pain is associated with depolarizing blockers (Neuromuscular blocking agents, 2021).

### Anaesthesia monitoring

#### Basic anaesthesia monitoring

Anaesthesia monitoring is a crucial control system to guarantee the correct physiological state of the patient under surgery. Several sensors are used to record data based on biomedical signals and parameters in order to analyse in situ the correct state of the patient and also to later process the data to obtain information and generate models, as it is the goal of this project.

The list of variables recorded in the CMA OR number 4 where the following:

Table

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Table 3: Recorded variables in this project. Redundant variables have been excluded, and we the same variables recorded for propofol have been recorded for remifentanil. (Altès, 2020, pág. 26)

**Electrocardiogram**

Electrocardiogram (abbreviated as EKG or ECG) is a relationship between voltage and time recorded from cutaneous electrodes positioned in different derivations. Willem Einthoven first invented it in 1902. An EKG is an integral part of the initial evaluation of a patient suspected of having a cardiac-related problem or, in our case, a biomedical signal recorded in the OR to detect cardiac abnormalities throughout the operation, either way produced by the general anaesthesia or the operation itself (Yasar Sattar, 2021).

Several parameters can be derived from ECG as heart rate (HR) and ST segment. HR changes might have relationship with hypnotic and analgesic effect (Jeanne, 2009, págs. 91-96). It is generally desirable to maintain HR between 40 and 100 beats per minute.

**Arterial blood pressure**

Arterial blood pressure can be measured invasively for accurate measurement, throughout the use of an arterial catheter with a pressure transducer attached to the end. This invasive approach is usually introduced in the radial arteria. On the other hand, non-invasive arterial blood pressure (NIBP), which is the usual approach unless specific indications are met, is measured with an automated oscillatory cuff every ... seconds (Gbenga Ogedegbe, 2010, págs. 571-586).

It is desirable to keep mean NIBP above 60mmHg and systolic NIBP and diastolic NIBP below 140 and 90mmHg, and there are drugs avaliable to modulate the NIBP of the patient.

**Pulse oximetry**

Pulse oximetry is a non-invasive method to measure the oxygen saturation in the blood by emitting light at specific wavelengths through tissue (most commonly the fingernail bed). Deoxygenated and oxygenated haemoglobin absorb light at different wavelengths (660 nm and 940 nm respectively), the absorbance at the characteristic wavelengths is then assessed to give a saturation value from 0 to 100% (Torp, Modi, & Simon., 2021).

**Capnography**

Capnography is the monitoring of the concentration or partial pressure of carbon dioxide (CO2) in the respiratory gases. During general anaesthesia the patient is intubated, and capnography shows the effectiveness of CO2 elimination through the lungs into the anaesthesia equipment. It is therefore useful to assess the correct intubation of the patient. Indirectly, it monitors the production of CO2 by tissues and the circulatory transport to the lungs (Pandya & Sharma., 2021).

#### Advanced monitoring systems

#### Electroencephalogram

EEG is a graph of voltage against time of the electrical voltage present at the places of the head where the electrodes are placed. Normally, EEG is assessed through superficial electrode placing, therefore obtaining information mainly from the cortical area of the brain, and indirectly from subcortical regions due to their straight electrical interaction (Patrick L. Purdon, 2015, págs. 937-960). By applying a Fourier transform algorithm to the EEG the signal the frequency behaviour of the signal can be obtained (Shaker, 2003).

