Closed-loop Control of Mean Arterial Blood Pressure during Surgery with Alfentanil

Clinical Evaluation of a Novel Model-based Predictive Controller

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Background: In contrast to hypnosis, there is no surrogate parameter for analgesia in anesthetized patients. Opioids are titrated to suppress blood pressure response to noxious stimulation. The authors evaluated a novel model predictive controller for closed-loop administration of alfentanil using mean arterial blood pressure and predicted plasma alfentanil concentration (Cp Alf) as input parameters.

Methods: The authors studied 13 healthy patients scheduled to undergo minor lumbar and cervical spine surgery. After induction with propofol, alfentanil, and midazolam and tracheal intubation, isoflurane was titrated to maintain the Bispectral Index at 55 (± 5), and the alfentanil administration was switched from manual to closed-loop control. The controller adjusted the alfentanil infusion rate to maintain the mean arterial blood pressure near the set-point (70 mmHg) while minimizing the Cp Alf toward the set-point plasma alfentanil concentration (Cp Alfref) (100 ng/ml).

Results: Two patients were excluded because of loss of arterial pressure signal and protocol violation. The alfentanil infusion was closed-loop-controlled for a mean (SD) of 98.9 (1.5)% of presurgery time and 95.5 (4.3)% of surgery time. The mean (SD) end-tidal isoflurane concentrations were 0.78 (0.1) and 0.86 (0.1) vol%, the Cp Alf values were 122 (35) and 181 (58) ng/ml, and the Bispectral Index values were 51 (9) and 52 (4) before surgery and during surgery, respectively. The mean (SD) absolute deviations of mean arterial blood pressure were 7.6 (2.6) and 10.0 (4.2) mmHg (P = 0.262), and the median performance error, median absolute performance error, and wobble were 4.2 (6.2) and 8.8 (9.4)% (P = 0.002), 7.9 (3.8) and 11.8 (6.3)% (P = 0.129), and 14.5 (8.4) and 5.7 (1.2)% (P = 0.002) before surgery and during surgery, respectively. A post-hoc simulation showed that the Cp Alfref decreased the predicted Cp Alf compared with mean arterial blood pressure alone.

Conclusion: The authors’ controller has a similar set-point precision as previous hypnotic controllers and provides adequate alfentanil dosing during surgery. It may help to standardize opioid dosing in research and may be a further step toward a multiple input–multiple output controller.

Although closed-loop control systems in anesthesia have been investigated for more than 40 yr, they are not currently used in clinical practice. Most recent studies have shown that control of hypnosis as represented by the Bispectral Index (BIS) is better achieved with closed-loop systems than with manual control.1–3 Given that adequate anesthesia requires not only adequate hypnosis but also adequate analgesia, closed-loop control of only the hypnotic may provide adequate anesthesia only if accompanied by sufficient analgesic drug concentration. This is illustrated by these previous studies where an adequate dose of opioids or even spinal anesthesia was given. Locher et al. 1 gave alfentanil at an effect site concentration around 180 ng/ml. Struys et al. 3 administered remifentanil at an infusion rate of 0.25 µg · kg⁻¹ · min⁻¹ during surgery, which would result in effect site concentrations of 6–7 ng/ml (simulation according to the parameters by Minto et al. for a 40-yr-old, 70-kg man). This remifentanil concentration corresponds to the optimal value revealed in the propofol–remifentanil interaction study by Mertens et al. 4 Only one closed-loop controller for alfentanil has been published using electroencephalographic median frequency as an input variable.5

Although parameters derived from electroencephalography such as BIS, spectral entropy,6 or auditory evoked potential index7 are frequently used parameters for hypnotic depth, there is still no parameter specifically measuring the analgesic drug effect in anesthetized patients. The arterial blood pressure response to noxious stimulation can be suppressed by opioids (in combination with a hypnotic or an anesthetic), and hemodynamic responsiveness may thus be considered as a surrogate for pain in anesthetized patients.8,9 Conversely, opioids have little effect on arterial blood pressure in the absence of noxious stimulation.10 Arterial blood pressure during anesthesia is therefore used to titrate analgesic drugs during general anesthesia in daily practice.

