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Technical Aspects of Closing the Loop in Depth-of-Anesthesia Control

Gorazd Karer

***Abstract*—**When performing a diagnostic procedure or surgery in general anesthesia (GA), a proper introduction and dosing of anesthetic agents is one of the main tasks of the anesthesiologist. That being said, depth of anesthesia (DoA) also seems to be a suitable process for closed-loop control implementation. To implement such a system, one must be able to acquire the relevant signals online and in real-time, as well as stream the calculated control signal to the infusion pump. However, during a procedure, patient monitors and infusion pumps are purposely unable to connect to an external (possibly medically unapproved) device for safety reasons, thus preventing closed-loop control. This paper proposes a conceptual solution to the aforementioned problem. First, it presents some important aspects of contemporary clinical practice. Next, it introduces the closed-loop-control-system structure and the relevant information flow. Focusing on transferring the data from the patient to the computer, it presents a non-invasive image-based system for signal acquisition from a patient monitor for online depth-of-anesthesia assessment. Furthermore, it introduces a User-Datagram-Protocol-based (UDP-based) communication method that can be used for transmitting the calculated anesthetic inflow to the infusion pump. The proposed system is independent of medical-device manufacturer and is implemented in MATLAB-Simulink, which can be conveniently used for DoA control implementation. The proposed scheme has been tested in a simulated GA setting and is ready to be evaluated in an operating theatre. However, the proposed system is only a step towards a proper closed-loop control system for DoA, which could routinely be used in clinical practice.

***Keywords*—**Closed-loop control, Depth of Anesthesia, DoA, optical signal acquisition, Patient State index, PSi, UDP communication protocol.

I. Introduction

When performing GA, it is necessary to use substances that enable unconsciousness, analgesia (pain relief), amnesia (memory loss), and muscle relaxation (movement prevention). A proper introduction of anesthetic agents is essential when performing surgery or a diagnostic procedure. GA and the related activities in the human body are very complex dynamic processes. They include various pharmacokinetic and pharmacodynamic mechanisms, which have not been fully studied yet – the improvement of underlying models is still ongoing research. However, there have been several attempts to model these mechanisms, some of the resulting models are also used in clinical practice [6]-[8]. During the GA, the anesthesiologist monitors the patient's vital functions and maintains the functions of vital organs. To achieve adequate GA, substances are introduced into the patient's body in different manners. In clinical practice, the most commonly used methods are the inhalation induction of anesthesia, whereby the patient inhales the substance from the breathing mixture, and intravenous induction of an anesthetic agent, i.e., injection of the anesthetic into a vein. The anesthesiologic technique, where all the substances are injected intravenously, is total intravenous anesthesia (TIVA). The goal of the anesthesiologist is to maintain the appropriate DoA by adjusting the inflow of the anesthetic agent. Naturally, the pharmacokinetics and pharmacodynamics of the anesthetic and the type of procedure must be considered. Too deep anesthesia can result in a blood-pressure and heart-rate frequency drop as well as a slow post-operative awakening of the patient. On the other hand, inadequate DoA is manifested in the activation of sympathetic nerves, or – in the most unlikely event – with the patient awakening, which must be at all costs avoided.

In the last years, an emerging paradigm in medicine seems to have grasped the idea of personalized medicine [1]. In the field of drug delivery systems, this includes modeling, control, analysis, and pharmacological studies. Control of DoA seems a suitable problem to approach using closed-loop control [2]. This would benefit the anesthesiologist by relieving the tedious task of constantly adjusting the inflow of the anesthetic agent. If one wishes to implement a closed-loop control system for DoA, one must first overcome several technical hurdles. A necessary condition for the system to work is to establish a reliable way of transmitting and receiving the relevant data and signals between medical devices, which are regularly used in anesthetic procedures, and the computer or device running the closed-loop control algorithm. However, this is not always easy to accomplish as most medical devices purposely prevent auxiliary connections to non-approved external devices, such as laptop computers, during the time they are being used. This seems to be primarily aimed to preventing any safety hazards for the treated patient. However, the lack of possibility to connect and transfer the relevant signals between the medical devices and the auxiliary computer actually hinders the possibility to implement a closed-loop control system.

