



## Predictability of BIS, Entropy and NeuroSENSE

Bibian, S & Zikov, T – NeuroWave Systems Inc., Cleveland Heights, OH, USA

**Introduction:** Automated brain activity monitors have become increasingly used in the Anesthesia specialty. Initially developed for preventing intra-operative awareness, the so-called ‘consciousness’ monitors have rapidly shown their ability to quantify anesthetic drug effect. This led to their use for patient-specific drug titration, and explains their popularity in procedures involving intravenous anesthetics, and in particular Total Intra-Venous Anesthesia (TIVA), where the anesthesiologist does not have the advantage of a MAC value to help administer the drugs.

Recently, there has been a regain of interest in closed-loop systems that use such cortical monitors as a feedback quantity to precisely determine the amount of drug needed to regulate the patient’s cortical depression. While closed-loop systems remain at the stage of investigational devices, clinical evidence suggests that they outperforms manual control [1] and can be used in high risk patient population [2,3]. Similar technologies are being investigated for the control of sedation in the ICU [4], and for special situations related to mass casualties, military operations, and humanitarian actions [5].

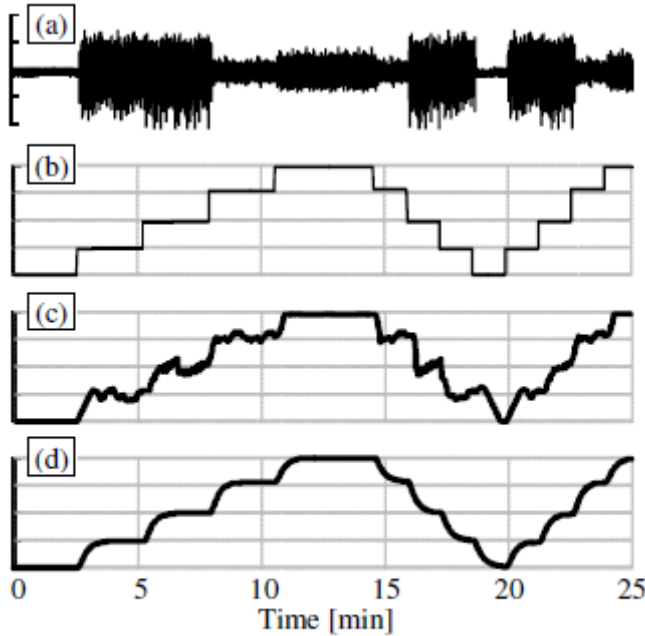
In this paper, we address the question of the suitability of cortical monitors for use as feedback sensor. In particular, we assess the *predictability* of 3 monitors: the BIS A2000 (Aspect Medical), the MEntropy (GE HealthCare), and the NeuroSENSE NS-701 (NeuroWave Systems). These monitors are all based on the acquisition of scalp electroencephalogram (EEG) signal(s), obtained non-invasively from the patient’s forehead. The BIS A2000 calculates the BIS index. The M-Entropy calculates the RE (Response Entropy) index, and the NeuroSENSE calculates the WAVCNS index [7]. All are bounded dimensionless values from 100 (‘awake’) to 0 (‘comatose’), and are derived using proprietary algorithms.

The issue of predictability is particularly important when it comes to the use of a given technology as feedback sensor in a closed loop scheme. Indeed, the performance and stability of a closed loop system heavily depend on the performance of the sensor used to measure the effect of the drug. It is typically required that feedback sensors meet a number of prerequisite characteristics before their use within a closed loop framework is considered. For instance, a common requirement is that the sensor provides a well-defined mathematical relationship between its output (typically a quantified value), and its input (i.e., the physical phenomenon being measured).

It is also strongly recommended that the input/output relationship be linear and time-invariant. Non-linearities and time variant processes within the algorithms can unexpectedly result in unstable control actions, leading to undesirable oscillations in the controlled endpoint (e.g., anesthetic-induced cortical depression). These sensors are also difficult to mathematically model. Therefore, their dynamic behavior cannot be directly accounted for when designing the controller. Proving the mathematical stability of the controller becomes therefore difficult when dealing with non-linearities and time variance, and must be based on empirical observations rather than a deterministic evaluation. In a heavily regulated field, the lack of scientific mathematical proof regarding the robustness of a closed-loop system may dramatically impede regulatory approvals. In addition, empirical control design typically requires a significantly larger cohort of patients for validation purposes.