In this study, we evaluated a previously described model predictive controller11 for control of mean arterial blood pressure (MAP) as the primary and predicted plasma alfentanil concentration (Cp Alf) as a secondary input variable for optimal dosing of an alfentanil infusion rate (output variable) under the condition of a hypnotic state defined according to BIS. Inhalation anesthetics such as isoflurane induce a dose-dependent decrease of arterial blood pressure, whereas opioids at lower to moderate concentrations do not cause substantial or relevant blood pressure decrease unless the patient is dependent on sympathetic stimulation (e.g., due to hy-
Opioids are known to suppress the hemodynamic stress response to noxious stimulation. A ceiling effect of opioids in decreasing the minimal alveolar concentration to suppress hemodynamic response to noxious stimulation (MAC BAR) of inhalation anesthetics has been reported, and even very high opioid concentrations cannot guarantee complete control of hemodynamic response to noxious stimulation but may induce acute opioid tolerance. With the predicted alfentanil plasma concentration as a second input variable and the reference plasma concentration in the lower range, we expected that excessively high opioid concentrations during surgery could be avoided, and that a minimal opioid concentration in periods without noxious stimulation could be maintained. The controller would thus act similarly to many anesthesiologists in clinical practice. The aim of this uncontrolled open-label study was to demonstrate the clinical applicability of this concept.

Materials and Methods

Patients
After approval by the ethics committee of the Canton of Bern (Bern, Switzerland) and obtaining written informed consent, 13 patients with American Society of Anesthesiologists physical status I or II who were scheduled to undergo neurosurgery during general anesthesia were enrolled. Patients younger than 18 yr or older than 65 yr and patients with a history of cerebrovascular insufficiency, coronary artery disease (angina or previous infarction, previous coronary artery bypass graft operation or percutaneous coronary intervention), or untreated arterial hypertension were excluded.

Study Plan

Anesthesia Protocol. At the time of arrival in the operating room 30 min after premedication with 7.5 mg oral midazolam, the patients were monitored with an electrocardiogram, a noninvasive blood pressure cuff, a pulse oximeter (Dräger PM 8060 from a Cicero Anesthesia workstation; Dräger GmbH, Lübeck, Germany), and an Aspect A-2000 monitor (BIS version 3.3; Aspect Medical Systems, Inc., Newton, MA). An infusion of Ringer’s lactate at 2 ml · kg⁻¹ · h⁻¹ was started through a venous catheter at the nondominant forearm. A 20-gauge arterial catheter was placed in the radial artery of the nondominant forearm during local anesthesia after the patency of the ulnar artery had been evaluated with the Allen test. Skin electrodes were placed on the ulnar nerve of the opposite arm and connected to a train-of-four watch (Organon Teknika BV, RM Boxtel, The Netherlands) for later monitoring of neuromuscular blockade. Anesthesia was induced with 2 mg/kg propofol (Disoprivan®; Astrazeneca, Zug, Switzerland). Alfentanil (Rapifen®; Janssen-Cilag, Baar, Switzerland) was administered with a

![Diagram of Closed-Loop Controlled Alfentanil Administration](image)

**Fig. 1.** The model predictive controller with mean arterial pressure (MAP) as the primary and predicted plasma alfentanil concentration (Pred Cp) as a secondary input variable is depicted. PK = pharmacokinetic.

Harvard 22 infusion pump (Harvard Apparatus, South Natick, MA) driven by the controller software. Sixty seconds before tracheal intubation, an alfentanil bolus of 30 μg/kg was given with the controller in the manual mode (see controller description in the next paragraph). Tracheal intubation was facilitated with 0.3 mg/kg mivacurium (Mivacron®; Organon, Pfaeffikon, Switzerland). After intubation, sufficient hypnosis was maintained with isoflurane. The end-tidal concentration was manually adjusted by increasing or decreasing the end-tidal concentration in steps of 0.1–0.2 vol% in case the BIS value exceeded the target range of 50 and 60 for longer than 3 min. After intubation, the alfentanil controller was switched from the manual mode to the closed-loop mode. An infusion of mivacurium (0.3–0.5 mg · kg⁻¹ · h⁻¹) was started to maintain neuromuscular blockade (train-of-four count 0–2 of four twitches). Patients were ventilated with oxygen in air and a fresh gas flow of 3 l/min to end-tidal carbon dioxide concentration of 35 mmHg. To determine the performance of the selected pharmacokinetic parameters for alfentanil (table 1), arterial blood samples were drawn during stable phases of the study periods (one sample in period 1, one or two samples in period 2). The samples were processed as further detailed in the appendix.

