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A Wavelet Based Method for Steady-State Detection in Anesthesia

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***Abstract*— With the recent concern on patient's outcome following general anesthesia, automatic control of drugs has been a field of interest. The Bispectral Index (BIS) is an EEG based hypnosis monitor, in current use at the operating theatre as a guiding tool for the anesthesiologist to titrate drugs, and prevent awareness. When trying to model a certain process, it's very important to obtain information of the system behavior under steady-state conditions. In this study the hypnotic and analgesic drugs' effect on the hypnosis index BIS was analyzed, in order to obtain steady-state information of the system response (inputs-output), and in the future model the drugs combined effect. A steady-state index was obtained using a wavelet analysis technique for trend detection. This tool may be used in the future to model the drug's combined effect on the hypnosis indices, and also to bring some insight on disturbances not related to drug changes.**

I. Introduction

General anesthesia is a drug induced state with three main components: hypnosis, analgesia and paralysis. Due to the developments in this field, several monitors were introduced in the operating room, providing the anesthesiologist with simple indices assessing patients' state on hypnosis and paralysis. For analgesia, there is not still a simple index translating the patients' nociceptive state, and anesthesiologists must rely on their experience to assess the nociceptive state of the patient, and titrate the analgesic drug.

For the hypnosis state, several monitors were developed and are in clinical use. These monitors derive simple indices from the electroencephalogram (0-100) and define boundaries for adequate anesthesia.

Due to the increasing concern about awareness during anesthesia, rapid recovery and short/long-term consequences following general anesthesia, automatic control of drugs administration is becoming more important, not only for it's superior results in achieving a desired target, but also for a more secure and stable anesthesia. This would provide a helpful tool to the anesthesiologist, allowing more time to perform other tasks in the operating room [1], [2]. When trying to develop a controller for the hypnosis it is very important to model the drugs' effect on the system's output in steady-state conditions, both on drugs (input) and on the depth of anesthesia index (output). Because drugs interact, it's important to consider combined effects and the different synergisms [3],[4].

The Bispectral Index (BIS) is an EEG based index varying from 0 (isoelectric EEG) to 100 (fully awake patient), with an adequate range for general anesthesia of 40-60, widely used in operating rooms. In this study BIS was analyzed using a wavelet based steady-state index[5] and crossing information with periods of steady-state for the input hypnotic and analgesic drugs. Analgesics and hypnotics have known dynamic interactions, and this information may be useful to model the drugs' combinations effect on the EEG derived indices[4]. Besides, if the drugs are stable and the output of the system is not, the discrepancy between the states of the inputs and the outputs may bring some insight on external stimuli intensity causing the effect measure to change when the system inputs are stable, demonstrating changes in noxious stimulus.

II. Pharmacokinetic Modeling

When administering a drug it's important to understand the drugs' metabolism in the human body from the infusion rate to the measurable effect. Propofol and remifentanil were used to maintain hypnosis and analgesia during general anesthesia.

A. Propofol and Remifentanil Pharmacokinetic Models

Schnider's pharmacokinetic model for the hypnotic (propofol)[6] and Minto's model for the analgesic (remifentanil)[7] were used in this study. Both models have a three-compartmental structure with flow constants between compartments: the central compartment represents the plasma compartment and side compartments the slow and rapid distribution compartments (Fig. 1).

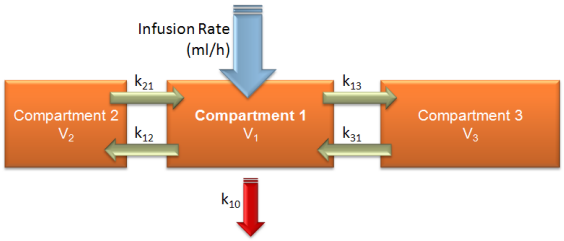

Fig. 1. Pharmacokinetic model with three compartments. k_{ij} is the rate constant describing the drug transfer from compartment i to compartment j. k_{10} denotes the rate constant of elimination.

The concentration in the central compartment (Compartment 1) is the plasmatic concentration (Cp) and it relates to the concentration in the effect organ, the effect-site concentration (Ce), according to Fig. 2.