The paper proposes a step towards the solution to the aforementioned problem. It consists of, firstly, a non-invasive image-based system for signal acquisition from a patient monitor for online depth-of-anesthesia assessment, and secondly, a UDP-based connection method that can be used for transmitting the calculated anesthetic inflow to the infusion pump. The whole system is based on MATLAB-Simulink

Gorazd Karer is with University of Ljubljana, Faculty of Electrical Engineering, Trzaska cesta 25, SI-1000 Ljubljana, Slovenia (phone: +386 1 4768 701; e-mail: gorazd.karer@fe.uni-lj.si).

environment, so it can conveniently be used and upgraded for more advanced DoA modelling, simulation and control.

The paper is organized as follows. Section II introduces important aspects of contemporary clinical practice. In Section III, the technical issues concerning closed-loop control implementation are introduced. Section IV describes the optical signal-acquisition system. Section V introduces the UDP-based control-signal transmission. In Section VI, we present the Simulink implementation of the closed-loop control structure. Finally, we give some concluding remarks.

II. Clinical Practice

In modern clinical practice requiring GA, the DoA is determined by assessing the relevant clinical signs (iris, sweating, movements), by interpreting hemodynamic measurements [3] and by processing EEG signals, which can be done by various established measurement systems, e.g. bispectral (BIS) index, Patient State index (PSi), Narcotrend, Scale – and Response Entropy.

A. EEG-Based DoA Measurement

BIS index is a non-invasive measurement method for DoA. The electrodes on the patient's head are connected to the BIS monitor and the BIS index is calculated from the measured EEG signals. The BIS monitor provides a single dimensionless number representing DoA, which ranges from 0 (equivalent to EEG silence) to 100. A BIS value between 40 and 60 is targeted in GA, whereas a value below 40 is considered appropriate for long-term sedation due to head injuries. The reference can thus be the respective value; the manner and speed of approaching the reference depend on the specific characteristics of the procedure and the pharmacokinetics and pharmacodynamics of the substance in the patient's body. Due to its non-invasive nature and simple implementation, BIS index has been extensively used in clinical practice.

Another very promising DoA measuring method based on EEG signals is the Masimo proprietary PSi [4], [5]. Masimo’s Next Generation SedLine features an enhanced signal-processing engine, which provides an enhanced PSi calculation. This represents a processed EEG parameter related to the effect of the anesthetic agents. The forehead sensor collects the patient’s EEG data from the frontal lobe on both sides of the brain.

B. Target-Controlled Infusion

There are various approaches to modeling the effect of propofol described in the literature: several pharmacokinetic and pharmacodynamic models have been developed, e.g. [6]-[13]. The models of propofol effect usually define the basic structure of the dynamic system, while the parameters depend on the individual patient's properties, e.g., weight, height, age, gender, as well as the patient's individual sensitivity to propofol and his ability to excrete it. Certain infusion pumps enable target-controlled infusion (TCI), where the pump sets the calculated flow of the medication with regard to the model. Various pharmacokinetic models can be employed for this purpose. However, the models often do not reflect the real dynamics, which also depend on the difficult-to-consider individual sensitivity of the patients to the substance. Since TCI procedures are based on open-loop induction, they often cannot ensure optimal performance, especially when dealing with a patient's discrepancy from the mean-population models is considerable.

C. DoA Control Concept

DoA supervision and control seems a suitable problem to tackle using a closed-loop control approach [2]. In such a manner, DoA is actively adjusted by changing the propofol inflow and accordingly reducing or increasing the DoA. It is essential that an anesthesiologist must always be present to supervise and assess the patient’s needs. EEG signals and thereof calculated indices (BIS, PSi) are definitely related to the effect of the anesthetic agents, e.g., propofol. However, these indices cannot fully represent them. They are nevertheless a good indicator of DoA and can effectively be used as the controlled variable in a DoA closed-loop control system.