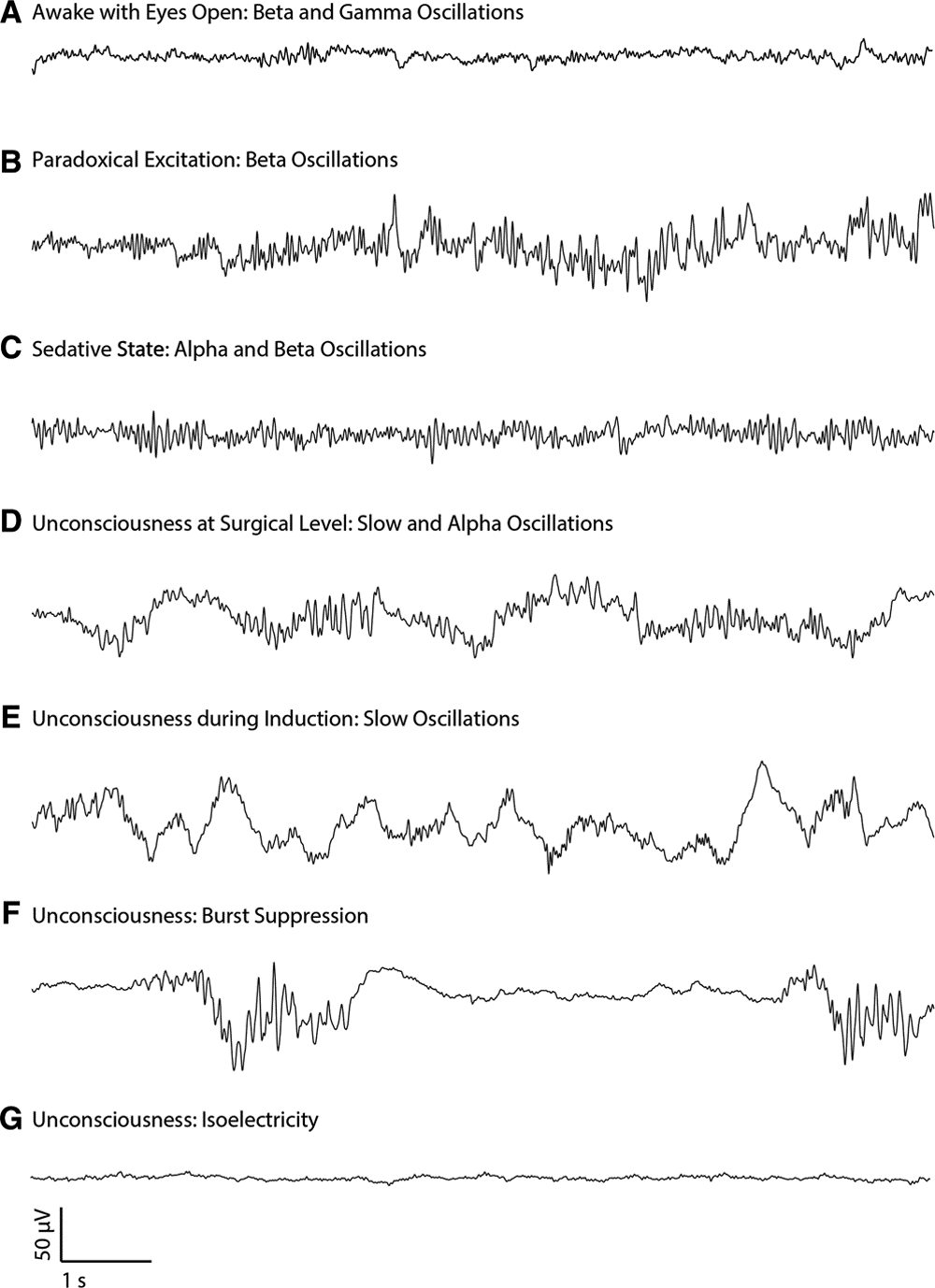
Many of the changes that occur in the brain with changes in anaesthetic states can be readily observed in unprocessed electroencephalogram recordings. Different behavioural and neurophysiological states induced by anaesthetics are associated with different electroencephalogram waveforms. For example, figure below shows the electroencephalogram of the same patient in different states of propofol-induced sedation and unconsciousness (Patrick L. Purdon, 2015, págs. 937–960).

Figure 4: EEG time domain visualizations in different unconsciousness levels (Patrick L. Purdon, 2015, págs. 937–960)..

EEG patterns in general anaesthesia are altered depending on the drugs used, the dose and duration of infusion, with significant variance between subjects. In general anaesthesia low frequency, high amplitude EEG profiles are enhanced as unconsciousness deepens (Emery N. Brown, 2010).

