

BIELEFELD UNIVERSITY

MASTERS THESIS

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# Simulating sedation-induced unconsciousness in a Neural-Mass-Model

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Neuroinformatics Group  
Faculty of Technology

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# *Abstract*


Faculty of Technology  
Neuroinformatics Group

Master of Science

## **Simulating sedation-induced unconsciousness in a Neural-Mass-Model**

by Felix FRIESE

*Patients with severe Traumatic Brain Injuries (TBI) often remain in a state of unresponsive wakefulness. Brain-Computer-Interface (BCI)-based systems promise to improve the state assessment and to open a communication channel for patients to express their intent while in conscious states. Developing such a BCI-System (e.g. with EEG), including the necessary algorithms to assess a patients current wakefulness or consciousness state from EEG data is a challenging task. Development, testing and evaluation of these algorithms requires labeled data (ground truth), which is almost impossible to obtain given the patients' lack of communication capabilities. Therefore, it would be desirable to generate a synthetic signal, which should ideally resemble real EEG data in all relevant features. We previously developed a simple ICA-based model, which generates a multichannel EEG from base-signals with configurable spectral features. While this proved useful for testing numerous components of our signal-analysis framework, it lacks biological plausibility and explanatory power to model the changes in the signal's properties given an altered state of consciousness. In this thesis, we propose an approach towards overcoming these issues while sticking with the original goal of generating realistic, practically useful surrogate data. A biologically motivated Neural Mass Model (NMM) on cortical-column level is implemented, which is able to approximate the effects of sedation-induced unconsciousness on the generated signal. The model is then shown to be able to reproduce the characteristic effects that sedation has on the EEG-Signals of real subjects. This is a first step to a model of consciousness-altering processes in the brain, which could ultimately be extended to realistically simulate other processes like sleep and trauma-induced DoC, facilitating better detection algorithms and furthering the goal to develop working BCI-Systems in the given context.*

 Todo

This is old! Re-write the abstract to match the new hypothesis! (very last thing to do)



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# List of Abbreviations

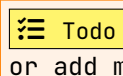
<b>BCI</b>	<b>B</b> rain <b>C</b> omputer <b>I</b> nterface
<b>DoC</b>	<b>D</b> isorder(s) <b>o</b> f <b>C</b> onsciousness
<b>EEG</b>	<b>E</b> lectroencephalography
<b>fMRI</b>	<b>f</b> unctional <b>M</b> agnetic <b>R</b> esonance <b>I</b> maging
<b>GA</b>	<b>G</b> eneral <b>A</b> naesthesia
<b>GABA</b>	<b>G</b> amma- <b>A</b> minobutyric <b>A</b> cid
<b>ICA</b>	<b>I</b> ndependent <b>C</b> omponent <b>A</b> nalysis
<b>[E/I]IN</b>	<b>[E</b> xcitatory/ <b>I</b> nhibitory] <b>I</b> nter <b>n</b> euron
<b>[L/R]OC</b>	<b>[L</b> oss/ <b>R</b> ecovery] <b>O</b> f <b>C</b> onsciousness
<b>NMM</b>	<b>N</b> eural <b>M</b> ass <b>M</b> odel
<b>PC</b>	<b>P</b> yramidal <b>C</b> ell
<b>[E/I]PSP</b>	<b>[E</b> xcitatory/ <b>I</b> nhibitory] <b>P</b> ost- <b>S</b> ynaptic- <b>P</b> otential
<b>TBI</b>	<b>T</b> raumatic <b>B</b> rain <b>I</b> njury





# Chapter 1

## Introduction

 **Todo** either remove this section and call chapter `Intro & Motivation` or add more sections

### 1.1 Motivation

The highly complex processes of changing states of consciousness in the human brain are still barely understood. States of consciousness have historically been defined based on behavioral observations such as responsiveness to stimuli. As no other indications, save simple physiological measurements such as pulse and respiration rate, were available, the concept of awareness was tightly linked to observable behavior. While the great majority of medical applications to determine levels of consciousness, even in practical clinical contexts [46], are still covered by these observations, there are cases in which the link between consciousness and displayed behavior falls apart; striking examples are some disorders of consciousness (DOC) as well as the total locked-in syndrome [6], where patients are unable to display any visible behavior, while maintaining some or even full awareness. Although cases like these are rare, they highlight that consciousness needs to be studied at its source – on the level of brain-activity – to fully understand the mechanisms that lead to its different states. Brain-activity can be measured directly or indirectly. Direct measurement with electrodes in the brain, while more accurate, poses the obvious problem of its invasive nature and faces the challenge of realistically

 **Todo** rephrase

only allowing very localized measurements [citation needed]. Various neuroimaging techniques, which indirectly measure brain-activity, have been used to study levels of awareness since their emergence. Already in the 1880's, Angelo Mosso measured scalp-pulse variations in subjects with skull-injuries during challenging tasks, and concluded an increased blood-flow to the brain [1]. Improved techniques like the fMRI and the EEG allow for non-invasive observation of brain-activity and have been used extensively to study the dynamics of the brain during sleep and loss and return of consciousness [citation needed]. Some phenomena, like predictable changes in signal-frequencies and some critical brain regions involved in consciousness-modulation, e.g. to induce sleep, have been identified and are well documented [citation needed]. Techniques to measure levels of consciousness via neuroimaging have been proposed [9], [27] and used in practise [47]. However, exact mechanisms behind state-changes are still object of fundamental research.

Controlled state-changes, like inducing loss-of-consciousness with anaesthetic drugs, are exceptionally well-suited for studying the underlying mechanisms of consciousness, as they allow for repeatable conditions. Furthermore, the neuro-chemical mechanisms of the drugs provide a good starting-point for modeling these processes. The sedative propofol is the most commonly used drug to induce controlled loss of consciousness during general anaesthesia. Propofol's neuro-chemical mode of action and its specific effects on synaptic receptors are well understood, which lays a solid foundation to study the brain-dynamics associated with loss of consciousness.

☰ **Todo**                      clarify/establish what exactly we simulate  
(``behavior'' is unspecific)

A promising approach to further our insights step by step, is to simulate controlled state-changes (such as anaesthesia) in computer-models to develop an understanding of the dynamics of brain-activity and its effects on consciousness. Computer-models of the brain (or parts of it) exist on different levels [44], including simulations of individual neurons and population-based approaches. Neural-Mass-Models (NMMs), members of the latter, model synaptic connections between populations of different types of neurons and have proven to replicate multiple abstract phenomena of brain-dynamics[30], [33] within a small cortical column. The simplifications they provide allow efficient real-time simulation of signals, while preserving many important characteristics of EEG or MEG signals.

☰ **Todo**                      maybe work in Steyn-Ross' argumentation, that loss of consciousness is a phenomenon global to the cortex which further justifies the choice of population models in contrast to single neuron simulation

☰ **Todo**                      WHY EEG & NMM? What are the alternatives?

☰ **Todo**                      improve explanation of NMMs

By combining the well-known properties of propofol with an NMM, we can hope to gain insights into the mechanisms that govern changes of brain-dynamics in the presence of consciousness-altering drugs. While the abstract nature of NMMs, along with its limitations must always be considered [43], the results of simulated experiments can provide valuable research indications.

☰ **Todo**                      start section ``contribution of this thesis:`` to lead into the following

One of the most commonly used models in the area of neural population models is the Jansen-Rit [10] (JR) NMM, which is based on efforts by Wilson & Cowan [2], Lopes da Silva et al. [3], [4] and Zetterberg et al. [5]. It is one of the most simple and basic population models, while retaining ‘a considerable degree of biological realism’ and ‘producing a surprisingly rich repertoire of dynamic behaviors’ [33]. Many efforts in the field are based on the JR NMM, e.g. [13], [17], [23], [25], [31], [39] and others.

Neural-Mass models have been widely used to simulate the properties

☰ **Todo**                      maybe specify

of different states of consciousness. Cona et al. [31] adapted multiple interconnected JR NMM modules to simulate effects of different stages of sleep. Their model accounts for thalamo-cortical modulation of cortico-cortical connectivity as an important mechanism to influence these transitions. Another sophisticated example is Bensaid et al.'s COALIA Framework [16], [39], which makes use of a similar connectivity structure,

while using over 60 interconnected NMM-modules and applying a transformation onto scalp electrodes using a realistic head-model with tissue conductivities. The resulting system is able to simulate the influence of Transcranial Magnetic Stimulation (TMS) during either a waking or sleeping state.

However, since we are looking to simulate propofol-induced unconsciousness, other approaches bear special consideration: To simulate phenomena specific to general anaesthesia, Steyn-Ross et al. [19], [26] developed a neural field model based on Liley et al.'s continuum model [12]. Neural field models are similar to neural mass models, but also take into account the continuity of the cortex and the spatial distribution of neurons [45], adding complexity to the model.

The JR model has its greatest advantages in its simplicity (even including extensions) and serves as 'Occam's Razor' for many applications in the field [36]. As its fundamental structures have proven to be a working local basis for sophisticated approaches as the COALIA framework, it appears desirable to evaluate its ability to simulate the effects of anaesthesia and serve as a simple tool to further consciousness research in that area. This work aims to reproduce the behavior observed in Steyn-Ross et al.'s neural field model [26] using a neural mass approach based on the JR model, thus helping to investigate the prerequisites for the emergence of the phenomena in brain-dynamics typical to anaesthesia - specifically the existence of propofol hysteresis and a biphasic effect as reported by [26]. While the basic JR model is able to produce rich patterns of dynamic behavior [25], large regions of its parameter-space generate sinusoidal signals with a single pronounced frequency, which might limit its ability to reproduce the expected phenomena (as noted by [36]). Therefore, the subpopulation-extension proposed by David & Friston [17] is also employed to produce a more realistic baseline frequency spectrum.



## Chapter 2

# Background & Starting Points

### 2.1 EEG

**⚠ Section Incomplete**

this section is obviously not written yet. low priority.

