Closed-loop control of anaesthesia
Michel M.R.F. Struys\textsuperscript{a}, Tom De Smet\textsuperscript{b} and Eric P. Mortier\textsuperscript{a}

Purpose of review
Closed-loop systems are able to make decisions on their own and try to reach and maintain a preset target. As a result, they might help the anaesthesiologist in optimizing the titration of drug administration without overshooting, controlling physiological functions and guiding monitoring variables. Thanks to the development of fast computer technology and more reliable pharmacological effect measures, the study of automation in anaesthesia has regained popularity.

Recent findings
This short review focuses on the most recently developed and tested feed-back systems in anaesthesia. Various new approaches for controlling the administration of intravenous and inhaled hypnotic-anaesthetic drugs have been published recently. For analgesics, a framework for further research has been presented in the literature. For other drugs, such as muscle relaxants and haemodynamics, a short review can be found.

Summary
Until now, most of these systems are still under development. The challenge is now to establish fully the safety, efficacy, reliability and utility of closed-loop anaesthesia for its adoption into the clinical setting. Besides the optimization of controlled variables and control models, these systems have to be tested in extreme circumstances.

Keywords
automation, closed-loop, drug administration techniques, feedback

Introduction
In contrast to the ‘open-loop’ control of drug administration, in which the anaesthesiologist makes a decision to maintain or change a desired target drug dose or concentration or a desired clinical effect (e.g. the depth of the hypnotic or analgesic component of anaesthesia), ‘closed-loop’ controllers are designed to maintain a targeted effect by adapting the administered amount of drugs. In closed-loop control, the anaesthesiologist only enters the desired variable to be maintained. Thanks to the development of fast computers and related technology, automated systems might improve the administration of drug delivery [1].

A number of basic components are required to develop a satisfactory closed-loop drug delivery system: (1) a system under control, which is the patient; (2) a controlled variable that measures the relevant drug effect; (3) a setpoint for this variable, which is the chosen target value specified by the user; (4) an actuator, which, in this case, is the infusion pump/vaporizer driving the administration of the drug; (5) a controller to control the actuator, which consists of an algorithm to translate a measured value of the controlled variable to a particular action for the actuator to steer the controlled variable closer to the target value [1].

Controlling the hypnotic component of anaesthesia
Several closed-loop systems for hypnotics have been proposed in the literature. The effectiveness of such controllers greatly depends on the reliability of the physiological signal to be controlled [2\textsuperscript{**} and on the optimization of the control algorithms. As the ‘depth of hypnosis’ is not measurable, surrogate measures have to be applied as a controlled variable. Using an electroencephalogram, several computerized univariate parameters such as spectral edge frequency and median frequency can be extracted, and have been used as controlled variables for closed-loop systems in the past [3]. However, several investigators have found disadvantages when using these indicators [4,5]. More recently, the bispectral index (BIS; Aspect Medical Systems, Inc., Newton, MA, USA) has been tested and validated as a promising measure of the hypnotic component of anaesthesia [6]. BIS combines several features extracted from the electroencephalogram, including higher order spectra of the signal that can reveal phase coupling of single waveforms. Multivariate statistics were used to combine the different features into a single indicator [2\textsuperscript{**}]. BIS values lie in the range of
0–100. BIS in the 90–100 range represent fully awake patients and ranges of approximately 60–70 and 40–60 indicate light and moderate hypnotic states, respectively. When lower than 40, the BIS indicates an excessive level of hypnosis. Although not ultimately perfect, the BIS offers a sensitivity of 100% and a specificity of approximately 55% to measure the loss of consciousness at values lower than 53 during propofol administration [7**].