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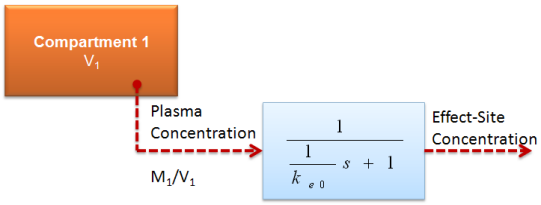

Fig. 2. Modeled relation between plasmatic and effect-site concentrations.

The k_{ij} flow constants obtained in these studies are adjusted to patient data: age, weight, height and gender [6],[7].

B. Target Controlled Infusion - TCI

Using the described models, a few commercial systems were developed to administer drugs using target controlled infusion (TCI), meaning, instead of using manual infusion, in which the anesthesiologist would decide the infusion rate that was the best for that patient, these systems based on patient data calculate the infusions automatically to obtain a desired drug plasmatic or effect-site target concentration. Fig. 3 presents the simulated response of a TCI system to changes in drug targets: it's difficult to reproduce the same result and obtain a desired effect-site concentration by manual infusion.

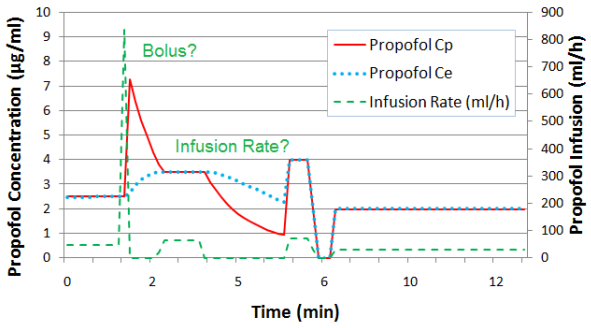

Fig. 3. Schnider's target controlled infusion simulation for a effect-site concentration target set to 2.5μg/ml, 3.5μg/ml and 2.0μg/ml (simulation of a male patient, 170cm, 70kg, 60 years): the figure presents how difficult it would be for the anesthesiologist to titrate the drug in order to have the same results, both for the bolus dose, to achieve rapidly the target, and for the infusion rate used to maintain the target.

III. Clinical Protocol

Data were collected every 5s during urological procedures following hospital protocols. All patients were monitored using BIS XP monitor; infusions were controlled by the TCI software RugloopII, with Schnider's and Minto's pharmacokinetic models, using effect-site concentration target steering.

Induction and maintenance of anesthesia were similar in all cases:

- Remifentanil effect-site concentration target is set to 2.5ηg/ml;
- When remifentanil Ce target is achieved, propofol infusion starts at 200ml/h (slow infusion) until loss of response to verbal and mechanical stimulus (LOC);
- Propofol's Ce is then set to the target at LOC, until intubation;
- After intubation, drug's Ce targets are changed according to patient needs.

Collected data were analyzed off-line using MatlabR2007®.

IV. Methods: Steady-State Detection

When modeling a process it's very important to obtain steady-state information of the process for the overall performance of the prediction model. Because of this, detecting steady-state conditions in the inputs and outputs of a system is important.

A. System Inputs: Drugs' Effect-Site Concentration

Due to the characteristics of TCI anesthesia and clinical protocol, it's simple to detect inputs steady-state periods: if the target Ce (Ct) and the pharmacokinetic model estimated Ce are different, this means that the inputs are not in steady-state conditions. This is true for both drugs, and if one wants to analyze simultaneous steady-state conditions in the inputs, a simple arithmetic rule can be defined (1).

$$|PropCt - PropCe| + |RemiCt - RemiCe| \leq 0.05 \Rightarrow SS \quad (1)$$

If the arithmetic rule was true for periods superior to 1 minute than steady-state for the inputs was considered.

B. System Output: Depth of Anesthesia Index

After detecting steady-state in the system inputs, the output measurable effect BIS was analyzed. This signal needs more robust analysis techniques than those used for drugs steady-state detection. A wavelet approach was used to extract BIS steady-state periods. Wavelets are currently widely used in several fields due to their properties, such as noise removal and feature detection. The method used was proposed by Taiwen Jiang and colleagues[5], and is summarized here.

