Depth of Anaesthesia: Measuring or Guessing?

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***Abstract*—This paper is a comprehensive literature review on the Depth of Anaesthesia (DoA) monitoring problem. We first investigate the current clinical practice, then briefly introduce the DoA monitors, finally we analyse and discuss the reliability and accuracy of current DoA assessment practice. In this study we find that most of the responses suppressed by anaestheic agents are not of the central nervous system (CNS) but are responses from the peripheral nervous systems (PNS). The responses generated for drug combinations across the therapeutic ranges show considerable variations in drug concentrations that constitute adequate anaesthesia for a particular stimulus. We propose to capture the decision process of anaesthetist using neural networks as neural networks are good at finding patterns in non linear, non stationary signals.**

I. INTRODUCTION

The primary reason for Depth of Anaesthesia (DoA) monitoring in general anaesthesia is to detect and warn the doctors that the patient's state is not suitable for the surgery.

DoA is often referred to as the probability of non response to a stimulus. This leads to the questions of which response and to what stimulus? Is representation of the DoA as an index, valid, in the context of the biphasic nature of DoA?

No general hypotheses exists [1] for the mechanism of anaesthesia. There is lack of consensus as to which physiological features constitute anaesthesia. In 1957, Woodbridge gave four components for general anaesthesia [2]; Sensory blockade, Motor blockade, Reflex blockade of autonomic reflexes and Loss of consciousness. In 1974 Eger had two components [1]; Amnesia and Immobility. In 1987 Prys-Roberts reduced anaesthesia to one component[3]; Suppression of conscious perception of noxious stimuli. And in 2002 Heinke used three components to define General Anaesthesia [1]; Unconsciousness, Amnesia and Immobility. In 2007 Orser gave the following components, Sedation, Unconsciousness, Immobility, Amnesia and other.[4] This presents a considerable challenge to those who wish to measure DoA.

These five definitions show the range of opinion as what should be measured. Movement has been measured with Phonomyography [5]. Sudomotor responses can be monitored with skin conductance [6]. Hemodynamic responses have been monitored from heart rate and blood pressure [7, 8].

Although there is a concerted effort to determine the limit of awareness [9-11], Amnesia, Conscious Perception and Unconsciousness, are not defined and hence not measurable. There is some concern that DoA monitors may increases the risk of awareness [9]

Current electroencephalogram (EEG) monitors infer metrics for conscious /unconsciousness from electrical changes in frontal lobe EEG wave forms [12-15]. The other anaesthetic responses are not of the central nervous system (CNS) they come from the peripheral nervous systems (PNS) [16]. There are a number of monitoring methods available for the non CNS responses;

This review will examine what we understand anaesthesia to be. The intrinsic limitations of DoA representations and how the uncertainty might be best resolved.

A. Anaesthetic practice

Kronen [17]shows a broader interpretation of the nature of anaesthesia and the reason to monitor. 'The purpose of anaesthesia is to produce a reversible state of unconsciousness, amnesia, analgesia and immobility by a controlled intoxication. It is the consequent purpose of anaesthetic monitoring firstly to make sure that the patient survives this intoxication, and secondly to detect deviations from normal body functions as early as possible in order to take counter measures when necessary'. Here DoA or awareness has little importance.

The Table I [18], demonstrate the relative importance of the vital signs to Anaesthetists. Six of the standard monitors relate to respiration, five relate to cardiac function and the remaining two relate to DoA.

TABLE I. STANDARD ANAESTHIC MONITORS

anaesthesia monitors
Arterial oxygen saturation (SpO 2)
Venous oxygen saturation (SvO 2)
Heart rate from ECG (HR)
Mean arterial pressure (MAP)
Mean Central venous pressure (MCVP)
Systolic pressure (BPsys)
Diastolic pressure (BPdia)
Depth of Anaesthesia
Measured Tidal Volume (TV)
End tidal concentration of oxygen (EtO2)
End tidal concentration of carbon dioxide (EtCO2)
End tidal concentration of anaesthetic (EtAgent)
Actual Respiratory Rate (RR)

The anaesthetist subjective monitors the DoA with following features:

- Autonomic responses
    - Hemodynamic changes
    - Lacrimation
    - Sweating
    - Pupilary dilation

Hemodynamic changes may be influenced by; body temperature, hemorrhage, drugs and medical conditions.