#### 2.1.0.1 Measurement

**☰ Todo**

how the EEG is measured technically and which neuronal processes it actually observes (signal amplification, pyramidal cells, ...)

#### 2.1.0.2 Advantages/Disadvantages

**☰ Todo**

spatial/temporal resolution, invasiveness, ...

#### 2.1.0.3 States of Consciousness in the EEG Signal

**☰ Todo**

how do the states differ in the signal

#### 2.1.0.4 Biphasic Effect

A biphasic effect (an initial increase of an effect, that decreases with higher concentrations) in the EEG can be observed for many sedatives [11], [14]. For propofol, a temporary steep increase in EEG amplitude in the 2–20 Hz ranges, loosely correlated with the onset of LOC, as well as ROC can be observed.


#### 2.1.0.5 Simulation

**☰ Todo**

what can we hope to achieve by simulating an EEG signal

**☰ Todo**

which tools are at our disposal (naive frequency mixing, population models, simulating individual neurons, ...)

 Todo

argue about models  $\Rightarrow$  why did we land on NMMs/population models?

## 2.2 Neural Mass Models

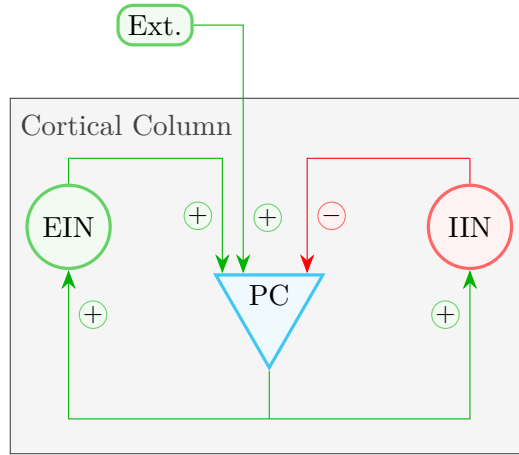
### 2.2.1 The Basic Jansen-Rit Model

The widely used Jansen-Rit Model [8], [10], is based on earlier models by Wilson & Cowan [2], Lopes da Silva et al. [3], [4] and Zetterberg et al. [5]. It represents a cortical column in the brain, which is made up of three main components, each modeling a population of neurons with distinct characteristics.

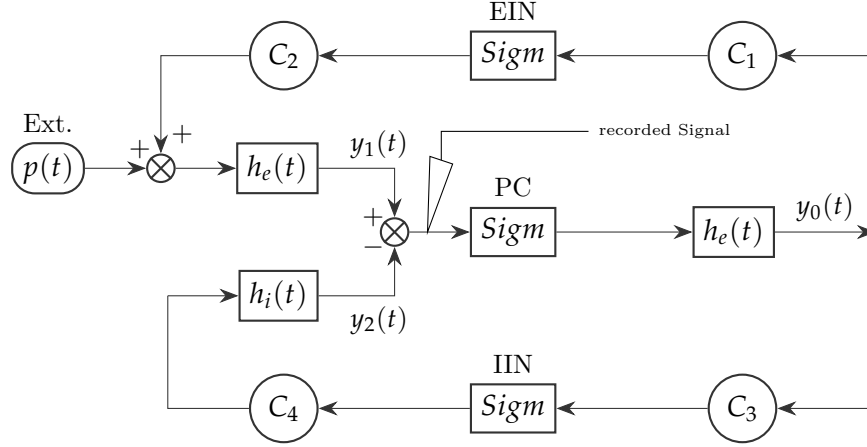
The basic schema of the model is visualized in Fig. 2.1, showing the connections between the main components. There is a population of Pyramidal Cells which receives input from two populations of inter-neurons, one of which is excitatory while the other is inhibitory. Each of the inter-neuron-populations receives the output of the PC population. Additionally, there is external excitatory input to the PC population from other regions of the brain.

The Block Diagram (Fig. 2.2) shows the individual modules of the model. A population consists of two types of blocks: The *PSP-Block* models the behavior of the synapses and neuronal somata. It can be either excitatory or inhibitory and converts the incoming average

pre-synaptic pulse density to an average post-synaptic membrane potential by convolving it with an impulse response function ( $h_e(t)$  and  $h_i(t)$ , for excitation and inhibition respectively). The second block (sometimes called *Potential-To-Rate-Block* after it's functionality) calculates the populations response to this stimulation, transforming the incoming average membrane potential back into an average pulse density of action potentials. It may be roughly viewed as a functional counterpart to the axon hillock by establishing a firing threshold and is usually implemented by a Sigmoid Function (*Sigm*). External input from other regions of the brain is represented by  $p(t)$ . The Connectivity Constants  $C_1$ ,  $C_2$ ,  $C_3$  and  $C_4$  are a proportional representation of the average number of synapses between the populations. The signal most closely related to the EEG and therefore the variable of interest, is the summed average membrane potential of the PC population ( $y_1(t) - y_2(t)$  in Fig. 2.2).



**Figure 2.1: Basic Schema of the Jansen-Rit Model:** Three populations of neurons



**Figure 2.2: Simple Block Diagram after [10]:** It's structure might be somewhat confusing when trying to visualize the biological analogy, where each population would have individual afferent PSP-Blocks. However, the fact that the two interneuron populations share a single excitatory PSP Block, because it produces identical results for both of them (disregarding their individual connectivity factor, which is simply applied afterwards), is a computational performance gain, thus likely explaining the authors' choice.

### 2.2.1.1 Potential-To-Rate Block

For a neuron to fire an action potential, its membrane potential needs to surpass a certain threshold. Since we are modeling not a single neuron but a whole population, we need an operator that can transform the mean membrane potential that the neurons of the population receive as input into an average firing rate for the whole population. While neurons within the population may have individual firing-threshold it can be assumed due to their sheer number, that these thresholds are normally distributed around some mean value  $v_0$ . An additional assumption that this approach rests on, is that the number of afferent (i.e. incoming) connections to the individual neurons is sufficiently large to justify the assertion that all neurons receive roughly the same stimulation. This must be modeled by a monotonically increasing function. The Potential-To-Rate Block represents this process with a Sigmoid. After multiple iterations by Zetterberg [5], Lopes da Silva [4] and others [7], Jansen and Rit [8], [10] landed on the following equation:

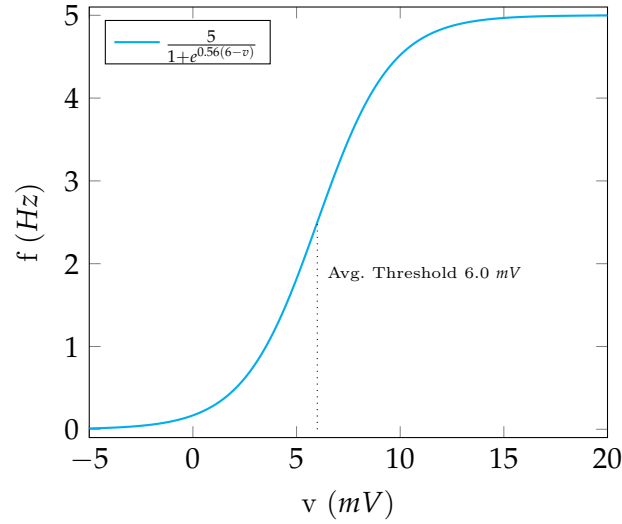
$$\text{Sigm}(v) = \frac{2e_0}{1 + e^{r(v_0 - v)}} \quad (2.1)$$

The parameter values (Table 2.1) are empirically determined [8]. The maximum firing rate the population can achieve is set at 5Hz. A mean membrane potential of 6mV (equal to the populations average firing threshold) elicits half of the maximum firing rate, while  $\frac{0.56}{mV}$  defines the steepness. The plot in Fig. 2.3 visualizes these properties.

Parameter		Default Value	Unit
half of maximum firing rate	$e_0$	2.5	Hz
average firing threshold	$v_0$	6.0	mV
sigmoidal steepness	$r$	0.56	mV <sup>-1</sup>

**Table 2.1:** Parameters of the Sigmoid Function





**Figure 2.3:** Sigmoid (Eq. 2.1) [8]

### 2.2.1.2 PSP-Blocks

In Physics, Linear Time-Invariant Systems (LTI systems) are oftentimes used to describe the response of electrical circuits to arbitrary input signals. They consist of a kernel function (or impulse-response function), that models the system's response to a single unit-impulse. The PSP-Blocks are an LTI system, fully represented by an impulse response function. It describes a PSP relative to the onset of a pulse. Since the PSP differs depending on the type of cell (excitatory or inhibitory), there are two different impulse-response functions. The parameters for the EPSP (Eq. 2.2) and IPSP (Eq. 2.3) are given in Table 2.2. The respective plots are visualized in Fig. 2.4.

Parameter		Default Value	Unit
Exc. max. amplitude / $e$	$A$	3.25	$mV$
Lumped repr. of sum of exc. delays	$a$	100	$Hz$
Inh. max. amplitude / $e$	$B$	22	$mV$
Lumped repr. of sum of inh. delays	$b$	50	$Hz$

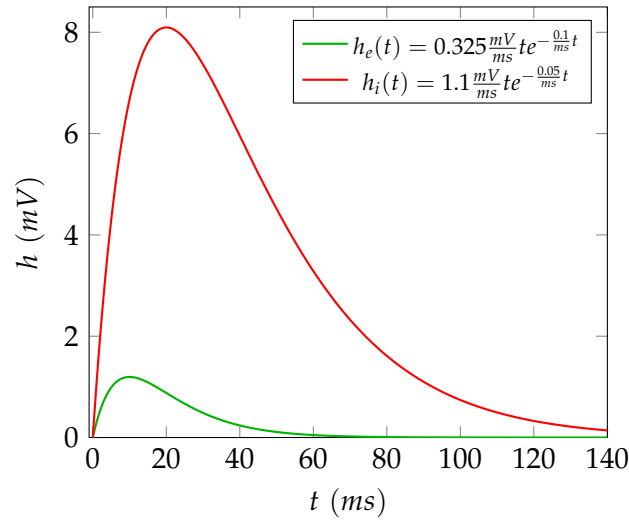
**Table 2.2:** Parameters of the PSP Blocks

Excitatory impulse response:

$$h_e(t) = \begin{cases} Aate^{-at} & t \geq 0 \\ 0 & t < 0 \end{cases} \quad (2.2)$$

Inhibitory impulse response:

$$h_i(t) = \begin{cases} Bbte^{-bt} & t \geq 0 \\ 0 & t < 0 \end{cases} \quad (2.3)$$



**Figure 2.4: Impulse Response Functions:** Note the small **EPSP** (Eq. 2.2) and the large **IPSP** (Eq. 2.3) [8]

Jansen and Rit [8] justify the difference in amplitude by referencing Lopes da Silva et al. [4] and stating that inhibitory neurons synapse closer to the somata of pyramidal cells (often on the cell body) than excitatory cells, increasing the effect of an inhibitory neuron about 10-fold.

