VIRTUAL BIOINSTRUMENTATION FOR THE IMPLEMENTATION OF AN EEG GUIDED ANAESTHESIA DELIVERY SYSTEM (EGADS)

J. Roca-Dorda*, J. Roca-González*, J. Jiménez-Martínez*, J.A. Álvarez-Gómez** and F.J. Gil**

* EIMED Research Group - Polytechnic University of Cartagena, Cartagena, Spain
** Hospital Sta. María del Rosell, Cartagena, Spain

joaquin.roca@upct.es

Abstract: Traditional dosing of intravenous anesthesic agents in the form of discrete boluses has been substituted by computer controlled continuous infusion. For this purpose, closed-loop controllers based upon Depth Of Anesthesia (DOA) measure have been proposed. This paper presents an EEG Guided Anesthesia Delivery System (EGADS), implemented within a virtual bio-instrumentation framework. Results for software metrics and execution profiling are included.

Introduction

The problem of dosing intravenous agents for anesthetic purposes is related to the metabolic principles of operation of the hypnotic used for sedation.

With the development of the pharmacokinetic modeling techniques, traditional dosing in the form of discrete boluses was substituted by total intravenous anesthesia (or TIVA) where the drugs were administered at a constant rate in function of the required dosage. Though this method proved useful for some drugs of simple kinetics (one compartment models), the performance at everyday clinical procedures was limited with other drugs that required of continuous operation by the anesthesiologist in order to correct the pumps rate according to the clinical sings related to the anesthesia state [1].

In order to overcome these limitations, model predictive controllers were proposed to drive the infusion of the hypnotic drug in function of the predicted behavior of the drug within the patient through the use of accurate models.

In this sense, the total amount of drug in the blood may be estimated by means of pharmacokinetic models (PK) that relate the plasmatic drug concentration with the drug uptake, elimination and internal redistribution among the different body tissues and organs. These models take the form of a simple set of differential equations reflecting the drug concentration variation in each one of the n-compartments; and can be written in terms of the inter-compartmental rate microconstants (K_{ij}), and the external drug input I_i associated to the so-called central compartment (of volume Vi) as:

$$\frac{dC_i(t)}{dt} = \sum_{\substack{i=1 \\ j=1 \\ i \neq j}}^{n} \left(\frac{I_i}{V_i} + K_{ji} C_j(t) - K_{ij} C_i(t) \right) \qquad (1)$$

The first device approved for clinical use, which was introduced in 1996 for the administration of propofol, used an embedded computer to simulate the plasmatic concentration of the drug in order to adjust the required perfusion rate, by means of an analytical solution of the associated three-compartment model [2][3]. This type of administration, also known as Target Controlled Infusion (or TCI), has renewed the hope on intravenous anesthesia, and has recently encouraged the development of new depth of anesthesia measurement methods suitable for closed-loop administration of the intravenous agents [4][5]. The second problem that the clinical specialists have to face up is that most of the drugs used for sedation do not present a linear relationship between plasmatic concentration and the observable therapeutic effect, so that an additional non-linear pharmacodynamic model (PD) for the effect-site has to be used in order to properly calculate the dosing required to reach a desired sedation state. On the other hand, as the PK parameters are derived after a specific sample population, some individuals may not be correctly modeled, so that significant differences are observed between actual and predicted plasmatic drug concentrations. For this reason, several authors have developed closed-loop control strategies for Depth Of Anesthesia (DOA) that automatically adjust the dose in function of the observed changes in several indicators of the sedation such as the blood pressure and the heart rate. The main drawback of this approach relies on inter subjects response variability, so that current trends are focusing on the analysis of cortical responses (EEG, AEP) as DOA estimators [6][7]. Despite of the fact that most of these efforts found feasible the development of efficient closed-loop controllers, no system is commercially available at this time (or at least, as far as our knowledge extents), due to the fear to legal claims in case of system malfunction, as happens with many other closed-loop systems for medical use. Our approach has focused in the development of a modified closed-loop controller that requires the validation of the control output by the specialist in charge of sedation [4].