- Patient Response to Surgical Stimulus (PSRT). Scoring system. See Fig. 1
- Isolated forearm technique

Requires a procedure that can cause dettermental out comes for the patient.

These subjective assessments require that the anaesthetist be diligent, Rall (2009) [19] explores this topic in some detail.

B. Anaesthetic depth monitors

There are currently a number of commercially available DoA monitors Grover [2] provides table II the anaesthetist has a considerable range of monitoring devices available .

A depth of anaesthesia monitoring index value has to be interpreted in the context of the drugs that have been given to produce it. Bouillon and colleagues [20] contains Fig. 2 showing the bispectral index values for the boundary 95% suppression of movement responses to the stimuli of shouting and shaking (solid line) and laryngosopy (dashed line) for Propofol / Remifentanil Anaesthesia. Depending on the relative concentrations, the index value ranges between 70 and 30 for 95% adequate hypnosis. The anaesthetist is interested in whether the patient is above or below the line (not anaesthetized / anaesthetized). The BIS monitor cannot directly answer the anaesthetist question. Is he patient above or below the hypnosis boundary line?

Aspect medical systems [21] provide table III to demonstrate the way in which there monitor should be used in conjunction with intraoperative response to manage anaesthetic producers.

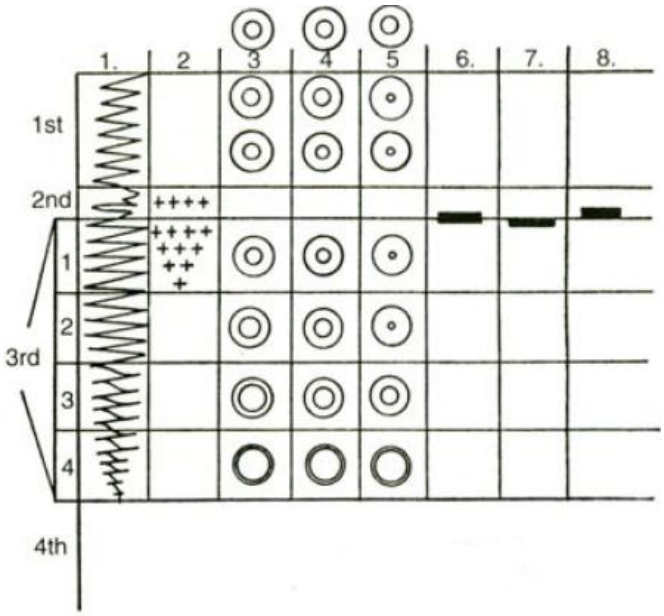

Figure 1. PRST scoring chart. Column 1 Resperation, coloumn 2 Eyeball activity, columns 3,4&5 Pupils, column 6 Eyelid reflex, column 7 Swalowing and column 8 Vomiting

TABLE II. DEPTH OF ANAESTHESIA

Monitoring methods
1. Spontaneous surface electromyogram (SEMG)
2. Lower oesophageal contractility (LOC)
3. Heart rate variability (HRV)
4. Electroencephalogram and derived indices
a. Spectral edge frequency
b. Median frequency
c. Bispectral index
d. Entropy
e. Narcotrend
f. Patient state index
g. Snap index
h. Cerebral state index
5. Evoked potentials
a. Auditory evoked potentials
b. Visual evoked potentials
c. Somatosensory evoked potentials
d. Auditory evoked potentials index
e. A-Line autoregressive index

TABLE III. ASPECT MEDICAL SYSTEMS GUIDE FOR THE USE OF BIS MONITOR

BIS Guided Hypnosis and Anaesthetic Management		
Intraoperative Response	***BIS value***	***Treatment***
Increase BP, HR, Autonomic or Somatic Response	>65	Increase Hypnotic - Increase Analgesic – Identify Strong Stimuli Source
	50-60	Rule out Artifact*, then Increase hypnotic
	<50	Support BP – Decrease Analgesic – Consider Amnesic
Stable	>65	Increase Analgesic / Maintain Hypnotic – Antihypertensive – add NMB
	50-60	Titration Target – Maintain Vigilance
	<50	Support BP + Decrease Analgesic
Hypotension / Unstable	>65	Decrease Hypnotic + Increase Analgesic +/- Antihypertensive
	50-60	Decrease Hypnotic + Decrease Analgesic
	<50	Support BP – Decrease Hypnotic and Analgesic
BP, blood pressure; HR, heart rate; NMB, neuromuscular blocking agents *Artifacts refers to interference from other sources and electromygraphic activity EMG		