⋮ Todo maybe go more into detail about the reasons for stronger inhibition

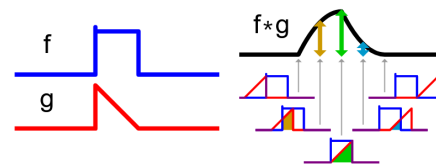
The output of the Linear System defined by the PSP-Blocks is calculated by a convolution (denoted by  $*$ ) of the incoming impulse density  $x(t)$  with the impulse response function  $h(t)$  (Eq. 2.4).

**Remark** (Convolution). *The convolution of two functions  $f(t)$  and  $g(t)$  is defined as the integral of their product after one function has been reversed and shifted <sup>1</sup>:*

$$f(t) * g(t) = \int_{-\infty}^{+\infty} f(\tau)g(t - \tau)d\tau$$

If  $f(t)$  is a unit-impulse  $\delta(t)$  (in our case that would mean each cell of the previous population firing a single action potential at the same time) the result is just  $g(t)$  (in our case representing a single full-amplitude impulse response as the mean membrane potential):

$$\delta(t) * g(t) = \int_{-\infty}^{+\infty} \delta(\tau)g(t - \tau)d\tau = g(t)$$



**Figure 2.5: Convolution:** The area enclosed by  $f(\tau)$  and  $g(t - \tau)$  is the value of  $(f * g)(t)$ .

By Cmglee - Own work, CC BY-SA 3.0  
<https://commons.wikimedia.org/w/index.php?curid=20206883>

<sup>1</sup>There is a very intuitive explanation of convolutions by Kalid Azad on his website <https://betterexplained.com/articles/intuitive-convolution/>

In the general case, this process can be used to mathematically model the integration of incoming action potential densities in the soma.

Importantly, the Convolution Theorem states that the convolution of  $f(t)$  and  $g(t)$  becomes a simple multiplication when applying the Laplace Transform:

$$\mathcal{L}\{f(t) * g(t)\} = \mathcal{L}\{f(t)\}\mathcal{L}\{g(t)\} = F(s)G(s)$$

That means you can calculate a convolution with the inverse Laplace-Transform of the multiplication of the functions' individual Laplace-Transforms:

$$f(t) * g(t) = \mathcal{L}^{-1}\{F(s)G(s)\}$$

Since the convolution in the time-domain is a computationally heavy operation, it is oftentimes faster to transform the equation into the Laplace-Domain (see Eq. 2.5), apply the Convolution Theorem and perform the multiplication there, and transform the results back to the time-domain. This results in a second order differential equation (Eq. 2.6) that can be efficiently solved by numerical integration. To obtain this form, we need the Laplace transform  $H_e(s)$  (in this context also called *Transfer Function*) of our response function  $h_e(t)$ :

$$H_e(s) = \mathcal{L}\{h_e(t)\} = \mathcal{L}\{Aate^{-at}\} = \frac{Aa}{(s+a)^2} = \frac{Aa}{s^2 + 2as + a^2}$$

With that, we can start to transform our initial equation into the desired Second Order System:

$$\underbrace{y(t)}_{\text{PSP}} = \underbrace{h_e(t)}_{\text{impulse response}} * \underbrace{x(t)}_{\text{impulse density}} \quad (2.4)$$

applying the Laplace-Transform eliminates the convolution:

$$\begin{aligned} \xleftrightarrow{\mathcal{L}} \quad Y(s) &= \underbrace{H_e(s)}_{\text{transfer function}} \cdot X(s) & (2.5) \\ \iff Y(s) &= \frac{AaX(s)}{s^2 + 2as + a^2} \\ \iff (s^2 + 2as + a^2)Y(s) &= AaX(s) \\ \iff s^2Y(s) + 2asY(s) + a^2Y(s) &= AaX(s) \end{aligned}$$

reversing the Laplace-Transform yields a differential equation in the time domain:

$$\begin{aligned} \xleftrightarrow{\mathcal{L}^{-1}} \quad \ddot{y}(t) + 2a\dot{y}(t) + a^2y(t) &= Aax(t) \\ \iff \ddot{y}(t) &= Aax(t) - 2a\dot{y}(t) - a^2y(t) & (2.6) \end{aligned}$$

which can be expressed as a system of two coupled first order equations:

$$\dot{y}(t) = z(t) \quad (2.7)$$

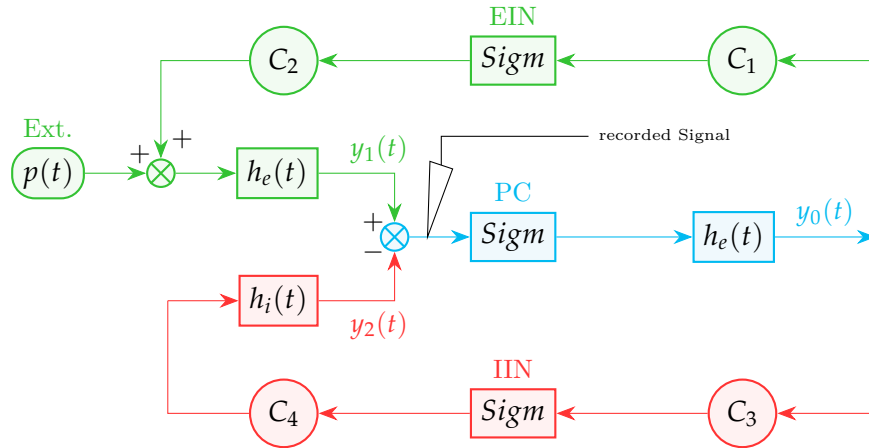
$$\dot{z}(t) = Aax(t) - 2az(t) - a^2y(t) \quad (2.8)$$

where  $y(t)$  is the resulting PSP and  $x(t)$  the incoming pulse density. This works analogously for the inhibitory case with  $h_i(t)$ .

### 2.2.1.3 Full Linear System

Taking the two first order equations for  $\dot{y}(t)$  (Eq. 2.7) and  $\dot{z}(t)$  (Eq. 2.8), and the Block diagram (Fig. 2.6) as a base, we can now state the equations for the full Jansen-Rit Model with it's three populations. Each PSP-Block  $h(t)$  needs it's own system of coupled differential equations. The value of  $x(t)$  can be easily taken from the Block Diagram.  $y_0(t)$  is the EPSP received by both the EIN and IIN population, while  $y_1(t)$  is the EPSP and  $y_2(t)$  the IPSP received by the PC population:


$$\begin{aligned}
 \dot{y}_0(t) &= z_0(t) \\
 \dot{z}_0(t) &= Aa\text{Sigm}[y_1(t) - y_2(t)] - 2az_0(t) - a^2y_0(t) \\
 \dot{y}_1(t) &= z_1(t) \\
 \dot{z}_1(t) &= Aa(p(t) + C_2\text{Sigm}[C_1y_0(t)]) - 2az_1(t) - a^2y_1(t) \\
 \dot{y}_2(t) &= z_2(t) \\
 \dot{z}_2(t) &= Bb(C_4\text{Sigm}[C_3y_0(t)]) - 2bz_2(t) - b^2y_2(t)
 \end{aligned} \tag{2.9}$$



**Figure 2.6:** Colored Block diagram, visualizing the components of (Eq. 2.9)


### 2.2.1.4 Connectivity Constants

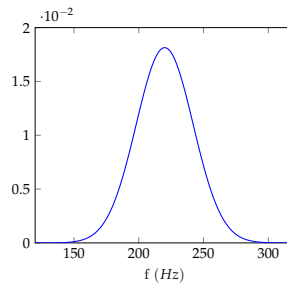
A sensible choice for the Connectivity Constants  $C_1$  to  $C_4$  was determined by Jansen and Rit empirically by defining a histologically motivated relationship between them ( $C = C_1 = \frac{C_2}{0.8} = \frac{C_3}{0.25} = \frac{C_4}{0.25}$ ) and varying  $C$  until the system produced the desired natural alpha-like activity at  $C = C_1 = 135 \Rightarrow C_2 = 108; C_3 = C_4 = 33.75$ . Varying  $C$  can account for common synaptic phenomena like neurotransmitter depletion [10].

 **Todo** go more into detail about the biological motivation and the effects of these constants on the generated signal

### 2.2.1.5 Model Input

The model input  $p(t)$  represents the average activity of populations outside the modeled column that synapse on the columns PC population. Since this activity's source is so diverse, it is modeled by white noise (120-320 Hz).