The idea of multi-scale representation is to have the signal as a limit of successive approximations (2).

$$f(t) = \underbrace{\sum_{i \in I_j} c_{J,i}\varphi_{J,i}}_{\substack{Low\ Frequency \\ Component:\ Scale\ J}} + \underbrace{\sum_{j=1}^{J}\sum_{k \in k_i} d_{j,k}\psi_{j,k}}_{\substack{High\ Frequency \\ Components:\ Scale\ 1\ to\ J}} \quad (2)$$

where $\varphi_{j,i}$ and $\psi_{j,k}$ are the dyadic scaling and wavelet functions, respectively.

Due to the known wavelet transform (WT) properties, the noise can be reduced using a soft threshold technique over the WT modulus (3).

$$d'_{j,k} = \begin{cases} 0 & |d_{j,k}| \leq \delta_j \\ sign(d_{j,k})(|d_{j,k}| - \delta_j) & |d_{j,k}| > \delta_j \end{cases} \quad 1 \leq j \leq J, 0 \leq k \leq K_j \quad (3)$$

where δ_j is the threshold value at scale j. At scale j=1 WT is dominated completely by noise and the threshold value δ_1 can be assigned as the mean of the modulus maxima. The following threshold values are calculated as

$$\delta_j = \delta_1 2^{(j-1)/2},\ 2 \le j \le J \tag{4}$$

Rapid changes in the signal can be detected using WT, since these changes in the signal are identified as a maximum in the corresponding WT. Two points, within a defined interval t_p, with a WT maximum and opposite signal identify an abnormality (5).

$$\begin{array}{c} |W_f(p_1)| \, and \, |W_f(p_2)| \ge T_1 \\ sign(W_f(p_1).sign(W_f(p_2) < 0,\ p_2 - p_1 \le t_p \end{array} \tag{5}$$

After detecting an abnormality, the duration of this event is determined as the nearest point t_a to the left of p_1 and the nearest point t_b to the right of p_2 that satisfy (6).

$$\begin{array}{c} |W_f(t_a)| \, and \, |W_f(t_b)| \ge T_2 \\ |W_f(t_a - 1)| \, and \, |W_f(t_b + 1)| < T_2 \end{array} \tag{6}$$

Threshold values T_1 and T_2 are computed from historic data as

$$T_1 = 3\lambda_1 w,\ T_2 = w \tag{7}$$

where w is the standard deviation of the wavelet modulus of historic measurements with noise eliminated, and λ_1 an adjustable parameter around 1.

A steady-state index β was used to measure the degree of steady-state of the signal: $\beta = 0$ for unstable status and $\beta = 1$ for steady-state. When trying to determine steady-state of a signal it's important to distinguish zero-crossing points of $W_j f(t)$. To do that the WT on $W_j f(t)$ is performed, obtaining a second order WT $WW_j f(t)$, proportional to the second derivative of $f(t)$. The calculus of $\beta(t)$ was based on these notions, detecting rapid changes in $W_S f(t)$ and distinguishing zero-crossing points with $WW_S f(t)$ values. S is the characteristic scale, meaning the proper scale to analyze the WT where the WT represents the process variations properly (8).

$$S = j = int(log_2 \frac{\tau}{t_s} + 0.5) \tag{8}$$

where t_s is the sampling interval, and τ the response time constant.

1) Steady-State Index: If $|W_S f(t)| > T_u$ then $\beta(t) = 0$ where T_u is the identification WT modulus threshold for unsteady status. If $|W_S f(t - \Delta t)| < T_s$ then $\beta(t) = 1$ where T_u is the identification WT modulus threshold for steady status, and Δt a long enough time interval, to identify steady-state. To detect zero-crossing points, the second order WT is used. If $|W_S f(t)| < T_s$ and $|WW_S f(t)| < T_w$ then $\beta(t) = 1$ where T_w is the second-order WT modulus threshold to identify zero-crossing point in the WT. In other cases the following is used

$$\begin{array}{c} \beta(t) = \xi[\theta(t)] \\ \theta(t) = |W_S f(t)| + \gamma \, |WW_S f(t)| \end{array} \tag{9}$$

$$\gamma = \begin{cases} 0 & |WW_S f| \le T_w \\ (|WW_S f| - T_w)/2T_w & |WW_S f| \in (T_w, 3T_w) \\ 1 & |WW_S f| \ge 3T_w \end{cases} \tag{10}$$

$$\beta(t) = \begin{cases} 0 & \theta(t) \ge T_u \\ \xi[\theta(t)] & T_s < \theta(t) < T_u \\ 1 & \theta(t) \le T_s \end{cases} \tag{11}$$

where ξ is a smooth transfer function with range [0, 1]. The following proposed ξ was used.