Furthermore, in section F of the figure we can observe a burst suppression event, where periods of high amplitude and frequency (called burst) are followed by low frequency and amplitude, even isoelectric zones (the suppression). It is a sign of unnecessarily high level of unconsciousness, and the facultative normally uses this information to adjust the anaesthetic dose or infusion rate.

As the raw EEG is complex to analyse without a lot of expertise, several approaches of EEG-based indexes have been developed to information of the state of the patient. This indexes generally extract parameters from the EEG through signal processing techniques, for later introducing this information into a confidential algorithm to obtain a 0-100 index representative of the state of the patient (Mathur S, 2021 Jan-. Available).

Bispectral Index (BIS) is one of the most popular EEG-based indexes, and it is prepared to assess the hypnotic effect of anaesthesia, being 0 completely unconscious and 100 completely conscious. Surgeries under BIS monitoring has shown to impact positively in patients’ time of extubation, postoperative recovery, memory loss and cognitive impairment in general (Carlos Rogério Degrandi Oliveira, 2017 Jan-Feb, págs. 72-84).

### Model theory

In general terms a system can be defined as a box (or transfer function), with a process happening inside of it, which takes some input arguments and delivers some output results. Depending on the processes inside the box and the type of inputs and outputs the system can be classified in several ways. If the processes inside the box is not known it is called a black box.

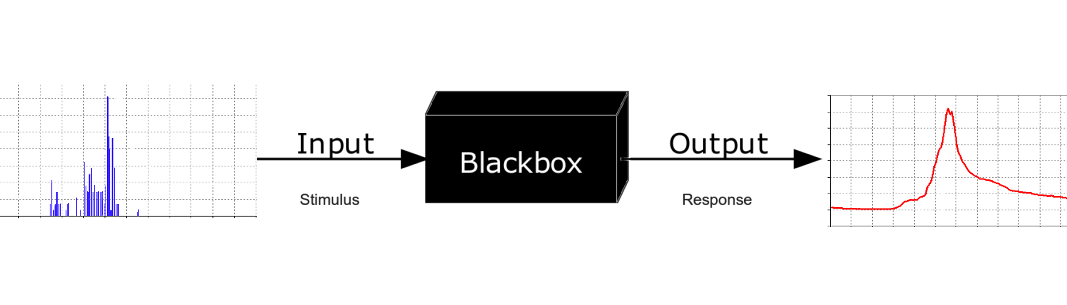


Figure 5: Example of a black box system transforming some discrete data (blue) to continuous (red).

As a matter of fact, any type of modelling is intrinsically a representation, numerical or not, of the part of the world surrounding us we wish to study. When models are developed, some input variables or characteristics are used, and some others are excluded; it is therefore straightforward that a models can be good enough to be useful or not but will never pretend to explain a real process in its whole complexity. Otherwise, they will try to simplify the studied system in a way the results have significance.

If a given system is particularly a mathematical model, which is a representation of the reality based on mathematical relationships, it can be classified in several ways explained below (Pospeev, 2019):

* Deterministic vs probabilistic: The model’s output is the same always for a given set of input values, or otherwise it has an intrinsic randomness which makes the output values vary even for the same set of input values. In this last case we usually see that state variables of the system are not described by unique values, but for probabilistic equations.
* Static vs. dynamic: In static models state variables are not time dependant, they are in steady state, while in dynamic models state variables do depend on time.
* Discrete vs. continuous: The equations inside the model follow a continuous paradigm or a discrete one. For instance, the parameters we measured in the OR room were recorded every 1 second, so our model will be discrete.
* Linear vs. nonlinear: Referring the distribution of the mathematical approximations to represent reality, if they are based on linear relationships or of higher order relationships.
* Etc.

#### Predictive modelling

When talking about predictive modelling, the adjective predictive stands for its finality to obtain information about what is going to happen in the future based on information of the past.

For instance, sophisticated predictive models are used to predict health events in patients and to screen high risk individuals, such as for predicting cardiovascular disease, breast cancer or anaesthetic complications and events. Predictive modelling does not inherently belong to any of the classifications stated above but takes different forms depending on its characteristics and those of the algorithms inside it.