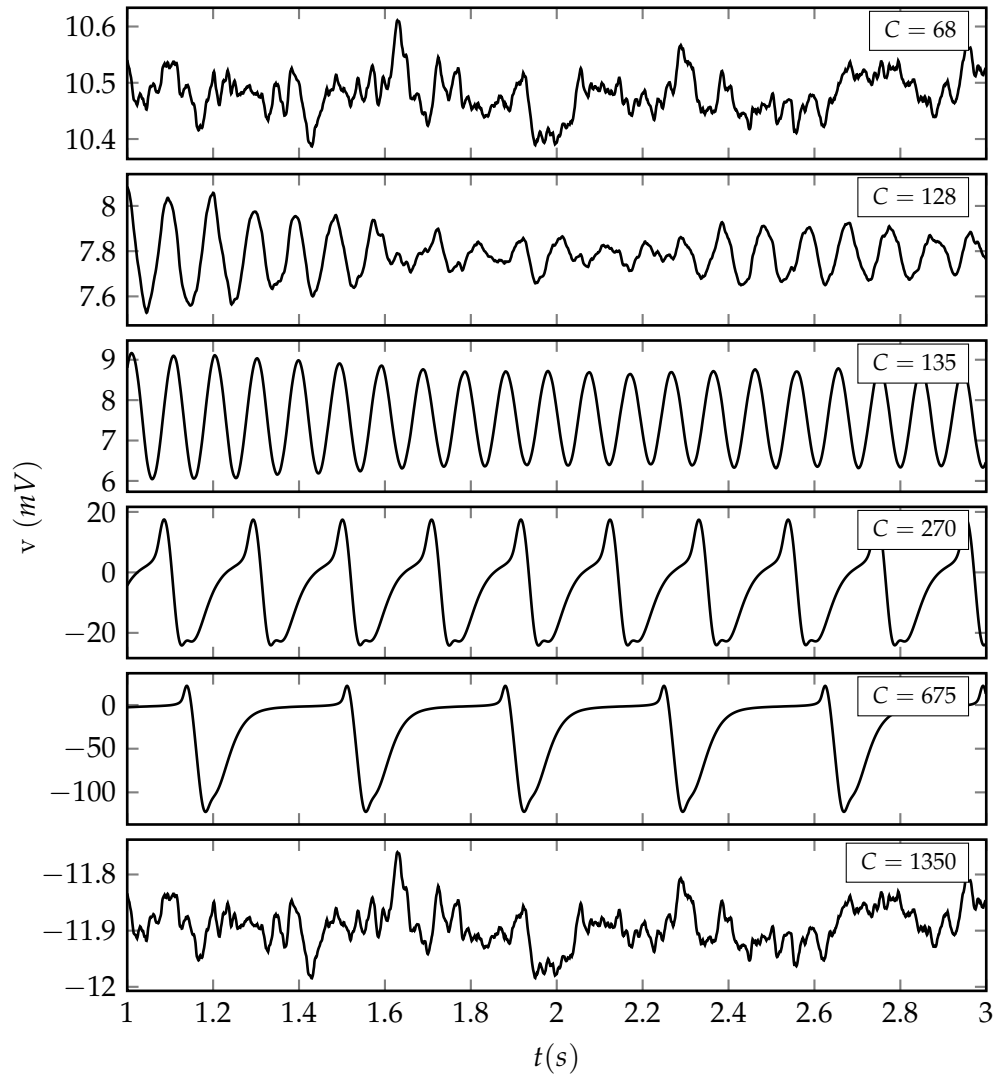
 go more into detail why the input is modeled like this



**Figure 2.7: Input distribution.** The input frequency representing  $p(t)$  is sampled from a normal distribution with  $\mu = 220$  and  $\sigma = 22$

### 2.2.1.6 Model Output

The simulated data from  $y_1 - y_2$  while varying  $C$  looks like this:



**Figure 2.8: Model Output for varying  $C$ .** Well defined alpha-activity is visible at  $C = 135$ .

☰ Todo

Explain Graph, generally provide more information to the systems output

### 2.2.2 The Sub-Population-Extension by David and Friston

**⚠ Section Incomplete**

the whole David-Friston-Section is still very much preliminary

While the Jansen-Rit model succeeds in generating realistic alpha activity, real EEG Signals contain much richer spectra [15]. David and Friston [17] proposed a modification to the Jansen-Rit model, that could produce a more realistic frequency spectrum by introducing sub-populations to the model. They can be tuned individually to produce oscillations in different frequencies.

#### 2.2.2.1 Introducing sub-populations

David and Friston slightly redefine  $h(t)$  by introducing the parameters  $H$  and  $\tau$  (see Table 2.3), which is just a minor alteration of  $A$  and  $a$ .

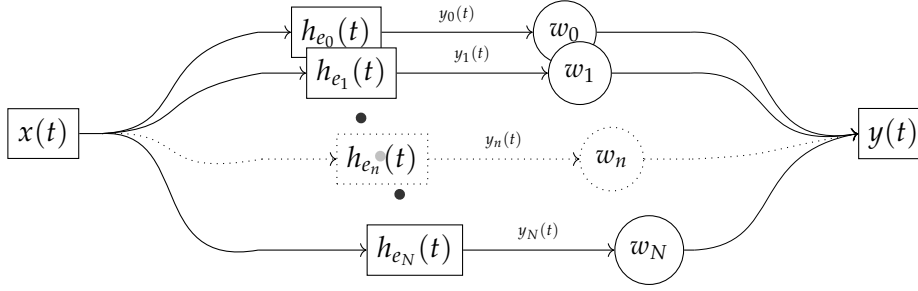
$$h(t) = Aae^{-at} \Rightarrow h(t) = \frac{H}{\tau} te^{-\frac{1}{\tau}t}$$

Furthermore, as they are tweaking these parameters to produce slower or faster sub-populations, they define the products  $H_e\tau_e = 0.0325mVs$  and  $H_i\tau_i = 0.44mVs$  as constants. This is done to preserve the oscillatory behavior of each population [17]. When varying  $\tau$ ,  $H$  is therefore adjusted accordingly ( $H_e = \frac{0.0325mVs}{\tau_e}$ ,  $H_i = \frac{0.44mVs}{\tau_i}$ ).

Parameter		Value	Unit	Relation to [10]
Excitatory delays	$\tau_e$	0.01	s	$\tau_e = \frac{1}{a}$
Inhibitory delays	$\tau_i$	0.02	s	$\tau_i = \frac{1}{b}$
Excitatory synaptic gain	$H_e$	3.25	mV	$H_e = A$
Inhibitory synaptic gain	$H_i$	22	mV	$H_i = B$

**Table 2.3:** Parameters of the PSP Blocks after [17]

**Attention:** From now on, the indices  $[0, \dots, N]$  for  $y$ ,  $h$ ,  $\tau$  and  $H$  refer only to the subpopulations within a single population. The indices used above in the formulation for the Simple Jansen-Rit Model (and the Block Diagram) should not be confused with these. However,  $e$  and  $i$  as indices still denote excitatory and inhibitory populations respectively.



**Figure 2.9:** Example of subpopulations ( $h_{e_0}(t), \dots, h_{e_N}(t)$ ) forming an excitatory population  $h_e(t)$

By introducing subpopulations, we split up the general impulse response function  $h(t)$  in  $N$  individual sub-functions:

$$h_n(t) = \frac{H_n}{\tau_n} t e^{-\frac{1}{\tau_n}}$$

The previously defined general PSP-Block Equation:

$$y(t) = h(t) * x(t)$$

then becomes:

$$y(t) = \sum_{n=0}^N (w_n \cdot h_n(t) * x(t)) \quad \text{with} \quad \sum_{n=0}^N w_n = 1 \quad \text{and} \quad 0 \leq w_n \leq 1$$

with  $N$  individually weighted ( $w_n$ ) and parameterized ( $h_n(t)$ ) subpopulations. We can then declare:


$$y_n(t) = h_n(t) * x(t) \quad \text{and} \quad y(t) = \sum_{n=0}^N (w_n y_n)$$

which produces the following differential equations for a single PSP Block:

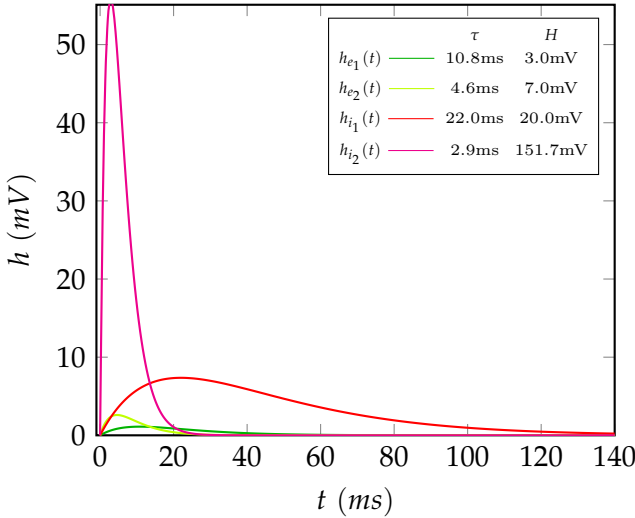
$$\begin{aligned} \dot{y}_0(t) &= z_0(t) \\ \dot{z}_0(t) &= \frac{H_0}{\tau_0} x(t) - \frac{2}{\tau_0} z_0(t) - \left(\frac{1}{\tau_0}\right)^2 y_0(t) \\ &\dots \\ \dot{y}_N(t) &= z_N(t) \\ \dot{z}_N(t) &= \frac{H_N}{\tau_N} x(t) - \frac{2}{\tau_N} z_N(t) - \left(\frac{1}{\tau_N}\right)^2 y_N(t) \\ y(t) &= w_0 y_0 + \dots + w_N y_N \end{aligned} \tag{2.10}$$

David and Friston further propose an example with two subpopulations for each population with the following parameters:  $\tau_{e_1} = 10.8ms$ ,  $\tau_{i_1} = 22ms$ ,  $\tau_{e_2} = 4.6ms$ ,  $\tau_{i_2} = 2.9ms$ . While the kinetics for the first subpopulation were still close to those of the original populations ( $\tau_e = 10ms$ ,  $\tau_i = 20ms$ , which produce alpha activity), the second population's parameters were chosen to produce gamma activity.