In this sense, the system proposed in figure 1, is configured as an EEG Guided Anesthesia Delivery System (EGADS), rather than a closed-loop controller, offering a suggestion for the concentration target required to hold the DOA level within the desired limits.

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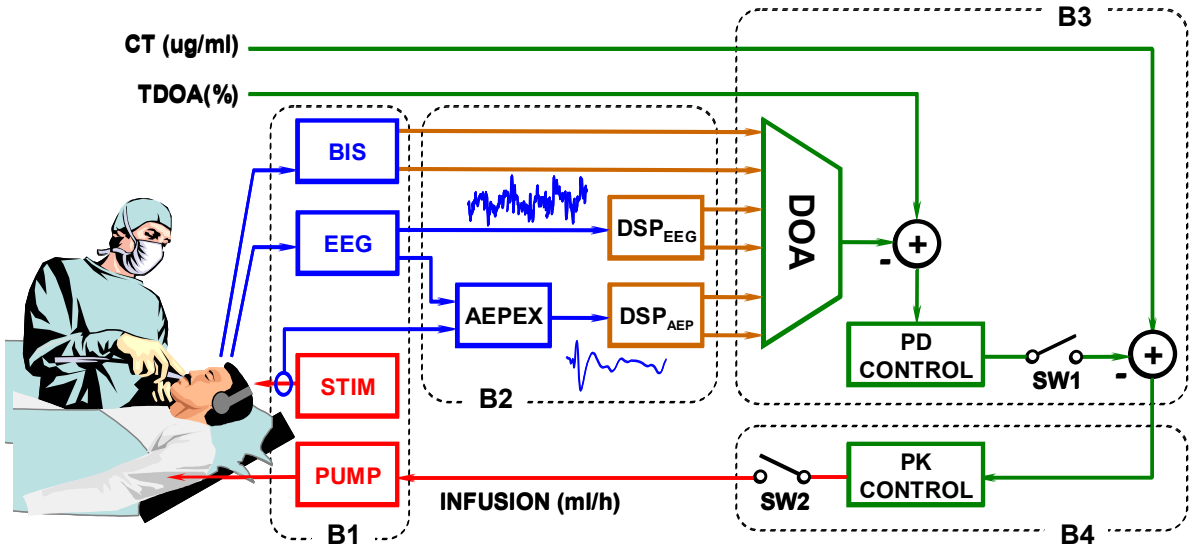

Figure 1: EEG Guided Anesthesia Delivery System (EGADS)

If the physician in charge of sedation considers this suggested target to be valid for its administration under the current condition of the patient, he/she may validate it (depicted by switch SW1), sending this concentration target to the TCI engine, which updates the pump infusion rate (which can also be manually set if desired).

Materials and Methods

At the early stage of the design, the conceptual sketch of the system was analyzed and four blocks were identified: Hardware input/output, digital signal processing, dosing agent and TCI controller.

Due to the nature and diversity of the computer routines that had to be implemented, Labview was considered as an ideal candidate, as it is specifically oriented for the development of real-time measurement systems.

The proposed EGADS is based around a PC running a dedicated computer program for the acquisition and processing of Medium Latency Auditory Evoked Potentials (MLAEP), obtained through a Biopac MP100 system and the accompanying amplifier ERS100.

Auditory Stimuli are generated by means of a custom designed oscillator (based around a PIC microcontroller) intended to generate 1 ms stimuli repeated at a rate of 8Hz (though these parameters are programmable by means of serial communication).BIS index is acquired by means of a BIS A-2000 monitor through a standard serial interface (BIS is acquired as an alternative measure for depth of anesthesia in order to drive the controller). Finally, the computer is also connected to the IVAC P6000 infusion pump used for the administration of the propofol.

A dedicated computer application has been programmed under Labview 6i as a base platform for the study of different control strategies and reference models for the TCI subsystem. This program has taken advantage of the multitasking capabilities of this graphical programming environment.

For this purpose, the different operations required for operation have been split into 7 different tasks, as shown in figure 2.