**Method and Results:** To determine the predictability of a feedback sensor, we assess whether its output can be inferred (i.e., predicted) from its input using a Linear Time Invariant (LTI) function. To make this determination, we use the following two tests. The first test is used for the identification of a LTI model describing the input/output relationship of the monitor, see Fig. 1.



**Fig. 1** Identification of a cortical monitor input/output LTI relationship. (a) Composite test EEG. (b) Equivalent sensor input (c) Sensor output (d) Model output.

This test is carried out by replaying in real-time a composite EEG waveform comprising of increasing and decreasing steps in cortical activity. The waveform is constructed based on quasi-stationary segments of pre-recorded EEGs obtained from volunteers and patients undergoing anesthesia procedures. A digital-to-analog converter with an attenuator stage is used to replay the waveform. The input signal in Fig.1.b is further determined based on the composite EEG and its correspondence with respect to the monitor scale. The input and output waveforms are then used to calculate the LTI model using a standard recursive least square approach. The goodness of fit between the model output and the true output is a measure of how well the model can predict the monitor output.

The second test is used as *validation* of the model based on a different composite EEG signal. The results of the validation test are presented in Fig. 2. The test was comprised of a number of stationary EEG segments randomly distributed over time. The minimum segment duration was 20 seconds (Fig.2.a). Based on the equivalent input signal, we predicted the sensor output using the models derived previously. We then compared the outputs of the monitor and the model to verify their agreement by calculating the goodness of fit, see Table I. The goodness of fit is defined as:

$$FIT = 100 \cdot (1 - \|y - \hat{y}\| / \|y - \bar{y}\|) [\%], \quad (1)$$

where  $y$  is the true sensor output,  $\hat{y}$  is the predicted output, and  $\bar{y}$  is the mean value of the true output. *FIT* captures the percentage of the output variations that is reproduced by the model (a higher number means a better model).



While all monitors performed well on the identification data, the validation data shows the inappropriateness of the models for the BIS A2000 and the M-Entropy, which highlights potential non-linearities and time variance in their algorithmic structure.

**Table I – Goodness of fit (in %)**

	BIS A2000	M- Entropy	NeuroSENSE NS-701
Test #1 (identification)	81.5	87.3	91.2
Test #2 (validation)	53.2	29.2	94.8

**Discussion:** Cortical monitors use complex algorithmic processes to determine the cortical state of the patient. The design of these algorithms often dictates the dynamic behavior of the sensor. For instance, the use of neural networks, fuzzy logic, discriminant analysis, switching rules, etc., typically translates into a non-linear, time variant process that may not be predictable. Such technologies are referred to as ‘interpretative’ or ‘intelligent’ since they mimic the human cognitive process to make an interpretation of the signal patterns.

Conversely, ‘deterministic’ technologies use direct quantification of EEG patterns. The advantage is that, regardless of past information, the quantification is always performed the same way, the output of the monitor being a repeatable measurement. These technologies typically offer the best predictability and suitability for closed-loop, but they are also the most difficult to develop as they do not offer the flexibility of interpretative technologies.

The NeuroSENSE was initially designed for closing the loop [7] and as such uses at its core a deterministic approach to EEG analysis. As a result, its behavior is fully captured using a unique LTI model that can easily be accounted for in a controller design. Closing the loop using the NeuroSENSE as sensor may speed-up the development of such systems and may ease regulatory approvals.

## References:

- 1 Liu et al. ‘Titration of Propofol...’, Anesth., 2006.
- 2 Liu et al., ‘Closed-loop control of consciousness during lung transplantation...’, J. Cardiothorac. Vasc. Anesth., 2008.
- 3 Hegde et al., ‘BIS index guided closed-loop anasesthesia...’, J. Clin. Monit. Comput., 2009.
- 4 Haddad et al., ‘Closed-loop control for ICU sedation’, Best Pract. Res. Clin. Anaesth., 2009.
- 5 Pauldine et al., ‘Closed-loop strategies...’, J. Trauma, 2008.
- 6 Zikov et al., ‘Quantifying cortical activity...’, IEEE Trans. Biomed. Eng., 2006
- 7 Bibian et al., ‘NeuroSENSE™ Monitor...’, White Paper, [www.neurowavesystems.com](http://www.neurowavesystems.com), 2008.