 Todo

put the values in a table



**Figure 2.10: PSP functions for Subpopulations:** — and — are faster subpopulations

## 2.3 General Anaesthesia

**⚠ Section Incomplete** this section is currently just a collection of information. it needs transitions between subsections and improvements to the text

### 2.3.0.1 Basics

General Anaesthesia is usually employed in surgical contexts to keep patients from experiencing the pain of the operation. Sedative drugs are carefully administered to the patient by trained practitioners to induce loss of consciousness, without causing permanent damage to the brain or other parts of the body

### 2.3.0.2 Units for propofol concentration

Some papers [20] cite propofol concentrations in  $\frac{\mu\text{g}}{\text{mL}}$ , while others [18], [22] use  $\mu\text{M}$  (micromolar =  $\frac{\mu\text{mol}}{\text{L}}$ ). To get comparable numbers, we first need to establish the following relation for Propofol (molar mass: 178.27 g):

$$1 \frac{\mu\text{g Propofol}}{\text{mL}} = \frac{1 \frac{\mu\text{g}}{\text{mL}}}{178.27 \frac{\text{g}}{\text{mol}}} = 5.609 \mu\text{M}$$

In this work, we will settle on  $\mu\text{M}$  and only mention values in  $\frac{\mu\text{g}}{\text{mL}}$  where they are taken from a source, but then provide the converted value as well.

### 2.3.0.3 Realistic propofol concentrations during general anaesthesia (GA)

During GA, effect-site concentrations ( $c_e$ , concentration near the synaptic receptors) of propofol may easily range up to  $5 \frac{\mu\text{g}}{\text{mL}}$  ( $\approx 28 \mu\text{M}$ ). Loss of Consciousness (LOC) occurs on average at  $c_e \sim 2.0 \frac{\mu\text{g}}{\text{mL}}$  ( $\approx 11.2 \mu\text{M}$ ), while the Recovery of Consciousness (ROC) averages at  $c_e \sim 1.8 \frac{\mu\text{g}}{\text{mL}}$  ( $\approx 10.1 \mu\text{M}$ ). Both values may vary substantially for individual subjects. LOC has a strong tendency to occur at higher concentrations than ROC [20], [41]. Throughout GA, effect-site concentration is commonly derived from measured blood-plasma concentration ( $c_p$ ) using more or less complex Pharmacokinetic (PK)-Models (e.g. [32], [34]), as direct measurement is impractical for obvious reasons. Since our model will work with  $c_e$  directly, we will disregard this for now - however, it should be kept in mind.

### 2.3.0.4 Effects of propofol on the IPSP

Research on the effect of propofol on the IPSC (Inhibitory Post-Synaptic Current) and EPSC has shown that propofol strongly affects the IPSP decay time [18], [22]. The EPSP and the amplitude of the IPSP are unaffected by propofol. Effect-site concentrations at clinically relevant levels increase the IPSP decay time significantly (e.g. around  $10 \mu\text{M}$  the decay time roughly doubles) [18].

**⚠ Section Incomplete** the 'manual fit' needs to be replaced with something 'more scientific'

Using the data-points from [18] and assuming a very rough manual logarithmic fit (see Fig. 2.11), the function

$$\mathcal{D}(c_e) = 0.65 * \ln((c_e/2) + 1) + 1$$

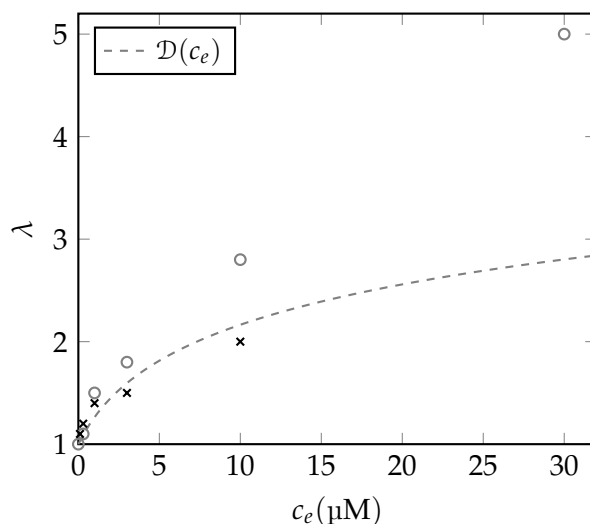
will be used to calculate the decay-time factor  $\lambda$  from a given effect-site concentration in  $\mu\text{M}$ .

As there unfortunately were only a few data-points (and none above  $10\mu\text{M}$ , leaving a large part of the relevant parameter space empty), a computational model-fit might have over-valued those points.

⚠️ Todo

mention that there ARE points over  $10\mu\text{M}$  [22], which may not be directly comparable. generally check [26] and others for their sources

A visually fitted logarithmic function (assuming eventual effect saturation) seemed like a sensible choice for this use-case. However, since inter-subject variations are substantial in any case, the exact values do not matter as much as the order of magnitude.



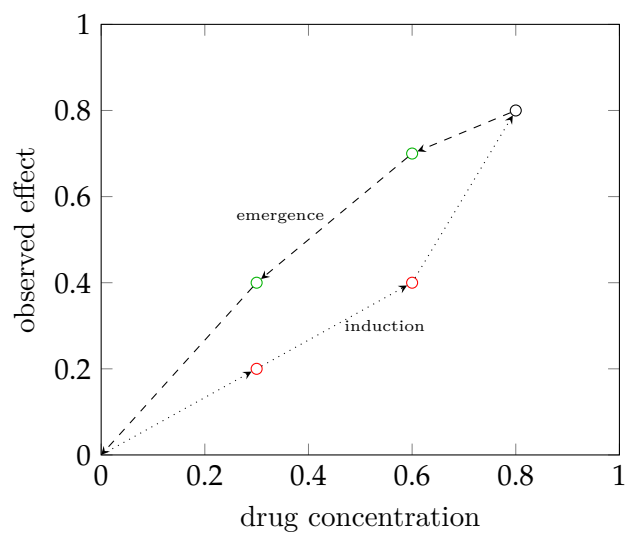
**Figure 2.11:** very rough manual logarithmic fit of decay-time factor to measured values from [18](x) and [22](o).

### 2.3.0.5 Hysteresis of propofol

If the state of a system depends not only on its parameters, but also the system's history, this dependency is called hysteresis. The human body often reacts differently to the same concentration of a drug, depending on whether the concentration is rising or decaying. Hysteresis is well documented during propofol-induced GA [11], [20], [38], [41], [42]. The most prominent effect being a counter-clockwise hysteresis for LOC and ROC (as mentioned in 2.3.0.3). The effects on responsiveness of subjects usually start at higher concentrations than they end. While some of that effect might be caused by inaccurate PK-Models, misgauging the actual effect-site concentration, there is a growing body of research that supports the notion that the observed effect is independent of pharmacokinetic interference [26], [42].

⚠️ Todo

possibly delete the following exemplary graphic:



**Figure 2.12:** Hypothetical example of counter-clockwise drug hysteresis

## 2.4 Effects observed in the Neural-Field-Model by Steyn-Ross

**? Question** should this section maybe be the FIRST instead of the LAST in this chapter?

**☰ Todo** MAKE THINGS MORE SPECIFIC (frequency ranges, concentrations, etc) WHERE APPLICABLE

Steyn-Ross et al. [19], [21], [26] developed their model of general anaesthesia based on Liley's [12] equations for a mean field model of the cortex. They demonstrated that phase-transitions in the model can account for the abrupt change in brain-state that occurs during induction of anaesthesia [19]. The transitions in their model occur due to the existence of multiple stable-states for certain ranges of the parameters that model the level of anaesthetic agent in the system.

An interesting finding of their research was the emergence of high-amplitude oscillations during the phase-transitions of the model. They correlated this behavior to the 'bi-phasic' effect occurring in general anaesthesia; at low drug-concentrations during induction (and roughly during loss of consciousness), there are surges of brain-activity, which disappear with further increase of the dosage and the onset of the comatose state. Similar observations have been made during the recovery of consciousness, when the steadily declining levels of the anaesthetic agent temporarily cause pronounced brain-activity before the subject fully regains consciousness.

Furthermore, the aforementioned effects are not "symmetrical", meaning the phase-transition on the return path from the "comatose" state is not just the reversal of the transition during induction. Their model predicts, that the transition to the comatose state occurs at higher levels of drug concentration than the return to the initial state. Steyn-Ross et al. draw parallels to the real effect of drug-hysteresis (see section 2.3).

**☰ Todo** why do these effects emerge? (partially answered in the beginning of the section, we won't go into mathematical details like bifurcation analysis here, so i'm not sure yet what to put here...)

**☰ Todo** what can we conclude from the findings?

These findings are especially intriguing, as the causes of observed hysteresis during induction of general anaesthesia are yet to be definitively determined [37], [38]. While there is mounting evidence for neural inertia [41], the observed time-lag might be sufficiently explained by pharmacokinetics. The existence of hysteresis loops in simulated models furthers the theory of neural inertia during loss and recovery of consciousness.

**☰ Todo** can we reproduce these effects with another model?

As has been stated before, one of the simplest approaches to population based modeling is the Jansen-Rit Model, which has already been described in detail in section 2.2.1. Trying to use it as Occam's Razor, it would be interesting to see if it can reproduce the these effects as well.