III. Closing the Loop: Overcoming the Technical Hurdles

To implement a closed-loop control system for DoA, we must be able to acquire the relevant signals online and in real-time, so that the appropriate inflow of the anesthetic agent can be calculated accordingly. Furthermore, the calculated inflow signal needs to be reliably transmitted to the infusion pump so that the needed inflow is constantly being applied during the procedure, which ensures a suitable DoA for the treated patient. Therefore, it is necessary to establish a reliable way of transmitting and receiving the relevant data and signals between the clinically approved medical devices and the external computer, which implements the closed-loop control algorithm. However, the problem of acquiring the relevant signals for DoA assessment, as well as transmitting the calculated control signals to the infusion pump has not been adequately solved yet. There are no universal producer-supported solutions for acquiring online data from commercially available monitors.

A. Signal Acquisition for DoA Assessment

To the best of the author’s knowledge, there are currently no medically approved DoA monitors capable of online feeding out a usable signal for further processing in an external computer, at least not as an officially supported feature. Despite the lack of connectivity, many patient monitors provide an option to record the relevant signals during operation. They also allow the recorded signals to be later acquired by connecting the patient monitor to an external device (e.g., a computer, a USB-connected data-storage device) and downloading them. However, none of the commercially available monitors seems to provide the option to acquire these signals online, which is a prerequisite for closed-loop control. This is of course due to safety reasons: any interference could compromise the safety of operation of the patient monitor, which could negatively impact the safety of the treated patient. Therefore, the need to come up with a system for reliable signal acquisition from a patient monitor for online DoA assessment is evident. Ideally, the developed system should work non-invasively so that it does not interfere with the medical devices that are routinely used during a diagnostic or surgical procedure. In such a manner, the developed signal acquisition can be implemented in clinical practice without prior approval, which is otherwise required for all medical equipment.

B. Signal Transmission for the Anesthetic-Agent Inflow

Another problem arises when dealing with the issue of transmitting the control signal, i.e., the calculated inflow of the anesthetic agent, to the infusion pump that is used in clinical practice. Several advanced infusion pumps provide a way of transferring the stored data to an external device. Furthermore, some infusion pumps can be connected to a computer network. This allows sending and receiving information through a local area network (Ethernet connection). However, it is usually only possible to transfer some patient-related (administrative) parameters to and from a centralized patient management system.

According to the author's investigation involving a number of infusion-pump producers, meetings with representatives from service as well as marketing departments, at the moment there seem to be no medically-approved infusion pumps available in Europe that feature a (contemporary and producer-supported) possibility to be conrolled using an auxiliary-signal control from an external device, such as a computer. Although some pumps allow data to be transferred from a computer, this can only be done offline, i.e., not during surgery. However, the possibility control the pump online during the surgery is an unavoidable requirement for the closed-loop control system to be actually used in a real clinical setting. In the past, there have been some commercially available infusion pumps that featured this kind of control (e.g., Alaris using a RS-232 connection), but a recent firmware update disabled this feature.

The reason for the lack of connectivity is to prevent any safety risks for the treated patient. However, the lack of possibility to connect and to transfer the relevant signals between the auxiliary computer and the infusion pump prevents the implementation of a closed-loop control system for DoA.

The need for developing an infusion pump capable of receiving an auxiliary control signal from a computer-based control algorithm is therefore evident. Such an infusion pump should be medically certified and well tested. Furthermore, it should provide suitable alarming and safe operation in case the signal is lost. In addition, the connections to the external computer should be galvanically isolated from the pump in accordance with MOPP (Means of Patient Protection) so as to prevent any possible problems due to, e.g., leakage electric currents.