Controller. A model predictive controller was implemented in an X-Oberon real-time system (Institute of Robotics, Swiss Federal Institute of Technology, Zurich, Switzerland) (fig. 1). In previous studies, only one input variable was used to control one output variable (single
input–single output). Conversely, this control system had two input variables and was targeted to keep the MAP (primary input variable) as close as possible to the set-point MAP (MAPref) while minimizing the predicted Cp Alf (secondary input variable). A detailed description of the controller algorithm and the algorithms for artifact detection was published elsewhere. Briefly, in subjects under noxious stimulation, a linear relation between MAP and effect site alfentanil concentration was assumed (equation 1) according to data from the literature and from a pilot study:

$$\Delta \text{MAP} = -k \times C_{eAlf}$$  

where $\Delta \text{MAP}$ = decrease in MAP (mmHg) induced by alfentanil, $k = 0.088$ (mmHg·ml·ng$^{-1}$), and $C_{eAlf}$ = effect site alfentanil concentration (ng/ml). The $k_{e0}$ relating the plasma and the effect site concentration was originally derived from electroencephalography data of alfentanil. Because a specific $k_{e0}$ for the hemodynamic effects was not available, we assumed that for our purpose the electroencephalography-based $k_{e0}$ would be adequate. Primarily, the controller estimated the effect site alfentanil concentration necessary to decrease the MAP to the MAPref according to equation 1 and computed the respective alfentanil infusion rate. If MAP was equal to the MAPref, the infusion would stop, and the alfentanil concentration would decrease. The second input variable (Cp Alf) with a set-point value of around 100 ng/ml was introduced to maintain a certain minimal Cp Alf if MAP was equal to or below the MAPref but above the lower constraint value of 60 mmHg and to avoid unnecessary high opioid concentrations. As a third element, constraints for MAP were defined (60 and 120 mmHg). A MAP exceeding the upper constraint induced a higher alfentanil infusion rate compared with the value derived from equation 1. In case the MAP was below 60 mmHg, the infusion temporarily stopped to allow the Cp Alf to decrease. The constraints for Cp Alf were 0 and 400 ng/ml, thus defining a maximal concentration while allowing a total elimination of alfentanil in case the lower MAP constraint was violated.

The controller was tuned to react with moderate changes of Cp Alf during stable periods where MAP lies within the physiologic range of 60–100 mmHg while minimizing the alfentanil consumption. The tuning was achieved by defining weighting parameters for the different input and output variables in the control function. The weighting parameters were selected such as to make the controller more sensible to deviation of MAP than of Cp Alf. Further, the controller was tuned to react more aggressively if the constraints were hit.

The set-point MAP (MAPref) was initially set at 70 mmHg, the set-point Cp Alf at 100 ng/ml in every patient. During surgery, the MAPref and the set-point plasma alfentanil concentration (Cp Alfref) could be changed at the discretion of the anesthesiologist to adapt to the individual requirements of the patient. The continuously measured MAP was compared with MAPref every 5 s, and the controller computed an alfentanil infusion rate to keep the MAP as close as possible to the MAPref. From the history of the recorded alfentanil infusion rates, the controller computed the Cp Alf using a three-compartment body surface area–adjusted pharmacokinetic model used by Shafer et al. in the STANPUMP program modified by Gentilini et al. (table 1). The Cp Alfref implied that a minimal Cp Alp was maintained even when the MAP was below the lower constraint of MAP (60 mmHg). In case of hypotension (MAP < 60 mmHg, longer than 30 s) in the absence of hypovolemia, 5 mg ephedrine was given intravenously.