Therefore, a model is predictive if it uses information from the past, e.g., past examples, in order to achieve a future prediction or output result. Even though the term Machine Learning model is frequently used, what we are handling is a predictive model, which inside it we are using a ML algorithm. Also, methods and algorithms used inside the model can be of several types and origins: basic statistics, time-dependant causal equations, AI algorithms such as ML and DL, and a long etcetera.

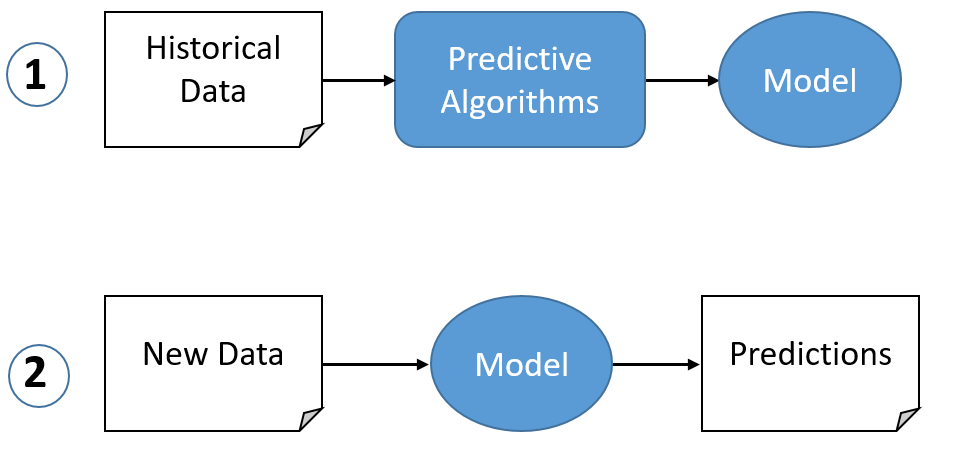


Figure 6: Predictive modelling scheme (Parthasarathy, 2021)

But what is exactly ML and what has in common with AI? AI is a set of algorithms and techniques which pretend to mimic or assemble human like mental processes to accomplish tasks which usually require of human intelligence. ML is a subset of the AI paradigm, which is characterised by being capable of learning without being explicitly programmed. Finally, DL is a subset of ML characterised by a brain-like net of artificial neural networks (NN) which the DL algorithm uses to learn, also without being explicitly programmed but using vast amounts of data. [8]

Diagram

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Figure 7: Visualization of algorithms vs. artificial intelligence vs. machine learning vs. deep learning (Author: Johannes Vrana, Vrana GmbH, Licenses: CC BY-ND 4.0) [8]

##### Statistical algorithms

##### ML algorithms

In this section we will review three of the most spread ML algorithms, Support Vector Components, Random Forest Classifier and K-Nearest neighbour.

**Support Vector Machine**

SVM is a supervised machine-learning algorithm that provides classification, regression, and outlier detection. SVM learns by creating a separating “line” between the two class points of the training data (e.g. drawn in a x-y plane). This “line”, which actually is a hyperplane, must perfectly separate the two classes, and its distance from both classes is to be maximized (Pushpa Singh N. S., 2021, págs. 80-111).

Chart, scatter chart

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Figure 8: SVM diagram (Pushpa Singh N. S., 2021, págs. 80-111).

Still regarding learning, the closest points to the margin (the hyperplane, also call decision boundary) are called “Support Vectors” and are the ones defining the behaviour of the SVM. The distance from the points to the decision boundary is computed, and, and the minimum value of this whole is considered the functional margin of the model respect to the dataset. Obviously, the larger the functional margin, the better predictive characteristics will be present in the model. Finally, if it is not possible to separate the two classes through a linear approach, the “Kernel trick” is use, meaning that the model projects the los dimensionality information provided to higher dimensional spaces where the separation easier (Pushpa Singh N. S., 2021, págs. 80-111).

Finally, after the training is done, the classifier just draws the new data, the one to be predicted, into the same plane, and depending on the side of the hyperplane where it falls it will be classified as one class or the other.