**☰ Todo** improvement idea: `it might be interesting to find the simplest possible model, which we will delve into in the following section...`



## Chapter 3

# Methodology

### 3.1 Implementation Details

**⚠ Section Incomplete**

preliminary

The whole PyRates section is still very much

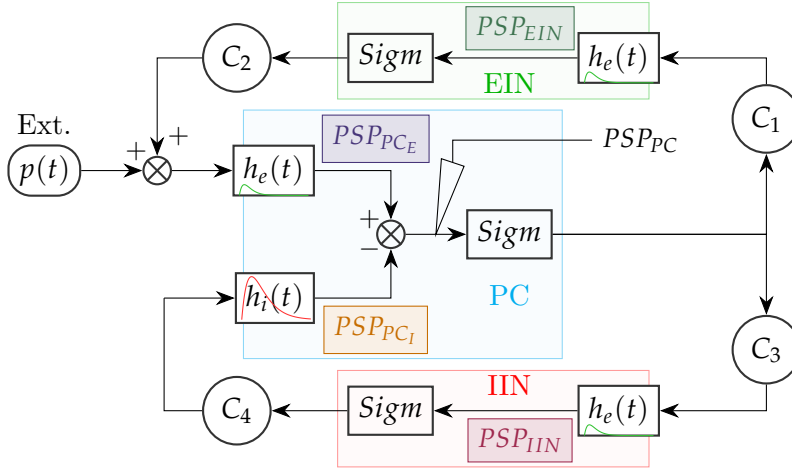
The PyRates Framework is a Python software framework, written by Richard Gast and Daniel Rose at the Max-Planck-Institute in Leipzig. It can simulate a wide range of graph-representable neural models, while setting a focus on rate-based population models [40]. It wraps computational backends like Numpy and Tensorflow and offers predefined nodes and edges (components that model units like cells or cell populations and the connections between them with mathematical equations) to be used, replaced or extended with custom equations. Furthermore it provides two simple ways to define these components and the derived network configurations: either by YAML-File or within Python code. These configurations are then compiled into optimized executable code with respect to the chosen backend before being executed. It comes with pre-configured model-definitions for some of the most frequently used models, e.g. the basic Jansen-Rit Circuit [10] and the Montbrio-Model [35], as well as some variations thereof. It's ease of use, the fact that it could easily reproduce the characteristics of the basic Jansen-Rit model out of the box, and the open-source character made it a sensible choice for this thesis.

#### 3.1.1 Implementation of the Basic Jansen-Rit Model

PyRates works with population models by compositing multiple operators, like the PSP- (or Rate-To-Potential-) and Sigmoid- (or Potential-To-Rate) Block into nodes. These nodes represent populations that can then be connected via edges (synapses). For example one might combine two PSP-Blocks (for excitatory and inhibitory input respectively) with a Sigmoid Block to create a PC-Node. This node can then receive rate-input to each of it's PSP-Blocks and produces rate-output from it's Sigmoid-Block. The EIN- and IIN- nodes are functionally identical and just combine an excitatory PSP-Block with a Sigmoid Block. By connecting these Blocks (see Fig. 3.1) and adding random input to the excitatory PSP-Block of the PC-Node, the

simple Jansen-Rit Circuit is already complete.

$$\begin{aligned}
 \frac{d}{dt}PSP_{EIN} &= PSP_{t_{EIN}} \\
 \frac{d}{dt}PSP_{t_{EIN}} &= \boxed{\frac{H_e}{\tau_e} \cdot C_1 \text{Sigm}[PSP_{PC}] - \frac{2}{\tau_e} \cdot PSP_{t_{EIN}} - \left(\frac{1}{\tau_e}\right)^2 \cdot PSP_{EIN}} \\
 \frac{d}{dt}PSP_{IIN} &= PSP_{t_{IIN}} \\
 \frac{d}{dt}PSP_{t_{IIN}} &= \boxed{\frac{H_i}{\tau_i} \cdot C_3 \text{Sigm}[PSP_{PC}] - \frac{2}{\tau_i} \cdot PSP_{t_{IIN}} - \left(\frac{1}{\tau_i}\right)^2 \cdot PSP_{IIN}} \\
 \frac{d}{dt}PSP_{PC_E} &= PSP_{t_{PC_E}} \\
 \frac{d}{dt}PSP_{t_{PC_E}} &= \boxed{\frac{H_e}{\tau_e} \cdot (p(t) + C_2 \text{Sigm}[PSP_{EIN}]) - \frac{2}{\tau_e} \cdot PSP_{t_{PC_E}} - \left(\frac{1}{\tau_e}\right)^2 \cdot PSP_{PC_E}} \\
 \frac{d}{dt}PSP_{PC_I} &= PSP_{t_{PC_I}} \\
 \frac{d}{dt}PSP_{t_{PC_I}} &= \boxed{\frac{H_i}{\tau_i} \cdot C_4 \text{Sigm}[PSP_{IIN}] - \frac{2}{\tau_i} \cdot PSP_{t_{PC_I}} - \left(\frac{1}{\tau_i}\right)^2 \cdot PSP_{PC_I}} \\
 PSP_{PC} &= PSP_{PC_E} - PSP_{PC_I}
 \end{aligned} \tag{3.1}$$



**Figure 3.1: Jansen-Rit Block Diagram as implemented in PyRates:** Each population can be clearly identified by one or more afferent PSP-Blocks and a single Sigmoid that calculates the populations output. This approach is more modular and simplifies conceptual understanding while staying mathematically equivalent. However, due to the explicit fourth PSP-Block it gives up the performance boost.

### 3.1.2 Implementation of Subpopulations

The subpopulation concept proposed by David and Friston can be easily implemented in PyRates. Fig. 3.2 shows the necessary adjustments to the operator template.



```

1 rpo_e = OperatorTemplate(
2     name='RP0_e', path=None,
3     equations=[
4         #-----
5         # Subpopulation 0:  $h_0(t)$ 
6         #  $\dot{y}_0 = z_0$ 
7         'd/dt * y_0 = z_0',
8         #  $\dot{z}_0 = \frac{H_0}{\tau_0} x - \frac{2}{\tau_0} z_0 - \frac{1}{\tau_0^2} y_0$ 
9         'd/dt * z_0 = H_0/tau_0 * x - 2./tau_0 * z_0 - (1./tau_0)^2. * y_0',
10        #-----
11        # Subpopulation 1:  $h_1(t)$ 
12        #  $\dot{y}_1 = z_1$ 
13        'd/dt * y_1 = z_1',
14        #  $\dot{z}_1 = \frac{H_1}{\tau_1} x - \frac{2}{\tau_1} z_1 - \frac{1}{\tau_1^2} y_1$ 
15        'd/dt * z_1 = H_1/tau_1 * x - 2./tau_1 * z_1 - (1./tau_1)^2. * y_1',
16        #-----
17        # Population output:
18        #  $y = \sum_{n=0}^N (w_n y_n)$ 
19        'PSP = w_0*y_0 + w_1*y_1'
20        #-----
21    ],
22    variables={
23        'PSP': {'default': 'output'},
24        **{var: {'default': 'variable'} for var in ['y_0', 'y_1', 'z_0', 'z_1']},
25        'x': {'default': 'input'},
26        'w_0': {'default': 1.0},
27        'w_1': {'default': 0.0},
28        'tau_0': {'default': tau_0},
29        'tau_1': {'default': tau_1},
30        'H_0': {'default': h_0},
31        'H_1': {'default': h_1}},
32    description="rate-to-potential operator")

```

Figure 3.2: PSP Block with two subpopulations in PyRates

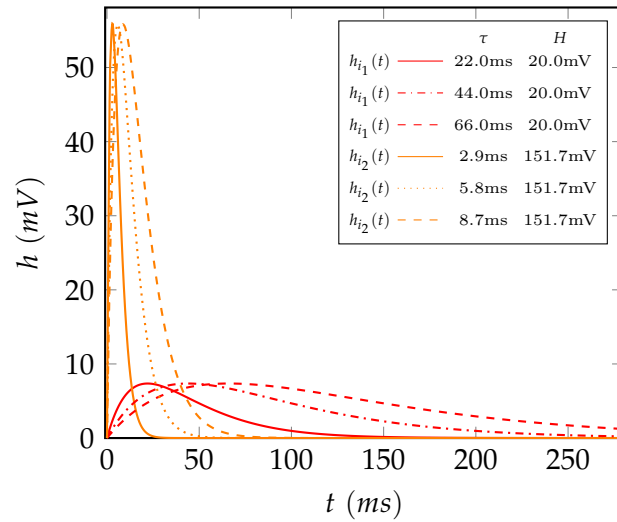
### 3.1.3 Implementing the Effects of Propofol

#### 3.1.3.1 Implementing decay-time modulation

To simulate the effects of propofol on the GABA<sub>A</sub> receptors, the IPSP (inhibitory response function  $h_i$ ) time-constant  $\tau_i$  is increased by a factor  $\lambda$  [24]:

$$h_i(t) = \frac{H_i}{\lambda \cdot \tau_i} t e^{-\frac{1}{\lambda \cdot \tau_i}}$$

The effect of increasing  $\lambda$  for  $h_{i_1}$  and  $h_{i_2}$  is visualized in Fig. 3.3.