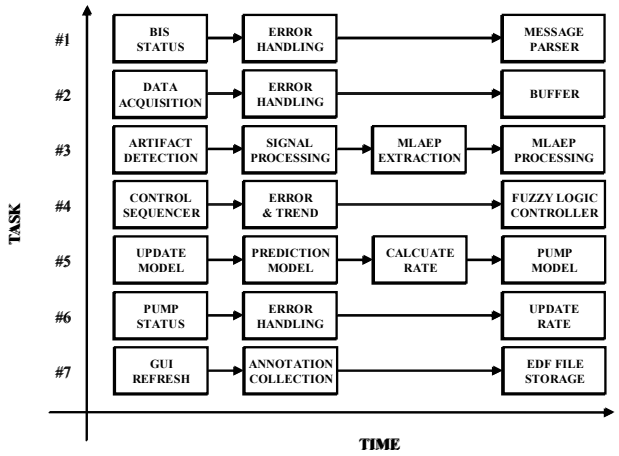

Figure 2: Task Distribution Used for the EGADS

Task #1 is dedicated to the management of the serial communications with the BIS A2000 monitor used for obtaining this index. Error handling routines are included for granting a robust operation under real uses conditions. In order to assure the proper reception of the transmitted data, a simple but yet effective state-machine has been implemented (see table 1).

Task #2, is related to the data acquisition routines required for operating the DAQ device (Biopac MP100) under burst-mode transfer, using a 1KHz sample rate. The hardware acquisition buffer, containing both signals (auditory stimulus and EEG), is read every 125 ms, and transferred into a software buffer.

This buffer is read in task #3 by the artifact detection module, which discards buffer contents in case of artifact detection, which is done by comparing amplitude, range and rise time thresholds.

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Table 1: BIS States

State		Description
1		BIS Initialization Procedure
1	1	On error retry initialization
1	2	Retrieve BIS data
1	3	Comms error/init failed
2		BIS Data Retrieval
2	2	BIS record incomplete
2	3	Comms error/data request failed
3		Error Handler
3	3	Error condition
3	4	Device/comms reset request
4		Reset
4	1	Reset complete
4	3	Fatal error

If the buffer content is found to be valid, the EEG input signal is handled by the signal processing module that apply the required composite Linear Phase FIR for rejecting the 50Hz power line interference (notch) and limiting the signal bandwidth down to 250 Hz.

Once the signal has been processed, the 125 ms segment of the EEG signal triggered after the stimulus enters into the averaging stack, where the MLAEP is obtained after averaging a total of 256 responses, yielding to a refresh period close to 30s.

At this point, the AEP index proposed by Mantzaridis & Kenny [8] is applied to the averaged response in order to obtain this measure for the depth of anesthesia.

Once this value is available, the error in the actual response of the patient and the desired sedation level is calculated (as well as its trend) in task #4, each time the control sequencers orders to.

The values of the error are then fed to the fuzzy-logic PID controller described in [4], which calculates the required increment (or decrement) in target concentration to be suggested for granting the desired level of sedation.

If the specialist in charge of the anesthetic procedure founds this suggestion to be useful, the controller updates the target concentration of the TCI algorithm running in task #5.

This process starts by updating the status of the reference pharmacokinetic model used for prediction, in order to recalculate the rate of infusion required to reach the new target, following the algorithms proposed by Bailey & Shafer [2].

This rate is sent to the infusion pump in task #6, where a state-driven communication driver is used (states listed in table 2). The control sequence begins with an enquiry of the pump status in order to detect device alarms and the actual infusion rate. In case of normal operation, the updated rate is sent to the pump.

Finally, the graphical user interface is refreshed in task #7, updating the panel indicators and charts. The annotation collecting subroutines are run in this same task in order to record all kind of events that may appear during operation. Finally, all of the collected signals and variables are stored in an EDF for posterior analyses.