Initially, Sakai et al. [8] performed some preliminary tests with a BIS (version 1.22) controlled closed-loop system, and concluded that their system provided intraoperative haemodynamic stability and a prompt recovery from the sedative–hypnotic effects of propofol. As the aim is always to optimize anaesthetic performance by applying closed-loop systems compared with manual (human) control, Morley et al. [9] investigated the performance of a closed-loop system for the administration of general anaesthesia, using BIS (version 3.1) as a target for control in combination with a modified proportional integral derivative (PID) controller for drug administration (see below). Anaesthesia was maintained by the intravenous infusion of a propofol/alfentanil mixture, or an isoflurane/nitrous oxide-based technique was used. The intravenous drugs were given via an infusion pump, the inhaled anaesthetics were injected in the inspiratory limb of the breathing circle. For each technique, patients were randomly allocated to receive either closed-loop or manually controlled administration of the relevant agents. Closed-loop and manually controlled administration of anaesthesia resulted in similar intraoperative conditions and initial recovery characteristics. Convenience aside, the closed-loop system showed no clinical advantage over conventional, manually adjusted techniques of anaesthetic administration. The main problem with the study might be the use of a PID control algorithm (see below).

Absalom et al. [10**] developed a similar closed-loop anaesthesia system using BIS as the control variable, a PID control algorithm, and a propofol target-controlled infusion system as the control actuator. Closed-loop performance was assessed in 10 adult patients undergoing major orthopaedic surgery under combined general and epidural anaesthesia. Induction was performed manually using a plasma compartment controlled infusion system. After the start of surgery, when anaesthesia was clinically adequate, the automatic control of anaesthesia was commenced using the BIS as the control variable. Thanks to the optimization of the PID controller with a pharmacokinetic-based infusion system, the system was able to provide clinically adequate anaesthesia in nine out of 10 patients. The authors concluded that further studies are required to determine whether control performance can be improved by changing the gain factors or by using an effective site-targeted, target-controlled infusion propofol system.

Various control strategies exist to guide closed-loop drug administration [11]. As illustrated above, PID controllers are used in several automated control systems, and require some explicit understanding of the input–output relationship in terms of some mathematical solution. PID controllers are essentially ‘ignorant’, that is, without knowledge of the drug metabolism and the realized (potentially dangerous) concentration values. Without fine tuning for the specific situation, these general controllers can be slow to establish control, and can be dangerous to use because of possible oscillations. The fine tuning of a PID controller is difficult in this particular setting because the human body is very complex. This may lead to several clinical difficulties because of the complex pharmacological behaviour of the products used, interindividual pharmacological variability and the patient’s reactions to external surgical stimuli. The model-based controller may be a better alternative. Here, the administration of drugs in response to the clinical effect (surgical manipulations) is based on the knowledge of the fate of the drug and its effect in the human body, concentrated in a mathematical model. Several different parametric and non-parametric pharmacokinetic-dynamic models have been described in the literature as basic predetermined models for anaesthesia applications. During control, the model might be updated to meet the patient’s individual pharmacological behaviour. Then, the controller is called ‘model-based and adaptive’.

Knowledge-based systems, like for instance fuzzy control, have the ability to control a process without the determination of an explicit mathematical model of the input–output relationship. It is therefore a suitable system when little is known about the patient [11]. To the best of our knowledge, fuzzy logic systems were never used for the automated administration of hypnotic agents in humans.

The model-based adaptive control of propofol administration with BIS was previously used in a closed-loop system for sedation during spinal anaesthesia by Mortier et al. [12] and, more recently, during general anaesthesia by Struys et al. [13**].

The last two reports (from the same research group) described a new closed-loop control system for propofol that uses the BIS as the controlled variable in a patient-individualized, adaptive, model-based control system. This means that a specific pharmacodynamic profile of the individual patient is explored during induction. Thereafter, this pharmacodynamic model is adapted during control. The pharmacokinetic-dynamic model applied in this system used an effect compartment
controlled infusion of propofol previously validated by the same authors [14]. An artefact-tolerant controller was also built in this system. When BIS data are corrupted, open-loop effect compartment control is automatically switched on. When BIS is back on line, the loop is closed again. In the most recent report, the authors compared their system with the manually controlled administration of propofol (in combination with the same fixed dose of remifentanil in both groups) using haemodynamic and somatic changes to guide anaesthesia. The performance of control during the induction and maintenance of anaesthesia were compared between both groups, using BIS as the controlled variable in the closed-loop controlled group (group I) and the reference variable in the manually controlled group (group II), and conversely, the systolic blood pressure as the controlled variable in group II and the reference variable in group I. At the end of anaesthesia, recovery profiles between the groups were compared. Although patients undergoing manual induction of anaesthesia in group II at 300 ml/h reached a BIS level of 50 faster than patients undergoing open-loop, computer-controlled induction in group I, manual induction caused a more pronounced initial overshoot of the BIS target. This resulted in a more pronounced decrease in blood pressure in group II. During the maintenance phase, a better control of BIS and systolic blood pressure was found in group I compared with group II. Recovery was faster in group I. The authors were able to conclude that this closed-loop system for propofol administration using the BIS as a controlled variable together with a model-based controller is clinically acceptable during general anaesthesia.