C. Closed-Loop-Control-System Structure and the Relevant Information Flow

The closed-loop control system is structured as shown in Fig. 1. The depicted modules show the technical aspects of the system with an emphasis on particular connections. The rounded modules represent the more medically-oriented part of the system, whereas the rectangles with sharp corners show the technically-oriented modules. The system operates as follows:

- The *Patient* is administered the anesthetic agent, namely propofol, by the *Infusion pump*. The *Infusion pump* sets the inflow of the anesthetic agent required for GA.
- The *Patient* reacts to the inflow of the anesthetic agent according to their particular pharmacokinetic and pharmacodynamic properties. The *Patient* reaches a certain DoA.
- The DoA in the *Patient* influences their EEG signals.
- EEG is measured by the *DoA monitor*, which converts the measurements to the appropriate EEG-index value, namely the PSi value. The PSi value is shown on the *DoA monitor* display.
- The displayed PSi value is captured optically using the *Camera* module. The *Camera* periodically grabs the displayed image and transmits it to the *Data acquisition system*.
- The *Data acquisition system* applies optical character recognition in order to extract the PSi value from the grabbed image.
- The extracted PSi value is periodically fed to the module with the *Control algorithm*.
- In every time step, the *Control algorithm* calculates the control signal, i.e. the most appropriate anesthetic inflow based on the acquired PSi signal.
- The calculated control signal is sent to the *UDP transmitter*, which transmits the controlled signal through the local area network using UDP communication protocol.
- The *UDP receiver* receives the control signal through the local area network. The control signal is finally applied to the *Infusion pump*.

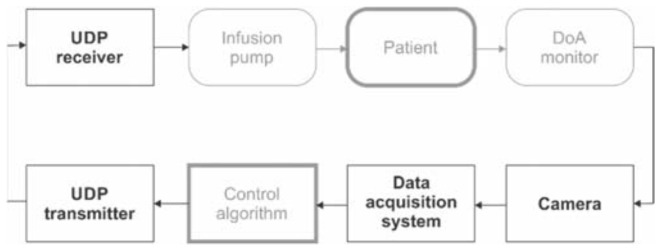

Fig. 1 The basic structure of the closed-loop control system for DoA

The procedure is carried out periodically according to the prespecified sampling time. Note that this contribution deals with the bolded modules, whereas the grayed-out modules are beyond its scope. An important aspect of the proposed structure is that it is medical-device manufacturer independent. Therefore, closed-loop control strategies can be tested using various medical equipment. The functionalities of the *Camera* and *Data acquisition system* modules will be presented in the next section. Following that, the *UDP transmitter* and *UDP receiver* modules will be discussed.

IV. Optical Signal-Acquisition System

A. DoA Monitor

Most patient monitors are purposely unable to connect to a (medically not approved) external device, such as a computer. Therefore, we have proposed a non-invasive system for optical signal acquisition from a patient monitor [14]. The system is image-based and thus does not interfere with the medical devices that are routinely used during a surgical or diagnostic procedure. This enables its use in clinical practice without prior approval, which is otherwise necessary for medical equipment.

B. Signal Value Acquisition

The proposed system for PSi signal acquisition from a patient monitor is based on periodic image acquisition. A camera grabs an image of the patient-monitor display and analyses it so as to extract the relevant information, namely the PSi signal value. The system operates in MATLAB-Simulink environment. It uses a simple USB camera for a periodic online acquisition of the image of the patient monitor's display and determines the PSi value by applying optical character recognition every sample time. In such a way, it is possible to acquire PSi signals online, in real-time (or with a minimal delay). Hence, the acquired data can be used in a closed-loop control algorithm.