Table 2: Infusion Pump States

State		Description
1		Pump Initialization Procedure
1	1	On error retry initialization
1	2	Retrieve initial pump data
1	6	Comms error/init failed
2		Pump Data Retrieval
2	2	On error retry request
2	3	Data retrieval complete
3		Stop Pump
3	3	On error retry stop command
3	4	Pump stop complete
3	6	Comms error/ stop failed
4		Standby
4	3	Stop command request
4	4	Pump status & rate request
4	5	Start/update rate command request
4	6	Comms error/ alarm
5		Start
5	4	Pump start complete
5	5	On error retry start command
5	6	Comms error/ start failed
6		Error Handler
6	4	Error/alarm condition cleared
6	6	Error/alarm condition
6	7	Device/comms reset request
7		Reset
7	1	Reset complete
7	6	Fatal error

Results

Since virtual instruments (VIs) programming is a relatively recent computer science discipline, traditional code analysis techniques for static testing are not fully developed at this time. Instead, exhaustive tests of the individual subroutines (called as subVIs) were performed on the developed system. Besides, in order to check the algorithms finally implemented, performance indicators and software metrics were profiled. An example of these results may be found in tables 3 & 4 which include the execution time and memory requirements metrics obtained for three different subVIs involved in AEP processing. Filter includes all the digital filtering required for processing the raw EEG signal before AEP extraction is carried out (within Extract). Finally, Average includes those routines required for AEP stack averaging process.

Table 3: Execution time metrics for the AEP subVIs

Execution	Filter	Extract	Average
VI	0,3004	4,9571	11,2562
SubVIs	3,6753	0	4,2261
Total	3,9757	4,9571	15,4823
N runs	5579	5579	5580
Avg	0,0001	0,0009	0,002
Min	0	0	0
Max	0,01	0,01	0,01

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On the one hand, the average time required for the digital processing (artifact detection and filtering) of a raw EEG segment of 125ms (125 samples) is close to 0,1 ms; which is fast enough to assure real-time operation of this block. The next column in that same table collects the metrics for the evoked response extraction process (by means of a software trigger generated after thresholding the acquired stimuli). This process takes place in an average time of 0,9 ms. Finally, the averaging of the stack of 256 evoked responses takes an average time close to 2 ms. All of these results assure that an averaged auditory evoked response may be found within 10 ms after it is acquired.

Table 4: Memory metrics for the AEP Processing VIs

Memory	Filter	Extract	Average
sizeAvg	27.068	41.356	15.473
sizeMin	27.068	38.504	15.451
sizeMax	27.068	46.712	15.512
blksAvg	27	47	20
blksMin	27	47	19
blksMax	27	51	21

On the other hand, memory requirements of these subVIs are summarized in table 4. As it may be seen in the first column, the filtering process requires of at least 27.068 bytes (or 27 memory blocks), which is minimum when considering the resources offered by today's computers. These results are similar to those obtained for the evoked response extraction process. In this case, an average of 38.504 bytes (or 47 memory blocks) are required for proper operation. In the last case, related to the averaging of the stack the average number of required bytes is 15.473 (or 21 memory blocks).

Table 5: Memory metrics for the AEP Processing VIs

Metric	TOTAL	EGADS	%
# Of nodes	3409	593	17
Structures	183	37	20
Diagrams	413	66	16
Max diag depth	-	5	-
Diag width (pixels)	-	1515	-
Diag height (pixels)	-	1110	-
Wire sources	4315	500	12
Controls	351	44	13
Indicators	314	52	17
Property reads	4	4	100
Property writes	8	8	100
Global reads	0	0	-
Global writes	0	0	-
Local reads	113	104	92
Local writes	122	116	95
Cins	0	0	0
Shared lib calls	6	0	0

Once the individual subVIs were analyzed, the main virtual instrument was checked. For this purpose, software metrics were obtained by means of the dedicated tools included within Labview [8]. The results of this test are summarized in table 5.

As the main virtual instrument was conceived as a front-end for all the individual subVIs, most of the nodes (data input-output points), structures (for loops, sequences, etc.) and diagrams are concentrated outside the EGADS. Since most of the local variables and property nodes are used for updating the graphical user interface, most of them are located within the main VI. Finally, the external library calls (those involved in data acquisition routines) are located outside the main VI.

Discussion

The results included in the previous section, give just a little image of the whole testing process that have been followed in order to complete the validation of the proposed EGADs prior to its functional testing within an approved clinical study. It should be said that the timing details are related to the execution of the mentioned system under a Pentium M notebook computer running at 1.6 GHz with 1GB of RAM.