Gentilini et al. [2**] developed a model and closed-loop system of hypnosis by means of BIS with isoflurane. The automated administration of inhaled anaesthetics yielded to a more complex situation than intravenous drug administration, as the control of the complete respiratory function has to be included in the system. These investigators [2**] created a model for control consisting of three parts: a model for the respiratory system, a pharmacokinetic, and a pharmacodynamic model. A cascaded internal model controller is employed. This controller consists of a master controller that compares the actual BIS and the reference value set by the user, and provides expired isoflurane concentration references to the slave controller. The slave controller manoeuvres the fresh gas anaesthetic concentration entering the respiratory system. Additional control functions (such as artefact-tolerant control) are implemented to optimize safety. The system was tested preliminary during some clinical cases and performed accurately.

As well as BIS, other electroencephalogram-derived indicators are currently being developed, such as approximate entropy [15] and Shannon entropy [16]. Until now, no closed-loop systems have been created using these indicators as the controlled variable. Previously, Kenny et al. [17] used a derived indicator from the mid-latency auditory evoked potential (MLAEP), called AEPindex, as the controlled variable. Unfortunately, this system is only available from the authors. So far, only one other MLAEP-derived indicator is commercially available, namely the Alaris AEP monitor (Alaris Medical Systems, Basingstoke, UK). They used a new method for extracting the MLAEP from the electroencephalogram signal by employing an autoregressive model with an exogenous input (ARX-model) adaptive method. This method allows extraction of the auditory evoked potential signal within 15–25 sweeps of 110 ms duration, resulting in only a 6-s response delay time. A new variable, called the AAI (A-line ARX-index), is then calculated from this fast extracted MLAEP wave [7**]. However, no closed-loop application with this monitor has been tested until now.

Controlling the analgesic component of anaesthesia

The application of closed-loop control for analgesics (mostly opiates) encounters the problem of a lack of an optimal measurement method. Clinical scoring systems and observations such as the visual analogue scale are available for the measurement of pain; however, when the patient loses consciousness, pain becomes only nociception. So far, limited expertise exists on the direct measures for nociception. Some years ago, Larson et al. [18] used pupillometry to measure reflex pupillary dilation in response to noxious stimulus. They concluded that alfentanil blocks this dilation.

Although it is known that most of the hypnotic drugs will also alter the haemodynamic status of the patient, anaesthesiologists mostly use these autonomic and somatic changes to guide their administration of peroperative opiates. As a result, a single input–single output controller for opiate control based on haemodynamic changes is not clinically feasible. More complex systems are required. Gentilini et al. [19] designed a model predictive controller for the control of mean arterial blood pressure (MAP) during anaesthesia. Alfentanil was selected as the opiate drug. Three innovative features in their algorithms are worth mentioning. First, opiate concentrations predicted by a pharmacokinetic model were used together with MAP by the controller algorithm to determine the future opiate infusion drug. This feature is particularly important when the MAP signal is either corrupted by artefacts or is unreliable for the assessment of the analgesic state of the patient. Second, the system is able to cope with user-specified constraints on both input (drug infusion rate) and output (MAP and opiate plasma concentration) variables. For instance, the controller will
not administer opiates if this results in overshooting user-defined predicted plasma drug concentrations. Third, the controller determines opiate infusion rates at each step using an optimization algorithm that aims at reaching target levels for both output variables, minimizing the drug consumption and maintaining the output and input variables within constraints. Their system was used in 13 volunteers and will be validated more in detail.