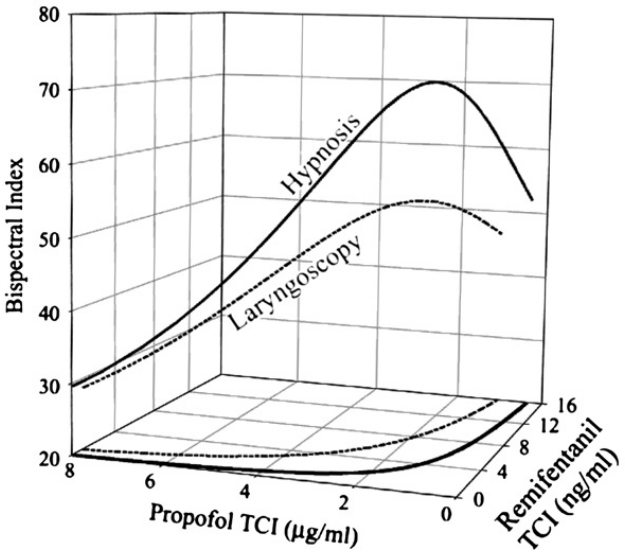

Figure 2. BIS values for 95% probability of no movement when stimuli is Hypnosis (shacking and shouting) and Laryngoscopy, for different concentrations of Propofol (hypnotic) and Remifentanil (analgesic)

C. Problems

Bowdel (2006) [22] and Voss (2007) [23] provide extensive review of anaesthesia monitoring . They list the following limitations to EEG in determining DoA:

- Low amplitude EEG
- Drug choice
- Paradoxical delta activity
- Processing time
- Sleep

Voss, in part he concludes'... there is no known qEEG measure that can be shown to be causally related to either consciousness or memory 100% of the time. Existing EEG monitors use cortical activity as a proxy for consciousness.'

Other researchers have questioned the underling tenet of EEG use to monitor DoA, that the primary site for anaesthesia is the CNS. Rampil (1993) [24] measured isoflurane minimum alveolar concentration (MAC) (effective dose 50% for movement) in rats before and after surgical decerebration and found that MAC was unchanged by removal of cortical and forebrain structures. Antognini (2002) [25] devised a goat model in which isoflurane could be delivered selectively to the brain or to the entire body. Isoflurane MAC was twice as large when only the brain received isoflurane, as when isoflurane was administered to the entire body. These studies further question the validity of measuring the changes in the EEG to predict DoA.

In 2006 the American Society of Anesthesia task force on interoperation awareness, did not recommend routine 'depth of anaesthesia' monitoring be included in the society standards of care.[26]

There is a wide range of other electrophysiological monitoring available to the anaesthetist. Miller's Anesthesia (2009) contain chapters on Cardiovascular Monitoring Schroeder [27], Electrocardiography Hillel [28], Respiratory Monitoring Eskaros [29], Neuromuscular Monitoring Viby-Mogensen [30] and Temperature Regulation and Monitoring Sessler [31]

A problem with all methods of non-clinical electrophysiological scoring of anaesthetic depth is the inter-individual variation between the values of different patients during similar clinical depths of anaesthesia and similar strengths of noxious stimulation. Although the mean values for a group of patients may be different at different levels of sedation and stimulation, there may be considerable overlap.

D. Better guessing

As physicians, anaesthesiologists are responsible for administering anaesthesia to relieve pain and for managing vital life functions, including breathing, heart rhythm and blood pressure, during surgery. After surgery, they maintain the patient in a comfortable state during the recovery, and are involved in the provision of critical care medicine in the intensive care unit

Currently monitors of DoA express their output as a number in the range zero to one hundred. This does not align with the Anaesthetist's understanding 'In the modern practice of anaesthesia, the term 'depth of anaesthesia' and the definition of stages are irrelevant. Anaesthesia is not 'deep' or 'light': it may or may not be adequate' [32]

There are fourteen standard stimuli that are applied to patients when determining DoA shown in table IV along with the ten standard responses. These produce a matrix of 140 stimuli response pairs over which, anaesthestist consider DoA [33]. Fortunately, it is not necessary to characterize the response to every stimulus. If we characterize the response to a benign stimulus, such as shaking and shouting, and several noxious stimuli, such as electrical tetanus, incision, laryngoscopy, and intubation, we will have captured the clinically relevant range of benign and noxious stimulation.