The graphical user interface, depicted in figure 3, has been designed according to our experience on the design of accessible systems and the requirements imposed by the clinical members of the research group, further studies should be carried out in order to maximize its global usability.

Once the feasibility of the system has been checked, the next step to be followed toward the development of a clinical device should cover a deep study of the reliability of the system (which should start with the study of each one of its individual components). At this point, the reader should not get confused, since ours was just an experimental approach to the solution and standard computer elements were used (both hardware and software). A formal design should require of elements of certified reliability for its integration within a biomedical device.

Conclusions

Virtual instrumentation, as defined by Olansen and Rosow [8], has enabled the development of an experimental EGADS for its application as a research platform within the neurological evaluation of patients under surgery. The visual programming language finally chosen (Labview) has proved useful for the development of the system. On the one hand, the multitasking capabilities of this environment have made possible to assure real-time operation of the different subsystems involved (see figure 4). On the other hand, software modularity has proved useful for code debugging and system validation. For the development of the different subVIS, several small stand-alone applications have been written (such as a small BIS monitor recorder, a generic TCI controller, and an EDF file viewer/converter). The system is now under evaluation under an approved clinical study.

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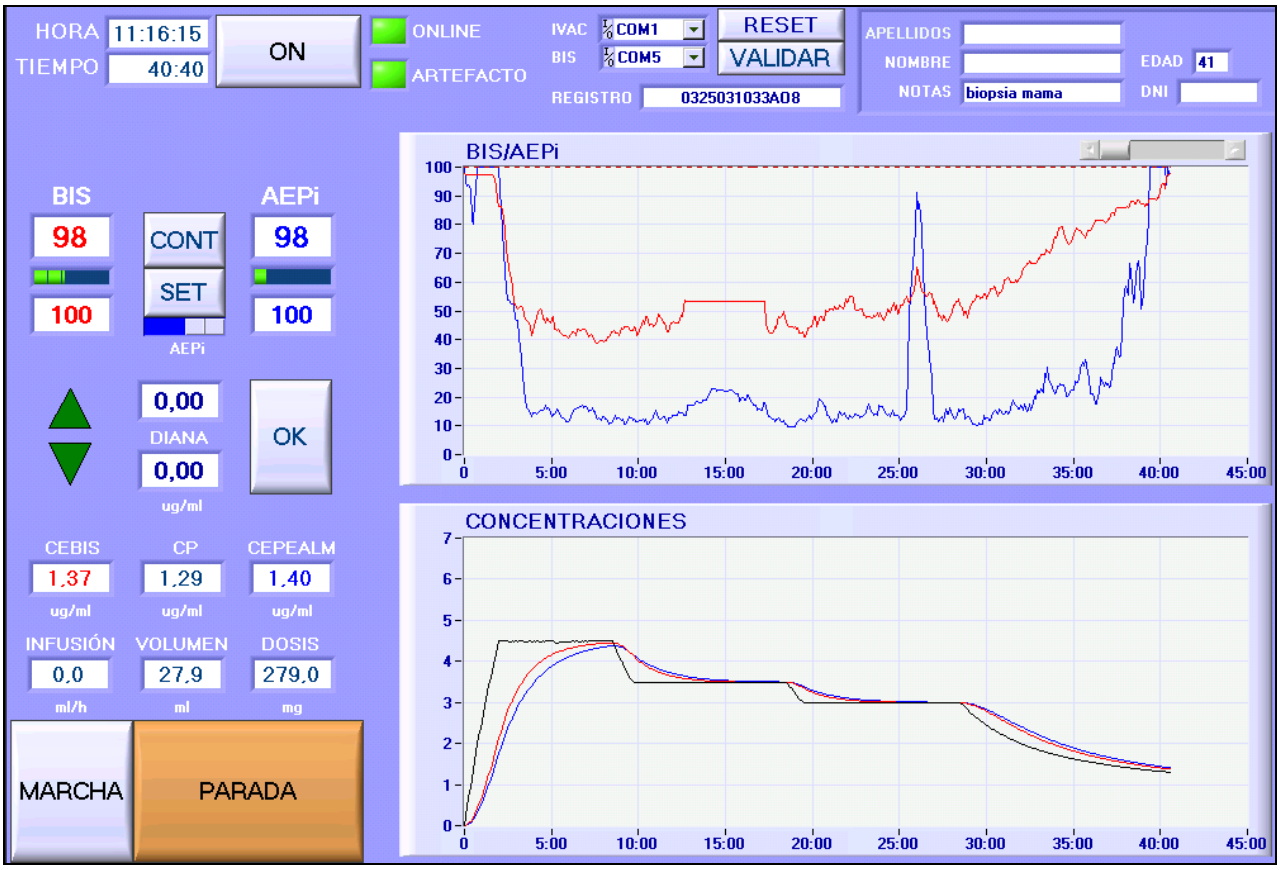