C. Software Operation

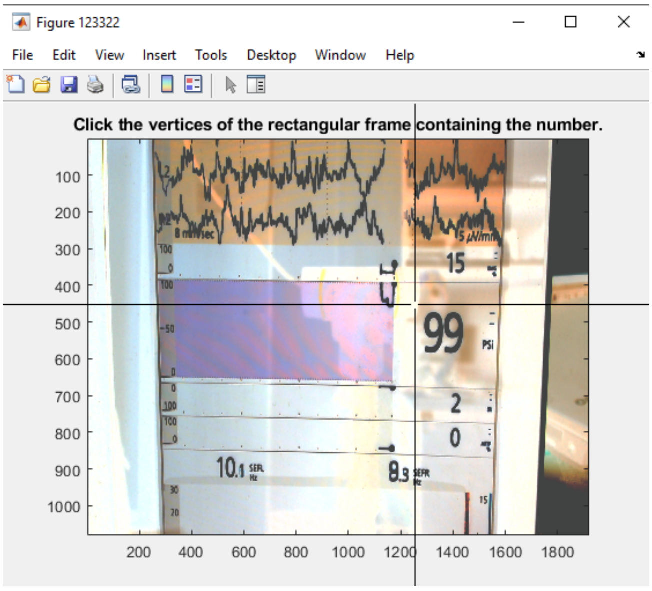

Fig. 2 Frame selection (image in negative colors)

First, the user must initialize the camera. According to the type of the detected USB camera, the initialization procedure first selects the native camera resolution. Next, the most appropriate aperture, shutter speed, and sensor gain for image acquisition depending on the camera model are set. The user has to select the frame containing the relevant signal-value number. As only the approximate position of the vertices of the rectangular frame containing the signal value need to be indicated, this is a very simple task (see Fig. 2).

After having properly initialized the system, it can be used for signal acquisition. The user can start the process by running the Simulink model. Every sampling instant the camera grabs an image and an optical character recognition algorithm [15] is carried out over the predefined-frame-constrained part of the grabbed image. The optical character recognition result is checked against several criteria. If it fails to meet any of the criteria, the system returns the last correctly recognized signal value instead. Besides, an audio beep is played, a red-light warning lights up and a warning message is displayed. The criteria are the following: the reading result is exactly one word, the reading result is a number, the reading result is a real number, the reading result is a value in the range between 0 and 100, and the reading confidence is at least 0.7 (70 %).

In case the optical character recognition result meets all of the aforementioned criteria, the system returns the actual signal value along with the reading confidence in every sample. Otherwise, the confidence value is set to 0 and a warning message is displayed. The procedure is repeated periodically with the time step specified by the user. The Simulink scheme also includes a convenient dashboard with graphical trends, gauges, and digital displays for showing the signals.

D. Testing the Operation

We tested the signal-acquisition system using a patient monitor Masimo Root with SedLine. The goal was to acquire the PSi signal from a simulated patient undergoing a surgical procedure. Therefore, a special demonstration SedLine module was implemented. As the patient monitor Masimo Root with SedLine refreshes its signal every 1.2 s, the sampling time in our case was set to 1 s. In such a manner, we made sure that none of the displayed values is skipped. The PSi signal was faithfully acquired. All the values displayed during the procedure have been accurately recognized and saved by the system. In the case where the camera view was obstructed, e.g., by putting a hand between the camera and the display, the system returned the last correctly recognized signal value, played an audio beep, displayed a red-light warning, and the corresponding warning message. If the signal was to be used in a closed-loop control algorithm, such error handling would be the most appropriate solution.

V. UDP-Based Control-Signal Transmission

A. Connecting the Infusion Pump

In every time step, the control algorithm calculates the control signal, i.e., the anesthetic-agent inflow, based on the current and the previously acquired PSi signal samples. The control signal must be implemented in the infusion pump, which actually sets the propofol inflow that is administered to the patient. Therefore, the infusion pump that is used in clinical practice must be able to receive the control signal and apply the proper anesthetic-agent inflow setting in the real-world operating theatre. Many modern infusion pumps provide both an RJ-45 socket for Ethernet connection to a local area network, as well as a USB port. The control signal can be transmitted from the computer running the control algorithm to the infusion pump either way. However, the use of Ethernet is preferable as it provides galvanic isolation by design. All connections are transformer-coupled, which alleviates safety issues concerning the connected medical equipment, e.g., leakage electric currents.