**Random forest classifier**

RF classifier is an ensemble method that trains several decision trees in parallel with bootstrapping followed by aggregation, jointly referred as bagging. Bootstrapping indicates that several individual decision trees are trained in parallel on various subsets of the training dataset using different subsets of available features, as seen in Fig.9. Bootstrapping ensures that each individual decision tree in the random forest is unique, which reduces the overall variance of the RF classifier (Siddharth Misra, 2020, págs. 243-287).

Diagram

Description automatically generated

Figure 9: Random Forest classifier diagram (Siddharth Misra, 2020, págs. 243-287)

Regarding the ensemble of trees, each internal node (seen as a circle in Figure 9) represents a 'test' on an attribute (e.g., whether a coin flip comes up heads or tails), each branch represents the outcome of the test, and each leaf node represents a class label (decision taken after computing all attributes).A node that has no children is a leaf (Donges, 2021).

For the final decision, RF classifier aggregates the decisions of individual trees; consequently, RF classifier exhibits good generalization. RF classifier tends to outperform most other classification methods in terms of accuracy without issues of overfitting and does not need feature scaling (Donges, 2021).

***k*-Nearest neighbour classifier**

KNN is a nonparametric, supervised machine-learning method used for classification and regression. Predictions are made for a new input (X) by examining the complete training set and summarizing the value or classification of the K nearest instances. Distance-based methods like Euclidean or Manhattan or Minkowski are used to define the K instances in the training dataset that are most similar or “near” in order to predict the output class label of the new input (X) (Pushpa Singh N. S., 2021, págs. 89-111).

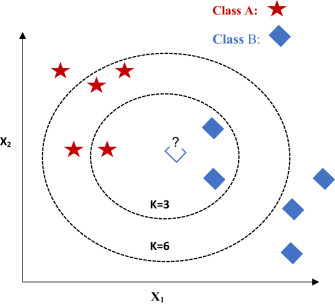


Figure 10: KNN diagram (Pushpa Singh N. S., 2021, págs. 89-111)

If for instance we take the Euclidean example in figure above, for k=3 we get that out new input X with classification unknown has two blue neighbours and one red, it will therefore be classified as blue. On the other hand, if K=5, we get 4 red neighbours and two blue, and the output would be therefore red.

#### Model performance

Evaluating a model performance is a crucial part of model construction, as the metrics obtained from this analysis and the concrete needs of the problem to be solved or predicted will determine if the model is valid or not for the purpose it was created. In general, several metrics are used to evaluate model performance depending on the type of problem to solve and the model used. In our concrete case, the most common methods used to evaluate ML binary classification model performance are confusion matrix and ROC curve.

**Confusion Matrix**

Confusion matrices represent counts from predicted and actual values. The output “TN” shown in the figure below stands for True Negative which shows the number of negative examples classified correctly as negative. Similarly, “TP” stands for True Positive which indicates the number of positive examples classified as positive. The term “FP” shows False Positive value, i.e., the number of actual negative examples classified as positive; and “FN” means a False Negative value which is the number of actual positive examples classified as negative.

Table

Description automatically generated

Table 4: Confusion matrix diagram

From confusion matrices we obtain these four values, which are later used to compute the metrics which evaluate the model, but they already offer a glimpse of the model performance at first sight. This mentioned metrics are Accuracy, Precision, Recall and F1-Score, which are explained below (Pushpa Singh, 2021, págs. 88-111).

The accuracy of a model is calculated using the given formula below.

Equation 1: Accuracy formula

As shown above, accuracy of an algorithm is represented as the ratio of correctly classified patients (TP+TN) to the total number of patients

Regarding precision or specificity of an algorithm, it represents the ratio of correctly classified patients as positive (*TP*) to the total patients predicted to be positive (*TP*+*FP*).

Equation 2: Precision formula

This metric gives us knowledge about how many patients are actually positive from the whole that has been classified as positive

Recall or sensitivity metric is defined as the ratio of correctly classified positive patients (*TP*) divided by total number of patients are actually positive.

Equation 3: Recall formula

The perception behind recall is how many patients have been classified as positive from the total amount of patients that actually are positive. Recall is also called as sensitivity, meaning the ability of the model to predict a positive when analysing one.