Fig. 3 shows the Hill equation for Alfentianil [33], which relates the drug concentration to the probablity of non response (movement) to different stimuli. The depth of anaesthesia would be adquate at any concentration that returns a probability of non response of 100% to the stimuli of interest. Similar response surfaces can be generated for drug combinations across the therapeutic ranges see Fig.4 and 5. Any combinations that lie in the upper plane would constitute adequate anaesthesia for the particular stimulus. The drug concentrations required vary considerably.

Esmaeili et al were able to show that a combination of EEG features are better suited to the determination of depth of anaesthesia [34].

TABLE IV. STANDARD ANAESTHETIC STIMULI AND THE RESPONSES THEY PRODUCE

Stimuli
Benign
Calling name
Light touch
Shouting
Shouting and shacking
Noxious
Pinprick
Electrical twitch
Electrical tetanus
Trapezius squeeze
Skin closure
Incision
Abdominal exploration
Rib retraction
Laryngoscopy
Intubation
Responses
Verbal
Memory; Implicit
Memory; Explicit
Movement; Purposeful
Movement; Involuntary
Ventilation
Sudomotor, Tearing
Sudomotor, Sweating
Hemodynamic, Blood pressure
Hemodynamic, Heart rate

Kaul 2002 concludes, 'measuring of anaesthesia represents one of the most controversial and subjective aspects of modern anaesthesia, with the introduction of balanced anaesthesia. It is unlikely that any single method will be found to measure the depth of anaesthesia reliably for all patients and all anaesthetic agents. Therefore, using more than one method at a time may provide more accuracy' [35].

Jensen (2003) [36]and Li (2007) [37] combined EEG (BIS) and Auditory Evoked potentials (AEP) to produce a hybrid index that could outperform the individual parameters.

Karlen (2009) [38] used a feedforward artificial neural network to classify ECG and respiratory effort signals into Sleep / wake classes. This suggests that EEG from an asleep patient should be classifable as not anaesthetised.

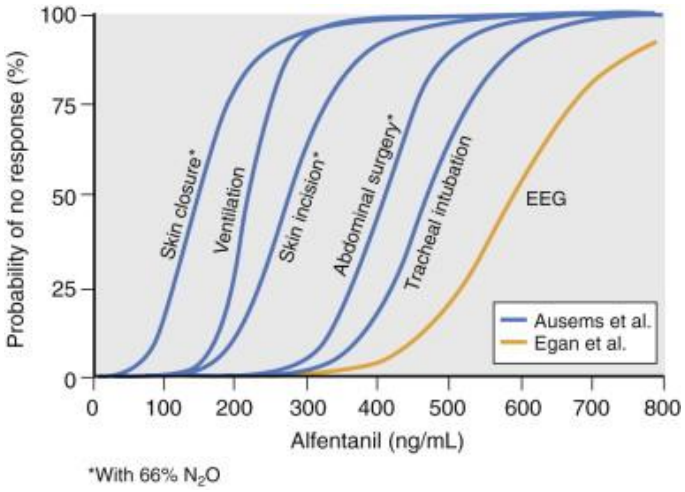

Figure 3. Response curves for Alfentanil concentration to different stimulus

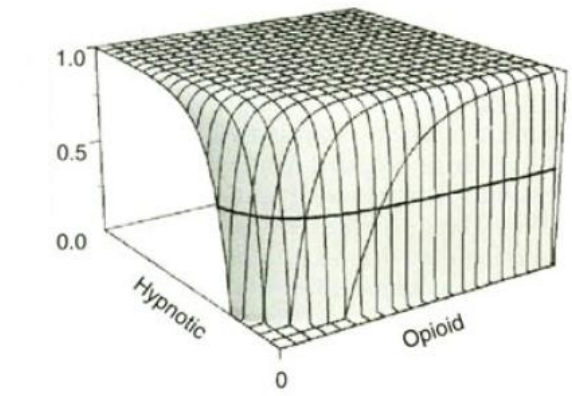

Figure 4. Response surface for mild stimulus, movement response to electrical tetanus