Three operating modes of the system were defined. In the passive mode, the target parameters were set while the drug administration was stopped. In the manual mode, alfentanil administration was allowed at fixed infusion rates set by the anesthesiologist while the computer ran the pump and recorded the infusion rate (open-loop system). In the control mode, the alfentanil infusion rate was adjusted by closed-loop control. The start and end of the manual and control mode periods were recorded in every patient. During anesthesia, the controller could be switched from manual to control mode by pressing one button on the touch screen, without interrupting data acquisition.

The artifact detection algorithms implemented in the controller have been described in detail previously. Briefly, a model-based and a signal-based approach were applied in parallel. With the system in the manual mode and the control mode, a real-time prediction of the MAP was computed according to equation 1. In case an artifact was detected in the arterial blood pressure signal, the MAP value sent to the controller was switched from the actual measured to the predicted MAP (with the prediction based on the previous five measured MAP values), and an alert was displayed on the screen. In case the artifact persisted for longer than 60 s, the infusion rate was set to zero and another alert on the screen prompted the anesthesiologist to switch from control to manual mode. Because it was a pilot system, the same anesthesiologist (C.B.) performed the anesthesia in all of the patients.

**Data Recording and Statistics.** Heart rate, arterial blood pressure, oxygen, carbon dioxide and isoflurane concentrations, oxygen saturation (pulse oximetry), BIS, the controller operating mode (passive, manual, closed loop), MAPref, Cp Alfref, alfentanil infusion rate, predicted plasma and effect site alfentanil concentrations, and the validity of the arterial blood pressure signal with artifact flag were recorded every 5 s on a computer hard disk. The data from intubation to 5 min before skin incision (period 1) and the data from 5 min before skin incision to skin closure (period 2) were analyzed sepa-
rately. Signs of inadequate anesthesia were defined according to Ausems et al. The number of episodes with inadequate anesthesia (longer than 60 s) was computed for both study periods from the automatic hemodynamic data records and the manual records of clinical data (sweating, flushing, etc.). In addition, the area under the curve of mean arterial blood pressure and heart rate beyond \( \pm 20\% \) of baseline was computed for the first and second study periods and for each subject. For comparison between subjects, the area under the curve values were normalized to the duration of time period, i.e., divided by the duration of the related study period.

The performance of the controller was evaluated with similar parameters as were used for evaluation of computer-controlled infusions and which have been used for evaluation of other closed-loop controllers. The performance parameters were calculated for MAP and \( C_p \) similarly by replacing measured MAP by predicted \( C_p \) ref in the following formulas.

The mean absolute difference (MAD) between measured MAP and \( MAP_{\text{ref}} \) was calculated according to equation 2 for each subject:

\[
\text{MAD}_i = \frac{1}{N_i} \sum_{j=1}^{N_i} |MAP_{\text{meas}}(i,j) - MAP_{\text{ref}}(i,j)|
\]  
(2)

where \( N_i \) = total number of measurements in subject \( i \).

The weighted performance error (PE) for the \( i \)th patient and the \( j \)th time window was calculated according to equation 3:

\[
\text{PE}_{ij} = \frac{MAP_{\text{meas}} - MAP_{\text{ref}}}{MAP_{\text{ref}}} \times 100
\]  
(3)

The median prediction error (MDPE), reflecting the bias, the median absolute prediction error (MDAPE), reflecting the inaccuracy, and the wobble, reflecting the variability, were then calculated according to equations 4–6:

\[
\text{MDPE}_i = \text{median}\{|\text{PE}_{ij}, j = 1, ..., N_i|\}
\]  
(4)

\[
\text{MDAPE}_i = \text{median}\{|\text{PE}_{ij}|, j = 1, ..., N_i|\}
\]  
(5)

\[
\text{Wobble}_i = \text{median absolute deviation of } \{\text{PE}_{ij}, j = 1, ..., N_i\} \text{ from } \text{MDPE}_i
\]  
(6)

where \( \text{PE}_{ij} \) represents the \( j \)th observation in the \( i \)th subject, \( N_i \) represents the total number of observations in the \( i \)th subject, and \( t_i \) represents the \( j \)th time window in the \( i \)th subject. MDPE, MDAPE, and wobble are given as percentages.