**Figure 3.3: Inhibitory PSP functions with varying  $\lambda$ :**

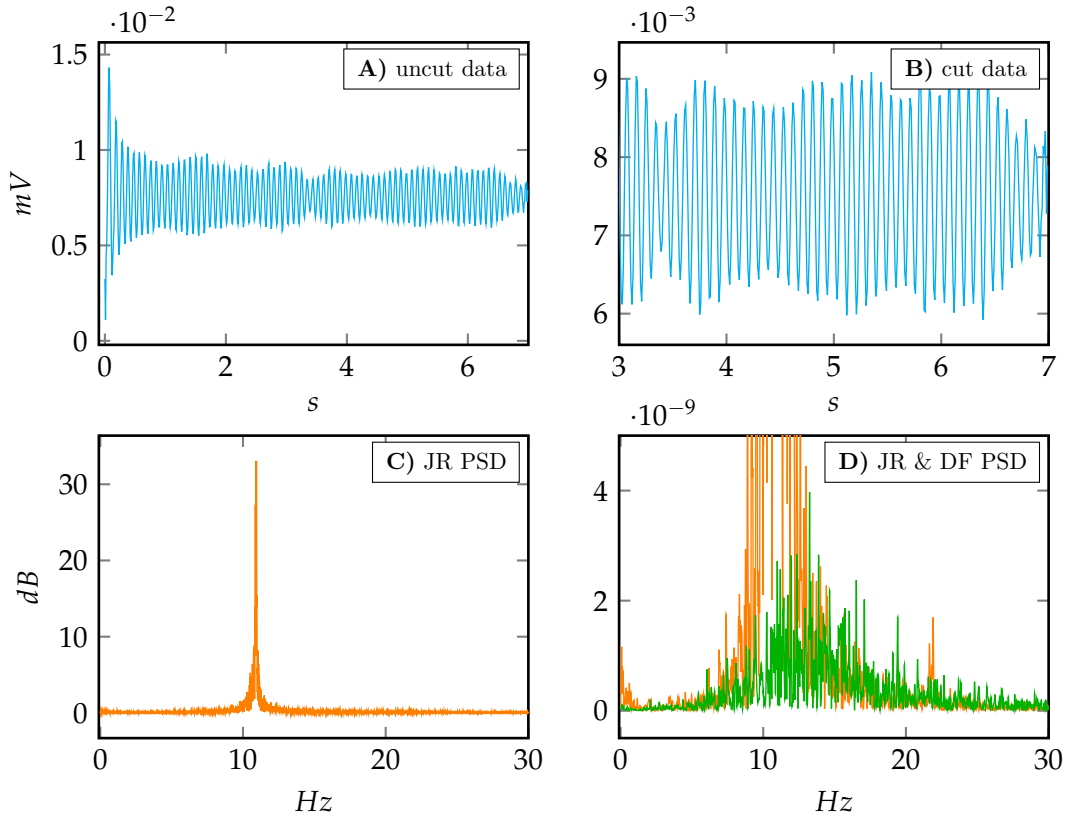
The duration of the effect increases while the amplitude stays constant, effectively increasing the charge transfer. ( $\lambda$  in [1.0 (no drug-effect, solid lines), 2.0 (dotted), 3.0 (dashed)])

Varying  $\lambda$  between 1 (0  $\mu\text{M}$ ) and 3.0 ( $\sim 30 \mu\text{M}$ ) appears to be a sensible choice for the clinically relevant range, given Fig. 2.11.

## 3.2 Data Analysis

☰ Todo

explain features of the raw data, postprocessing steps



**Figure 3.4: Processing of simulated data.**

- A) & B): removing initially unstable signal by cutting off the first 3s of the data (generated by Simple Jansen-Rit Model with  $C = 135$ ).
- C) & D): Power Spectral Density of Jansen-Rit and David & Friston Model (Multi-tapered)



## Chapter 4

# Results

To generate a signal with the desired effects, it is imperative to design the change of parameter values over the course of time.

☰ Todo name goals of simulation

☰ Todo explain reasoning behind linear increase (close to realistic sedation, but focus on structural exploration of the possible values)

☰ Todo CLARIFY ALL THE HEADINGS!!!! APPLIES TO WHOLE THESIS!!!

### 4.1 Exploring realistic parameter ranges

When simulating a linear increase and subsequent decrease over the selected parameter space for  $\lambda \in [1, 3]$  (see Fig 4.1 **A**), the following phenomena can be observed:

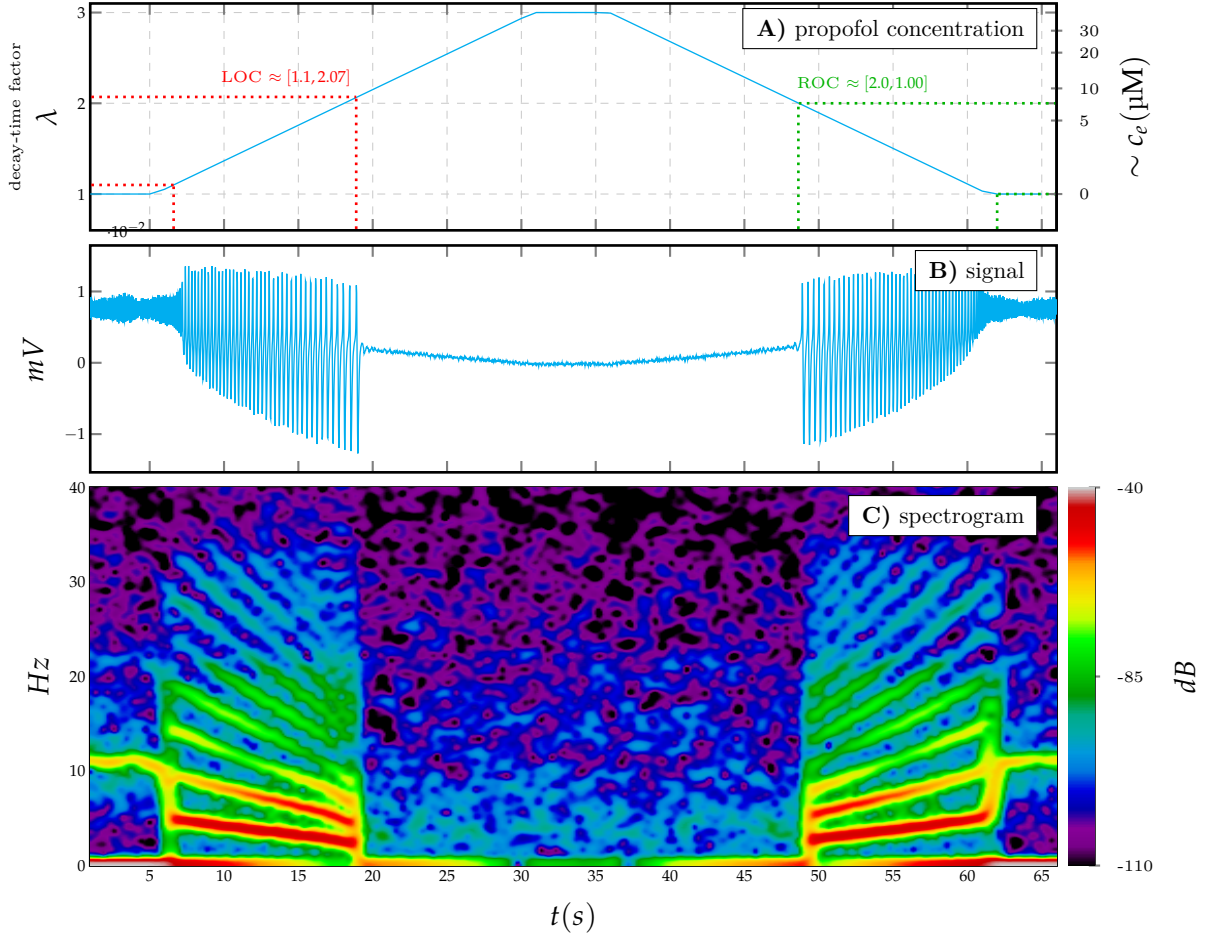
#### 4.1.1 Phenomenology of the Basic JR Model

In the baseline state ( $\lambda = 1$ ), the model produces the expected well-defined alpha-activity, with a sharp frequency peak at 12 Hz.

**Remark** (Spectrogram Amplitude). *At this point it should be noted, that even though the spectrogram (Fig 4.1 **B**) appears to contain a frequency range from roughly 6 – 18Hz, this is misleading. The extremely high-amplitude 12 Hz peak has noisy flanks with low amplitudes (compare to the spectrum in Fig. 3.4 **C** & **D**), which are highlighted by the chosen colormap and value range. Their relative contribution to the signal is close to insignificant in this case.*

Increasing the simulated propofol levels first leads to the single dominant frequency at 12 Hz descending towards 10 Hz. When reaching  $\lambda \approx 1.1$ , there is an onset of heavy oscillations, characterized by dramatically increasing signal amplitude with frequencies peaking at around 0 – 10, 12 – 20 and 30 Hz, but extending up to  $\sim 35$  Hz. Further increase of the concentration shifts the frequency peaks of the disturbed signal slowly towards lower values, also decreasing their distance to each other. Additionally, higher values of  $\lambda$  appear to linearly decrease the mean signal voltage. Another sudden change occurs around  $\lambda \approx 2.07$ , where the disturbances disappear again, with the system having apparently reached a different stable state with very low activity. Signal amplitude is drastically reduced, with remaining activity mostly below 10 Hz. From there on, the mean signal voltage slowly continues to slightly

decrease as before, however the frequency distribution appears to have settled. Maintaining peak dosage has no further effects. Subsequent decrease has the expected reverse effect at first: only the signal voltage slightly increases as well. Disturbances begin to form again at  $\lambda \approx 2.0$ . The system undergoes similar effects in reverse on the return path as it did during induction. It takes a moment after  $\lambda$  returns to its initial value until the initial state is restored.