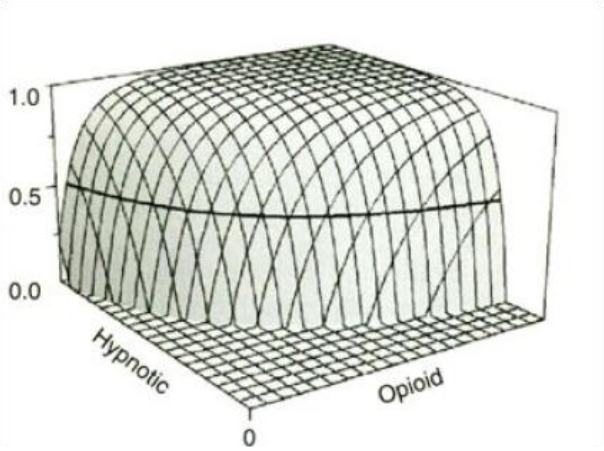

Figure 5. Response surface for profound stimulus, movement response to intubation

Gjerstad (2007) [6] using skin conductance was able to distinguish between propofol anaesthesia and propofol / remifentanil anaesthesia with the same OAAS score.

Yang (2007) [18] found that factor analysis out preformed principal component analysis in detecting the subtle changes in multivariate clinical monitoring produced by a intraoperative haemorrhage.

Can these diverse data sets be combined to extract an assessment of the DoA, give that the individual features are not valid across the total spectrum of the patient continuum. Endogenous arousal control systems are intrinsically bistable; use of an index to quantify anaesthetic effects on these systems poses a conceptual problem for the anaesthetist. Neural networks can be designed and trained to produce a variety of outputs. From linear to bistable (hard limit). It should be possible to make a number of bistable output that represent the clinically relevant stimuli / response pairs Gelb provides three stimuli (calling name, incision and intubation) and three responses (verbal answer, purposeful movement and pulse / blood pressure) [33].

Neural networks are used to capture a process. The use of a network in anaesthesia research is not new. Robert (2002) [39]

reviews previous applications of neural networks in anaesthesia.

Sharma and Roy [40] used EEG, heart rate, blood pressure to achieve a 94% prediction of movement. Hemmerling and Charabati [7] developed a system that uses heart rate and mean arterial pressure for the closed loop application of reifentanil. Li et al combined EEG bispectrum and AEP with a neural network to calculate a DoA index. Ranta (2002) [41] used a neural network to predict awareness from end-tidal carbon dioxide concentration, arterial blood oxygen saturation, systolic and diastolic blood pressure, and heart rate.

The work of Zbinden *et al.* [42] shows that hemodynamic responses to stimuli under isoflurane reflect the relative stimulus as well as the drug concentration.

There are considerable numbers of monitoring systems available to the anaesthetist, the output of which requires interpretation with regard to other information streams. Often the trend of the feature is indicative of changes in the patient's state. Dynamic neural networks can be constructed to take advantage of the trend information.

Training sets may contain conflicting exemplars. This may be resolved through the inclusion of more features. Patient information like age, sex, and weight are known to influence the drug requirements. These three features could be included to remove conflicts in the training set.

II. Conclusion

The determination of the level of unconsciousness during a general anaesthetic is a considerable challenge to the professionals that administer the anaesthetic. General anaesthesia is a dynamic process that really runs to plan. There is a lack of devices that can monitor the level or depth, of anaesthesia without the need for interpretation. There are a number of limitations to these monitoring systems. They fail under certain conditions.

However, before an anaesthesia monitor can be constructed it must be clear what anaesthesia – related quantity the monitor should measure. This requires an understanding of the mechanisms of anaesthesia. 'Insensibility to pain as demanded by the American Board of Anesthesiology does not necessarily imply unconsciousness or total unawareness and lack of sensation' [1].Urban (2002)

Neural networks are good at finding patterns in non linear non stationary signals. It should be possible to train a network to determine the depth of anaesthesia using a number of these medical signals and the decision process of a series of practitioners under optimum conditions. The authors believe that a neural network based DoA monitor will improve the outcomes of patient under anaesthesia based on our research results.

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