B. The Communication Protocol

Selecting the most suitable communication protocol that can be implemented in the infusion pump for receiving the control signal from the computer running the control algorithm is not a trivial task.

UDP is often used for fast data acquisition. It is relatively simple to implement and runs quite robustly. However, in our case, there is no need to have extremely short sampling times. Therefore, TCP/IP might also be appropriate as it ensures data delivery despite more overhead. The drawback is that error checking is done on the system level, which is not very transparent. Furthermore, it seems it may cause crashes caused if each connection is not properly closed, which makes it harder to re-establish a connection after a crash. This can usually be solved by restarting the application (and the device), but it is of course not a very elegant or robust solution.

Another possibility would be Modbus TCP, which is a well-proven industrial protocol and is usually quite easy to use. The control value can be written to (or read from) the appropriate register in the pump. Implementing a full TLS protocol (with handshaking, digital certification, etc.) provides the safest alternative that can be used in an open local area network. However, it requires suitable drivers and may thus be too complicated for our needs.

There are no special requirements for the control signal: the control value (propofol inflow) is calculated in MATLAB-Simulink and we need some way of transferring the signal to the pump: this means the software would have to establish a connection to the pump, send a newly calculated control value in every sampling time (and possibly receive a reception confirmation).

Although not strictly necessary, it is sensible to establish a two-way communication so that the pump could send the actual inflow value back to MATLAB-Simulink. This is a useful feature in the case of manually overriding the control signal at the pump to prevent the PK-PD model running in MATLAB-Simulink from losing track.

In our case, a very important aspect is also error handling and alarming, e.g., if the cable gets disconnected. Furthermore, there must always be a way for the anesthesiologist to manually override the calculated control-signal value in case something goes wrong. Therefore, it seems that the most suitable way to transmit real-time propofol inflow setting to the infusion workstation would be by opening a port for a UDP connection. UDP is relatively simple to implement as it does not require a session to be opened before or during data transmission. The endpoints (namely, the infusion workstation and the computer running the control algorithm in MATLAB-Simulink) can thus start sending UDP packets between them without first arranging the connection details. UDP has advantages in real-time operation and is simple to set up.

VI. Simulink Implementation of the Closed-Loop Control Structure

A. Simulink Scheme

The part of the closed-loop control structure (see Fig. 1) that connects to the medical devices used in GA has been implemented in Simulink. The proposed block diagram is shown in Fig. 3.

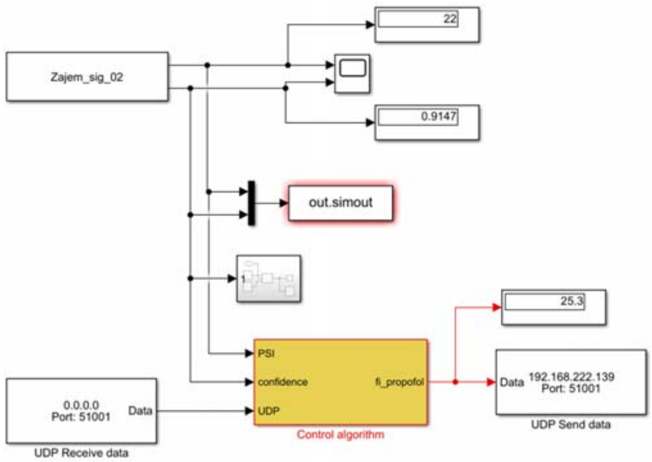

Fig. 3 The proposed Simulink implementation

The main blocks in the Simulink implementation scheme are as follows:

- *Zajem_sig_02* block represents the Data acquisition system module. It is used for providing 2 signals, PSi value, and confidence value.
- *Control algorithm* block contains the algorithm for calculating the control signal, i.e. the propofol inflow *fi_propofol*.
- *UDP Send data* block transmits the control signal to the infusion pump using UDP communication protocol.
- *UDP Receive data* block receives the actual propofol inflow setting from the infusion pump.