**Figure 4.1: Simulation of a sedation:**

**A):** timeline of the simulated IPSP stretch factor  $\lambda$  (roughly representing  $c_e$ )

**B):** timeline of the simulated signal

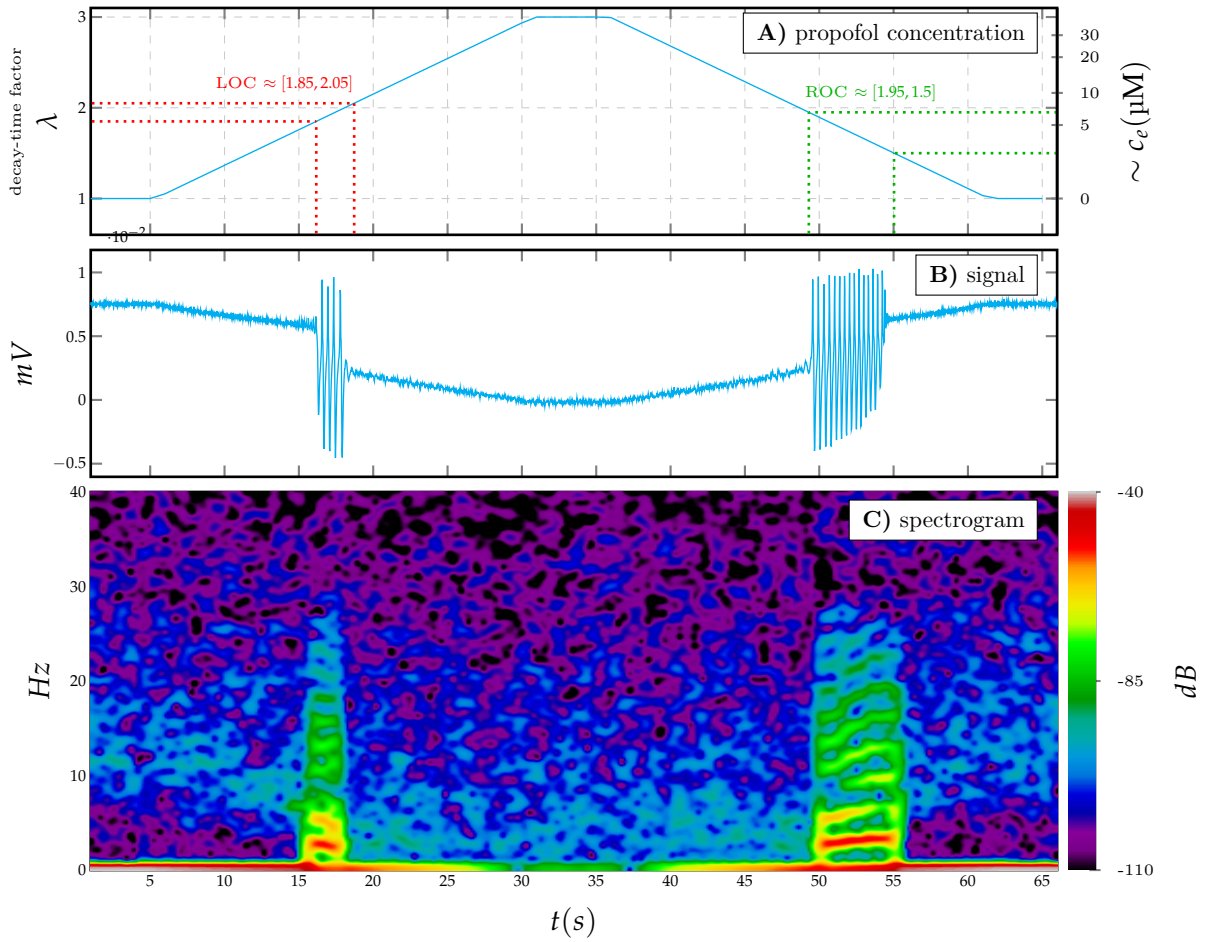
**C):** spectrogram

#### 4.1.2 Phenomenology of the David Friston Extension

The subpopulation extension of the David & Friston model introduces the mixture of slow and fast kinetics within a population. This results in an initial frequency spectrum, that lacks the distinct high-amplitude peak and instead has a wider distribution with far lower amplitude.

**Remark** (Spectrogram Amplitude). *Fig. 4.1 C and Fig. 4.2 C have the same colormap and amplitude-range. In contrast to the spectrogram of the JR-Model, the low-amplitude activity is significant from the start here, as it makes up the whole baseline signal.*

The DF model initially produces a dominant frequency range at 10 – 20Hz, which slowly shifts towards 5 – 10Hz (C) when  $\lambda$  starts to increase. The mean signal voltage concurrently decreases, while oscillation-amplitude is maintained (Fig 4.2 B). The system appears to be in a stable state until  $\lambda \approx 1.85$ , where the sudden onset of dramatically increasing signal amplitude with strongly pronounced activity below 25 Hz creates multiple strong frequency peaks. Unlike in the JR model, the oscillations do not exceed 30 Hz. Further increasing  $\lambda$  has the same minimal effects on the disturbed signal, as the increase had before exiting the stable state. The heavy oscillations remain until  $\lambda \approx 2.05$ , where the dominant frequencies move below 10 Hz. Continuing, the signal voltage slowly decreases as before, however the frequency distribution appears to have settled. Maintaining peak dosage has no further effects. Decreasing the simulated propofol levels again first increases the mean signal voltage, until the stable state dissolves into heavy oscillations around  $\lambda \approx 1.95$ . The unstable state prevails until  $\lambda$  reaches  $\approx 1.5$ .




**Figure 4.2: Simulation of a sedation:**

**A):** timeline of the simulated IPSP stretch factor  $\lambda$  (roughly representing  $c_e$ )

**B):** timeline of the simulated signal


**C):** spectrogram

## 4.2 Differences

 **Todo** highlight relevant ("striking") differences and similarities

There are a few striking differences between the two simulation sessions: In the initial state ( $\lambda = 1$ ), the JR model produces mainly alpha-activity

Three, distinguishable states can be observed, t Induction and Emergence are asymmetrical. The system predicts that the frequency range below 25 Hz receives a temporary amplitude boost during the phase transitions, which disappears while the parameter changes continue in the same direction. In the ‘unconscious’ state, frequency distribution stabilizes independent of further increasing decay-time (**slow-wave-activity saturation?** [28]).

 **Todo** transition into discussion



## Chapter 5

# Discussion

The shared objective of Steyn-Ross et al. and this thesis, is to further understanding of the loss and emergence of consciousness, by capturing anaesthetic effects in an abstract model of brain activity. Steyn-Ross et al. were able to show, that their model produces hysteresis and a biphasic effect [26]. The general question of this thesis was, whether there are simpler models, that are able to reproduce these phenomena. The first and arguably most obvious candidate for this was the widely used Jansen-Rit Model, which is well known for a wide range of dynamics, despite its simplicity. Generally, the results do suggest that the basic JR model has intrinsic properties that produce effects similar to those reported in the neural field model [26]: the default configuration of the famous 1995 model [10] produces a strong biphasic response (see Fig. 4.1), when increasing the inhibitory decay-time constant. Also a minor hysteresis can be observed, as the transitions in and out of the ‘unstable’ state are not perfectly ‘symmetrical’.

☰ **Todo** quantify

The biphasic effect occurs very quickly after increasing the IPSP duration, which may in part be due to the default parameters lying close to a region that produces what David and Friston call ‘hypersignals’[17].

☰ **Todo** maybe mention kuhlmann here, their criticism of JR limits

Given the basic model’s inability to output realistic frequency distributions or a pronounced hysteresis, this motivated the next tier of model sophistication, namely the extension of David & Friston[17]. Their contribution of splitting the populations into subpopulations with different PSP properties, enables the model to produce signals with much richer frequency distributions. Indeed, the spectra generated during simulated sedation sessions with the default David-Friston model (see Fig .4.2) bear strong similarities to those observed in real EEG recordings during general anaesthesia [29].

☰ **Todo** describe spectral features


☰ **Todo** describe difference between spectral features of LOC and ROC

☰ **Todo** draw comparison to real EEG spectra during anaesthesia [29]


### 5.0.1 draft: argumentation


The fact that relatively simple computational models can predict the general frequency dynamics occurring during the drug-induced loss of consciousness, invites the speculation that effects such as hysteresis and the biphasic effect observed in real EEG recordings can at least in part be attributed to universally inherent brain-mechanics on population level.

While the effects observed during these simulations provide little to no specific information about the factors involved in the emergence of consciousness, they suggest that abstract population dynamics might play a crucial role in modulating the necessary preconditions. While the results of the system are promising, it must always be kept in mind that the spatial abstractions of a population model are not the only simplification in the system used in this thesis. Many key-concepts and parameters of the model are strictly rooted in neuro-biological evidence, but there has also been parameter tuning to match desired outputs (e.g. the choice of weights for the subpopulations in [17] was ultimately motivated by the resulting frequency-spectra). The chosen weights do lie well within the plausible ranges [citation-needed], but should not be considered a given.

 **Todo** soften this harsh criticism...


Additionally, studying the generated signal of a single macro-column cannot be used to make dependable general statements about processes as complex as the loss and emergence of consciousness.


 **Todo** ... the breakdown of stability in small columns is however a good indication for the loss of necessary conditions for consciousness in the system as a whole


 **Todo** maybe something like "despite severe limits [...], it is remarkable that the simple model can [...]"

Some of these concerns can be addressed by "whole-brain" network-models, which consist of many of these columns, ideally spatially realistically interconnected and with propagation delays between regions that are further apart.

### 5.0.2 draft: kuhlmann/coaliala

 **Todo** reference COALIA

 **Todo** better lead into kuhlmann: something like `similar motivation with different angle`

 **Todo** describe kuhlmann paper in more detail

Kuhlmann et al.'s [36] efforts to use the basic JR model for depth-of-anaesthesia tracking did produce encouraging results, even though they concluded that the model might be too simple for their approach. They experimented with a slight modification of adding self-inhibition to the IIN population without notable success. It would be interesting to validate this method with the subpopulation extension used in this thesis, as it appears to be able to model a rich palette of realistic signal states and frequency distributions.

## 5.1 Outlook

**⚠ Section Incomplete** i'm not happy with this section yet...

**☰ Todo** possible extension: modeling further dynamic effects of anaesthesia? (which exactly?)

**☰ Todo** How could the model be extended: e.g. more realism by incorporation into a whole-brain system like COALIA, ...

**☰ Todo** Possible practical applications: Depth-Of-Anaesthesia-Tracking [36], ...

The development of models that aim to simulate anaesthesia is not only valuable for consciousness research. An application like the Depth-Of-Anaesthesia-Tracking that Kuhlmann et al. [36] proposed, could estimate multiple clinically relevant physiological variables like the PSP amplitude and rate constant

**☰ Todo** rephrase

. When matured, such a system could have advantages that would set it apart from current methods, which rely on algorithmic evaluation of extracted EEG features. In practice, anaesthetic agents like propofol are often administered in combination with analgesic (pain-reducing) agents (e.g. remifentanyl). This substantially lowers the concentration requirements for the anaesthetic agent to achieve the same level of sedative effect, while also helping to increase the quality of anaesthesia, stabilizing the blood pressure and improving recovery [citation needed].

**☰ Todo** note that current methods might not be able to correctly work with or disentangle the actions and interactions of multiple drugs

Being able to model and estimate physiological variables during general anaesthesia could be a valuable tool for clinical practice.



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