Figure 3: Graphical User Interface of the EGADS

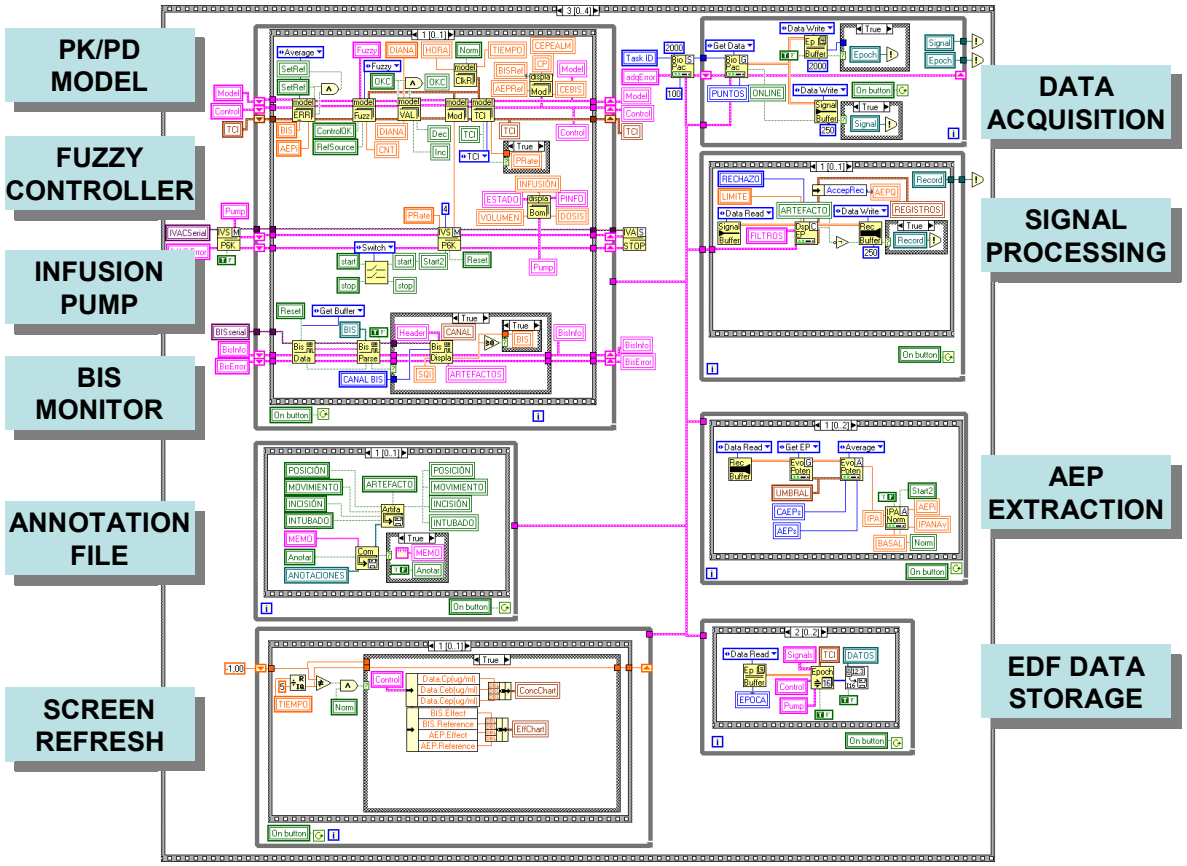

Figure 4: Main Diagram of the EGADS Virtual Instrument

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