In this case, the control signal is transmitted to the infusion pump using UDP communication propofol. The infusion pump IP address is 192.168.222.139, port 51001.

B. Real-World Implementation

The proposed closed-loop control scheme has been tested in a simulated GA setting. The commercially available medical infusion pumps cannot be controlled by an auxiliary signal from an external device, such as a computer, which would set the anesthetic-agent inflow remotely. However, as many modern infusion pumps are able to connect to an Ethernet local area network, it would be relatively easy for a manufacturer to upgrade the infusion-pump software by opening a port for a UDP connection and allowing the anesthetic-agent inflow to be set remotely. This would enable further experimentation with closed-loop control algorithms for DoA, which would relieve the anesthesiologist from having to constantly adjust the inflow. Furthermore, it would benefit patients by providing improved safety, individualized treatment, and thus alleviation of adverse effects during and after surgery.

Despite obvious advantages, closed-loop control systems have yet to become routinely used in daily clinical practice. The reasons for this probably lie behind regulatory issues, questions about safety, and especially the lack of evidence representing an improvement of clinical and patient outcome. As was outlined by the authors in [16], there are numerous steps necessary for the successful development of a DoA control system. From the beginning of the developing process, precise control and software engineering concepts should be followed in order to improve the likelihood of regulatory bodies' approval. Upon acceptance, the system should be preliminary tested for evidence of feasibility, effectiveness, and safety. Only after that large multicentric clinical studies could be conducted, which should not only demonstrate the safety of closed-loop systems but should also undoubtedly present any medical product depends on the assessment of the risk vs. benefit [16], [17].

VII. Conclusions

The paper proposes a step towards solving the problem of closing the DoA control loop by connecting the routinely used medical equipment to the computer running the control algorithm. The technical issues concerning closed-loop control implementation are introduced: the signal from DoA monitor is acquired using the optical signal-acquisition system, and the calculated control signal is transmitted to the infusion pump using UDP-based signal transmission. The system is implemented in MATLAB-Simulink environment. An important aspect of the proposed structure is that it is manufacturer-independent. Therefore, various closed-loop control strategies can be tested, regardless of the medical-equipment implemented in GA.

The proposed closed-loop control scheme has been tested in a simulated GA setting. As many modern infusion pumps are able to connect to an Ethernet local area network, it should be relatively easy for a manufacturer to upgrade the infusion-pump software by opening a port for a UDP connection and allowing the anesthetic-agent inflow to be set remotely. This would enable further experimentation with closed-loop control algorithms for DoA, which would finally relieve the anesthesiologist from having to constantly adjust the inflow. Furthermore, it would benefit patients by providing improved safety, individualized treatment, and thus alleviation of adverse effects during and after surgery.

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References

[1] C. M. Ionescu, M. Neckebroek, M. Ghita, and D. Copot, “An Open Source Patient Simulator for Design and Evaluation of Computer Based Multiple Drug Dosing Control for Anesthetic and Hemodynamic Variables,” *IEEE Access*, pp. 1–1, Jan. 2021, doi: 10.1109/access.2021.3049880.

[2] G. A. Dumont, “Closed-loop control of anesthesia - A review,” in *IFAC Proceedings Volumes (IFAC-PapersOnline)*, Jan. 2012, vol. 45, no. 18, pp. 373–378, doi: 10.3182/20120829-3-HU-2029.00102.

[3] I. Potočnik, V. N. Janković, T. Štupnik, and B. Kremžar, “Haemodynamic changes after induction of anaesthesia with sevoflurane vs. propofol,” *Signa Vitae*, vol. 6, no. 2, pp. 52–57, 2011.