$$\xi(x) = \frac{1}{2}\left[cos(\frac{x - T_s}{T_u - T_s}\pi) + 1\right] \tag{12}$$

The thresholds T_u, T_s and T_w are calculated from historic measurements, after selecting steady-state periods, and performing WT and second-order WT. Then the standard deviation of the WT modulus σ_{W_f} and the median of the second-order WT modulus σ_{WW_f} are obtained, and the thresholds defined as

$$T_s = \sigma_{W_f}\ T_u = 3\lambda_2 \sigma_{W_f}\ T_w = \sigma_{WW_f} \tag{13}$$

where λ_2 is an adjustable parameter around 1.

The steady-state index $\beta(t)$ was used to extract steady-state periods in the output, by thresholding its value: if $\beta(t) \ge 0.9$ for more than one minute than the output was considered to be in steady-state.

V. Results

Data were collected during 20 urological procedures under general anesthesia, with TCI of propofol and remifentanil using Schnider's and Minto's pharmacokinetic models. RugloopII software was used to collect data every 5s. Five patients' trends were visually analyzed to determine steady-state periods and extract the needed information incorporated in the wavelet based detection algorithm. The tuned algorithm was then applied to the 15 remaining data sets to test its' performance. Afterwards the described methods were applied to the 20 patients' data to extract combined input-output steady-state periods.

A. Input and Output Steady-State Detection

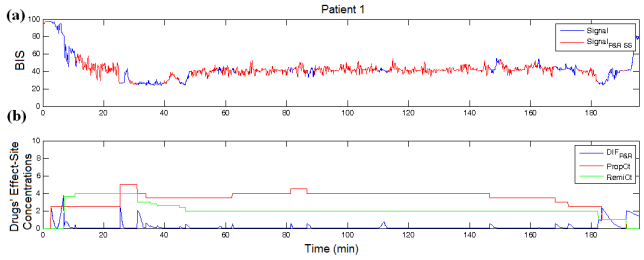

Fig. 4. Steady-state detection of the inputs: (a) BIS trend and overlapped BIS periods with input steady-state; (b) Propofol (hypnotic) and remifentanil (analgesic) drugs effect-site concentration targets, and the sum of the absolute difference between estimated and target effect-site concentrations (DIF_{PR} is the quantity in (1)).

Fig. 4 presents the results for the inputs steady-state detection in one patient from the test group, showing the BIS trend and the overlapped input steady-state periods.

Steady-state in the inputs is not always accompanied by output steady-state Fig. 4, which may be explained to changes in the noxious stimuli, and other drugs interference. Detecting discrepancies between states brings important information on the patients' stability.

Fig. 5 presents the result of the wavelet based algorithm applied to the same patient, showing the original, filtered

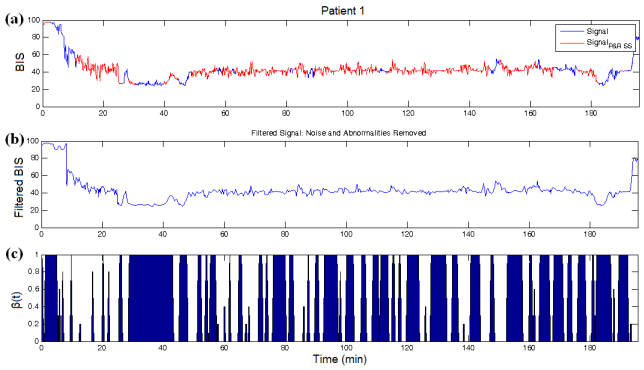

Fig. 5. Steady-state detection of the output BIS: (a) BIS original trend with overlapped input steady-state periods; (b) Filtered BIS. (c) Steady-state index (30s smoothing).

signal, and the corresponding steady-state index. The steady-state index is consistent with the BIS trend, and is robust to the signal variability.