F1 score is also known as the F Measure. The F1 score states the equilibrium between the precision and the recall with the formula below:

Equation 4: F1-Score formula

As seen in Equation 4, F1-score is computed as the harmonised mean between precision and recall. This metric is useful because dumb models predicting unbalanced data can generate an output classifying every sample as the major category, therefore being useless as a classificatior but presenting good metrics in, for instance, accuracy and recall. Harmonised mean (HM) is an operator that strongly penalises extreme values. This means that if precision and recall are different from each other, as in the situation explained above, the HM will penalise the metric more than the arithmetic mean. Therefore F1-score is more sensible to extreme precision and recall values and gives us more meaningful information of the performance of the model (Tavish Srivastava, 2019).

**Receiver Operating Curve (ROC)**

ML predictive models usually provide a probability for the classification, instead of an actual classification, and later a threshold is defined to determine at which probability we consider the value to one output or the other. For instance, if we are classifying binary between 0 and 1, the model gives us a probability of 0.82 to be 1, if we put the threshold at 0.8, the output would be classified as 1, but if we put it at 0.9 it would be classified as 0. It is then desirable to determine at which threshold the model classifies better the observations, and in this scenario is where the ROC acquires importance.

A receiver operating characteristics (ROC) graph is a technique for visualizing, organising, and selecting classifiers based on their performance (Fawcett, 2006, págs. 861-874). But an actual binary classifier represented in a ROC would be drawn as a point. The characteristic curve, which usually resembles something like in the figure below, is the different values of sensitivity and 1-Specificity that present the binary classifier for each of the possible thresholds defined. This way we can assess the point, depending on our interests, where we will define the final threshold of the model.

Chart

Description automatically generated with medium confidence

Figure 11: ROC critical points (Zoronza, s.f.)

In the figure above we can observe some critical points and depending on the problems’ necessities we will choose a point or another as the final threshold. For instance, if it is not so important to detect all real positives but it is to avoid false positives, point B would be chosen as it never classifies a negative person as positive, while it still correctly classifies some of the real positives.

The most common way to assess the whole performance of the model at all the thresholds is to compute the area under the curve (AUC), which is a parameter that goes from 0 to 1, with 1 being a perfectly accurate model, that is, sensitivity equals 1 even when specificity equals 1, and 0.5 representing half of the predictions right, that is, random probability which is illustrated by a straight line from origin to top right corner in ROC curve shown in figure 8.

## State of the art

# Market analysis

# Solution implementation

## Concept engineering

Ingeniería de concepción (funcional) de la solución. Esquemas de principio, balances y predimensionados

### Different solutions

Aqui hauriem de tractar les diferents solucions possibles al problema (estadistica, ML, DL...)

### Proposed Solution

Justificar la solucio triada sobre les altres

## Detail engineering

En la ingenieria de detalle pondriamos todos los planes, especificaciones, condiciones que se empezaron a describir en la ingenieria de concepcion

### Data processing

### Exploratory analysis

### Model training

### Model Validation

# Chronogram and execution

Definición de tareas, tiempos y asignación de

responsabilidades. Establecimiento de fases e

hitos. Análisis de caminos: camino critico

Diagramas de PERT, GANT

Cronograma. Penalizaciones

EDT, Análisis de precedencias, CPM/PERT y

GANTT

# Technical

## Specifications and technical characteristics

## DAFO

Debilidades y fortalezas. Resistencias. Puntos criticos

Mantenibilidad, fiabilidad, disponibilidad y calidad

Seguridad

Suministros y repuestos

Asistencia tecnica

# Economic viability

Estudio de costes y presupuestos

Planificación económica

Estudios de costes

Estudios de financiación

Análisis de rentabilidad: Payback, VAN, TRI

Análisis de sensibilidad

# Legal aspects

# Results

# Discussion and Future Prospects

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# Annex

Validació prospectiva d’un model de supervivència, que preten donar una probabilitat de que el pacient romangui conscient en funció de la dosi de propofol (Hipnotic) administrada.

Loss of consciousness refers to a state in which an individual lacks normal awareness of self and the surrounding environment. The patient is not responsive and will not react to any activity or stimulation. Syncope is the medical term for temporary loss of consciousness.