**Controlling other drug administration by means of closed-loop systems**

Many closed-loop control systems for muscle relaxants have been reported in the past [20], but only a few could cope with the introduction of the latest shorter acting neuromuscular-blocking drugs. Geldner et al. [21] published the most recent report on a control system using mivacurium. A closed-loop system using a neural network as a predictor could be established. The system proved to be reliable for a closed-loop infusion of mivacurium in order to maintain a predefined degree of neuromuscular blockade of 95% during routine surgery.

Hoecksel et al. [22] investigated the effects of the computer control of blood pressure with sodium nitroprusside and nitroglycerin on haemodynamic stability when compared with conventional manual control. They concluded that, compared with manual control, the computer control of systemic hypertension significantly improved haemodynamic stability during cardiac surgery.

**Multiple input–multiple output systems**

In a recent editorial, Glass [23] stated that the interaction of hypnotics and opioids for achieving two major endpoints in general anaesthesia (the loss of consciousness and the inhibition of movement at skin incision) are based on the evidence that the loss of consciousness and response to skin incision are not a single continuum of increasing ‘anaesthetic depth’ but rather are two separate phenomena, nevertheless interfering with one another. Using response surface methodology [24], Gentilini et al. [25**] proposed a framework for multiple input–multiple output control systems. Although the interaction models have been applied during pharmacological investigations, several other trials are required before these automatic interaction controllers can be applied in closed-loop systems. Also, one has to realise that the side effect of the hypnotic drug (for example, hypotension) might be the measured effect of the analgesic.

**Discussion**

The study of the performance of anaesthesiologists and models of the cognitive task demands during anaesthesia shows that increasing the complexity and shortening the response time of anaesthesia delivery and monitoring systems may create new demands for clinicians’ attention and cognitive resources [26]. Also, new long-lasting surgical procedures (micro-surgery, etc.) might decrease the vigilance level of the anaesthesiologist during the maintenance phase of anaesthesia [27]. As the overall complexity of the anaesthetic systems might be too extended for the human user, the application of automated feedback systems, also called ‘closed-loop systems’, might allow better control. Automated systems are able to make decisions on their own, and try to reach and maintain a preset target. As a result, they might help the anaesthesiologist in optimizing the titration of drug administration without overshooting, controlling physiological functions and guiding monitoring variables. Moreover, they may take advantage of drug synergies, for which a proper modelling framework has now been developed [24]. Furthermore, if tuned properly, closed-loop systems should be able to compensate interindividual variability and tailor the drug administration profile to the particular stimulation intensity of each surgical procedure. Also, closed-loop systems can be used for research as a ‘reference’ anaesthesiologist during clinical studies [28].

A disadvantage of all the systems that have actually been developed is their limited scope of action and their extent of authority. The human operator is expected to accommodate these limitations by employing the automation only when appropriate and by regaining control when the limits of automation are reached. Intelligent alarms might help in these circumstances [29].

The ultimate goal of closed-loop controllers is their general acceptance in clinical practice. So far, all the closed-loop systems developed have been used in well controlled scientific trial environments. In a recent editorial, Glass and Rampil [30**] questioned the essential requirements of closed-loop technology. They stated that closed-loop delivery systems are no longer esoteric. Rather, the challenge is now to establish fully the safety, efficacy, reliability and utility of closed-loop anaesthesia for its adoption into the clinical setting. Besides the optimization of controlled variables and control models, these systems have to be tested in extreme circumstances. Glass and Rampil [30**] formulated some questions regarding this: will the control system work well if large adjustments have to be made, and will it be fast enough without causing under or overshoot in control, thereby creating dangerous side effects? These are questions that need to be answered in future research.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


11. The authors described and tested a new PID controller for the BIS-guided closed-loop administration of propofol during major orthopaedic surgery under combined general and regional anesthesia.


In this editorial, some critical requirements are proposed to test the safety and acceptability of closed-loop systems for clinical practice.