[4] D. Drover and H. R. R. Ortega, “Patient state index,” *Best Practice and Research: Clinical Anaesthesiology*, vol. 20, no. 1. Best Pract Res Clin Anaesthesiol, pp. 121–128, Mar. 2006, doi: 10.1016/j.bpa.2005.07.008.

[5] F. A. Lobo and S. Schraag, “Limitations of anaesthesia depth monitoring,” *Curr. Opin. Anaesthesiol.*, vol. 24, no. 6, pp. 657–664, Dec. 2011, doi: 10.1097/ACO.0b013e32834c7aba.

[6] B. Marsh, M. White, N. Morton, and G. N. Kenny, “Pharmacokinetic model driven infusion of propofol in children,” *Br J Anaesth*, vol. 67, pp. 41–48, 1991.

[7] T. W. Schnider *et al.*, “The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers,” *Anesthesiology*, vol. 88, no. 5, pp. 1170–1182, 1998, doi: 10.1097/00000542-199805000-00006.

[8] T. W. Schnider *et al.*, “The influence of age on propofol pharmacodynamics,” *Anesthesiology*, vol. 90, no. 6, pp. 1502–1516, Jun. 1999, doi: 10.1097/00000542-199906000-00003.

[9] J. Schüttler and H. Ihmsen, “Population pharmacokinetics of propofol: A multicenter study,” *Anesthesiology*, vol. 92, no. 3, pp. 727–738, 2000, doi: 10.1097/00000542-200003000-00017.

[10] G. N. Kenny and M. White, “Intravenous propofol anaesthesia using a computerised infusion system,” *Anaesthesia*, vol. 46, pp. 204–209, 1990.

[11] D. J. Eleveld, P. Colin, A. R. Absalom, and M. M. R. F. Struys, “Pharmacokinetic–pharmacodynamic model for propofol for broad application in anaesthesia and sedation,” *Br. J. Anaesth.*, vol. 120, no. 5, pp. 942–959, May 2018, doi: 10.1016/j.bja.2018.01.018.

[12] S. Goutelle *et al.*, “The Hill equation: A review of its capabilities in pharmacological modelling,” *Fundamental and Clinical Pharmacology*, vol. 22, no. 6. Blackwell Publishing Ltd, pp. 633–648, 2008, doi: 10.1111/j.1472-8206.2008.00633.x.

[13] G. Karer, V. Novak-Jankovič, A. Stecher, and I. Potočnik, “Modelling of BIS-Index Dynamics for Total Intravenous Anesthesia Simulation in Matlab-Simulink,” *IFAC Pap.*, vol. 51, no. 2, pp. 355–360, 2018, doi: 10.1016/j.ifacol.2018.03.061.

[14] G. Karer, “Image-Based PSi Signal Acquisition from a Patient Monitor During a Medical Procedure,” *Int. J. Priv. Heal. Inf. Manag.*, vol. 8, no. 1, pp. 70–87, Jan. 2020, doi: 10.4018/IJPHIM.2020010104:

[15] R. Smith, “An overview of the tesseract OCR engine,” in *Proceedings of the International Conference on Document Analysis and Recognition, ICDAR*, 2007, vol. 2, pp. 629–633, doi: 10.1109/ICDAR.2007.4376991.

[16] P. J. Manberg, C. M. Vozella, and S. D. Kelley, “Regulatory challenges facing closed-loop anesthetic drug infusion devices,” *Clinical Pharmacology and Therapeutics*, vol. 84, no. 1. Clin Pharmacol Ther, pp. 166–169, Jul. 2008, doi: 10.1038/clpt.2008.79.

[17] G. A. Dumont and J. M. Ansermino, “Closed-Loop Control of Anesthesia,” *Anesth. Analg.*, vol. 117, no. 5, pp. 1130–1138, Nov. 2013, doi: 10.1213/ANE.0b013e3182973687.