University of Southern Queensland
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Depth of Anaesthesia Assessment and Higher Brain Function Modelling for Consciousness

A thesis submitted by

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Abstract

Anaesthesia is the corner stone of modern surgical medicine. Despite a long period of enquire beginning with Snow (1847) anaesthesia remains a field in which there are more questions than answers. This thesis reports findings on three different aspects of anaesthesia.

1. Initially, a method for calculating a population pharmacokinetic model for propofol infusion is described. This method greatly reduced the time required to calculate the model (0.1 seconds per iteration) compared to the NONMEM method (hours per iteration (Minto, Schnider, Egan, Youngs, Lemmens, Gambus, Billard, Hoke, Moore, Hermann, Muir, Mandema & Shafer 1997)). The resultant model achieved improved fit to the data than the model of Schüttler & Ihmsen (2000*b*) achieving a mean squared error of 0.2835 compared to 0.6413 respectively.

2. Second, a neural network (NN) method is presented to assess Depth of Anaesthesia from long segments of raw EEG. The proposed method was able to approximate the output from a BIS XP monitor for the training data. The linear regression, between the NN and the BIS monitor, resulted in an R value of 0.99963. The network was able to approximate the BIS monitor output for new (unseen) data.

3. Finally, a lumped parameter neural mass, anaesthesia, model is presented. This model is capable of generating changes in EEG associated with increasing doses of γ-aminobutyric acid type A ($GABA_A$) hypnotic agent (propofol). This model was not a fitting exercise rather it was constructed based on known brain physiology, and the changes to α_1 $GABA_A$ receptors conductance caused by propofol. Encompassing the regional interactions, that are thought to be, altered by GABA hypnotic agents.

The model is capable of producing five distinct EEG patterns (β, α, θ, δ and isoelectric) in response to different levels of hypnotic agent. The model is reactive capable of switching from α to β band EEG when the eyes open. Anaesthetic supresses the models transition to a higher state EEG.

The model suggest that the *effect site* for propofol as α_1 $GABA_A$ receptors of slow interneurons of the cortex.

Certification of Dissertation

I certify that the ideas, designs and experimental work, results, analyses and conclusions set out in this dissertation are entirely my own effort, except where otherwise indicated and acknowledged.
I further certify that the work is original and has not been previously submitted for assessment in any other course or institution, except where specifically stated.

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ENDORSEMENT

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Signature of Supervisor/s

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Date

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Notation

	Pharmacokinetic modelling
A	Initial concentration compartment A
B	Initial concentration compartment B
C	Initial concentration compartment C
$C_1(t)$	Concentration compartment one over time t
$C_2(t)$	Concentration compartment two over time t
$C_3(t)$	Concentration compartment three over time t
$C_p(t)$	Plasma concentration over time t
$C(s)$	Concentration function Laplace domain
$I(t)$	Infusion over time t
$I(s)$	Infusion function Laplace domain
V_1	Volume of the central compartment
k_{10}	Clearance rate constant compartment one
k_{12}	Rate constant compartment one to two
k_{13}	Rate constant compartment one to three
k_{21}	Rate constant compartment two to one
k_{31}	Rate constant compartment three to one
α	Decay constant compartment A
β	Decay constant compartment B
γ	Decay constant compartment C
	DoA estimation
a_k	Coefficient of k^{th} output
p	Model order
P_i	Power of i^{th} frequency
$\overline{P}$	Total power of signal
SE	Spectral entropy
x_n	Zero mean white noise input
y_n	Current output
y_{n-k}	k^{th} past output

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Brain modelling

I_i	Current i^{th} ion channel
V_i	Reversal potential i^{th} ion channel
V_m	Membrane potential
$V_m(t)$	Membrane potential as a function of time t
g_i	Conductance per unit area i^{th} ion channel
I_m	Membrane current per unit area
C_m	Membrane capacitance per unit area
m	Activation gating variable
h	Inactivation gating variable
$\overline{g_i}$	Maximal value i^{th} conductance
α	Activation constant
β	Inactivation constant
$u(x,t)$	Neural field representing the local activity of a population of neurons at position x and time t
$w(y)$	Strength of connections between neurons separated by a distance y
Φ	Temporal decay rate of synapse
$u(x-y,t-\frac{\lvert y\rvert}{v})$	Axonal conduction delay arising from the finite speed of signals travelling over a distance y
$P(t)$	Average pulse density of action potentials
A	Maximum amplitude of the PSP
a	Reciprocal, lumped representation, passive membrane and all other spatially distributed delays in the dendritic network
t	Time
$V_n(t)$	Single neuron membrane potentia
C_i	Synaptic connectivity constant
$p_i(t)$	Unit impulse function
$h_i(t)$	Synaptic response
$V_m(t)$	Membrane potential neural mass
$P(t)$	Average pulse density of action potentials
$2e_0$	Maxium firing rate neuronal population
S_0	Resting membrane potential
v	Steepness, sigmoid function

Acronyms & Abbreviations

AAI	A-Line autoregressive index
AEP	Auditory Evoked potentials
AIC	Akaike information criteria
ANN	Artificial neural network
ANS	Autonomic nervous system
AP	Action potential
AR	Autoregressive
ARMA	Autoregressive moving average
Ac	Afferent cortex
Ap	Afferent pain
BIS	Bispectral Index
CNS	Central nervous system
CS	Cerebral State index
C_e	Concentration effect Site
DoA	Depth of Anaesthesia
ECG	Electrocardiogram
EEG	Electroencephalograph
EMG	Electromyogram
EOG	Electrooculogram
eIN	Excitatory interneurons
ePSP	Excitatory post synaptic potential
FFT	Fast fourier transform
fEITER	Functional electrical impedance tomography by evoked response
fIN	Fast interneurons
fMRI	Functional magnetic resonance imaging
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid type A
HR	Heart rate
HRV	Heart rate variability
IN	Interneurons, thalamus
IoC	Index of Consciousness

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iPSP	Inhibitory post synaptic potential
LGIC	Ligand gated ion channels
LMA	Laryngeal mask airway
MAC	Minimum alveolar concentration
MAP	Mean arterial pressure
MSE	Mean squared error
NONMEM	Non-linear mix effect models
NMB	Neuromuscular block
NMDA	N-Methyl-D-aspartic acid
NLTEO	Nonlinear total energy operator
NN	Neural network
NO_2	Nitrogen dioxide
NT	Neural transmitter
nACHr	Nicotinic acetylcholine receptor
OAAS	Observers Assessment of Alertness and Sedation
PD	Pharmacodynamics
PK	Pharmacokinetics
PNS	Peripheral nervous systems
PPG	Photoplethysmography
PSA	Patient State Analyser
PSC	Post synaptic current
PSD	Power spectral density
PSP	Post synaptic potential
PY	Pyramidal cells
qEEG	Qualitative EEG
RTN	Reticular nucleus
SE	Spectral entropy
SnS	Shaking and shouting
SWT	Stationary wavelet transform
sIN	Slow interneurons
TEO	Total energy operator
TRC	Thalamic relay cells
TRF	Thalamic reticular formation
VB	Ventrobasal nucleus
VGIC	Voltage gated ion channels
5HT3	5-hydroxytryptamine