B. Combined Input-Output Steady-State Periods

After testing the robustness of the methods by visual assessment, the simultaneous steady-state periods were extracted, and represented in a 3D plot. Fig. 6 presents the result of all the simultaneous inputs-output steady-state periods for the 20 data sets, and the relation between the drugs' Ce and average BIS on those intervals. This information is useful to model drugs' combined effects on depth of anesthesia indices, meaning the dynamical effect of drugs' on cerebral activity measured by BIS.

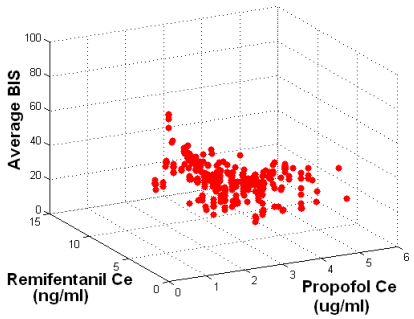

Fig. 6. Combined periods of steady-state input-output for the 20 patients' data: relation between drugs effect-site concentrations and average BIS.

VI. Discussion

A tool for steady-state detection was developed, considering the patient as a system, hypnotic and analgesic drugs as inputs and the BIS as an output. The wavelet analysis technique performed satisfactorily for steady-state detection in these biomedical signals.

Visual analysis of the detection results revealed adequacy in detecting both steady-state on the input drugs and on the output measurable effect BIS, using the arithmetic rule (drugs) and the wavelet based detection algorithm (BIS). The detected combined intervals of steady-state can be used to model the relations between drugs and synergistic effects on BIS, and provide a model that could later be used in the control of the administration of drugs, providing a more secure and stable anesthesia. Some dispersion of the combined steady-state periods data was observed, this may be explained by the use of all patients in the representation. Maybe there's a need to adjust the combined effect model with parameters depending on patients demographics, similar to what happens in pharmacokinetic models.

With recent concerns on patients' homeostasis and outcome following general anesthesia, the discrepancies between drugs and BIS states can bring useful information on events not motivated by drug changes but by external stimuli. A steady-state index for depth of anesthesia indices can complement the information contained in these indices and provide some insight in the patients' nociceptive state.

VII. Conclusions and Future Work

A steady-state detector with application to general anesthesia was developed, with adequate performance in detecting steady-state on drugs and depth of anesthesia index BIS.

In future work the information contained in the detected steady-state periods (propofol Ce, remifentanil Ce and BIS), will be used to model the combined effects of drugs on anesthesia indices.

The steady-state detector can be used as an indicator to the clinician of the patient's state, and bring some insight on the nociception component of the patient, complementing the information in the depth of anesthesia index value. This technique will be extended to the multivariable approach incorporating other signals related to nociception such as heart rate, and blood pressure, providing an easy to use and simple index; this may be considered as an assistant measure of the patients' stability and homeostasis during general anesthesia.

The wavelet based detector will also be applied directly to the infusion rate of drugs, instead of using the arithmetic rule for the effect-site concentrations. This will provide a more robust method that can be applied to manual intravenous anesthesia, not only target controlled infusion anesthesia.

References

[1] P. S. Myles, K. Leslie, A. Forbes, J. McNeil and M. Chan, B-Aware, *The Lancet*, vol. 364, 2004, pp 841-842.

[2] T. G. Monk, V. Saini, B. C. Weldon, J. C. Sigl, Anesthetic management and one-year mortality after noncardiac surgery, *Anesthesia and Analgesia*, vol. 100, 2005, pp 4-10.

[3] A. Castro, C. S. Nunes, P. Amorim, F. G. Almeida, Hypnotic administration for anesthesia using sliding-mode control, *30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, 2008.

[4] A. Absalom and M. MRF Struys, An Overview of TCI & TIVA, *Academia Press*, Gent, 2005.

[5] T. Jiang, B. Chen, X. He, P. Stuart, Application of steady-state detection method based on wavelet transform, *Computers and Chemical Engineering*, vol. 27, 2003, pp 569-78.

[6] T. W. Schnider, C. F. Minto, S. L. Shafer, P. L. Gambus, C. Andersen, D. B. Goodale and E. J. Youngs, The influence of age on propofol pharmacodynamics, *Anesthesiology*, vol. 90, 1999, pp 1502-1516.

[7] C. F. Minto, T. W. Schnider and S. L. Shafer, Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application, *Anesthesiology*, vol. 86, 1997, pp 24-33.