To evaluate the effect of the second input variable (reference alfentanil concentration), post hoc simulations were performed using the controller software fed with the recorded MAP values from the study, the recorded reference MAP and \( C_p \), and the height and weight from each patient. The alfentanil infusion rate, the predicted plasma and effect site alfentanil concentrations, and the alfentanil total dose were computed with the \( C_p \) ref considered (double input–single output [DISO] mode) and ignored (single input–single output [SISO] mode). The parameters from the two simulations were compared with a paired \( t \) test, with a significance level of 0.05.

### Results

#### Patients

Thirteen patients were enrolled in the study; 2 patients were excluded from data analysis because of loss of arterial blood pressure signal and because of protocol violation at induction. The characteristics of the 11 patients (5 women and 6 men) included in the analysis are summarized in table 2.

#### Table 3. Description of Anesthesia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Presurgery</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of study period, min</td>
<td>51 (20)</td>
<td>86 (25)</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>72 (4)</td>
<td>82 (7)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>63 (25)</td>
<td>71 (11)</td>
</tr>
<tr>
<td>Carbon dioxide (end tidal), mmHg</td>
<td>32.8 (2.0)</td>
<td>33.9 (1.5)</td>
</tr>
<tr>
<td>Bispectral Index</td>
<td>51 (4)</td>
<td>52 (4)</td>
</tr>
<tr>
<td>Isoflurane (end tidal), vol%</td>
<td>0.78 (0.1)</td>
<td>0.86 (0.1)</td>
</tr>
<tr>
<td>Alfentanil dose until intubation (manual), ( \mu g/kg )</td>
<td>28 (9)</td>
<td></td>
</tr>
<tr>
<td>Alfentanil dose until intubation (closed loop), ( \mu g/kg )</td>
<td>56 (11)</td>
<td></td>
</tr>
<tr>
<td>Alfentanil dose until closure (closed loop), ( \mu g/kg )</td>
<td>125 (33)</td>
<td></td>
</tr>
<tr>
<td>Plasma alfentanil, ng/ml</td>
<td>122 (35)</td>
<td>181 (58)</td>
</tr>
<tr>
<td>Effect site alfentanil, ng/ml</td>
<td>128 (34)</td>
<td>179 (57)</td>
</tr>
</tbody>
</table>

Data are mean (SD).
Anesthesia

The characteristics of anesthesia between intubation and skin incision (period 1) and during surgery (period 2) in the 11 patients are summarized in table 3. Short episodes of inadequate anesthesia according to the criteria by Ausems et al.\textsuperscript{17} (systolic arterial blood pressure 15 mmHg greater than individual normal in 2 or tachycardia greater than 90/min\textsuperscript{2} longer than 1 min) in period 1 (before surgery) were recorded in 6 patients (one episode in 1 subject due to hypertension; a median [range] of 3 [1–3] episodes due to tachycardia in 5 additional subjects). The median duration (range) of these episodes was 115 (65–195) s. In period 2 (surgery), such episodes were recorded in 6 patients, with a median (range) of 1 (1–4) episodes per subject due to hypertension and 4 (1–5) due to tachycardia. The median (range) duration of these episodes was 110 (80–160) s. No flushing, sweating, or movement was observed.

The mean (SD) normalized areas under the curve of MAP beyond 20% of baseline were 2.8 (2.2) and 5.1 (3.9) mmHg between induction and incision and between incision and skin closure, respectively. The mean (SD) normalized areas under the curve of heart rate beyond ±20% of baseline in the two study periods were 5.8 (8.3) and 4.3 (9.3) beats/min, respectively.

The median performance error of the predicted Cp Alf compared with the measured value was −30.2%, signaling a bias toward underdosing (fig. 2). The median absolute performance error was 30.2%. These numbers are in the range of previous data.\textsuperscript{16,20}

The isoflurane concentrations and the BIS values of every subject are presented in figures 3A and B. Only minimal changes of the isoflurane concentrations were necessary to keep the BIS within the target range, even upon skin incision. In the presurgery period, there were some accidental sharp and short-lasting isoflurane increases (spikes in fig. 3A) because of moving of the patient and rapid BIS increase during positioning (prone position).

Ephedrine (5 mg) was given in 9 of 11 subjects during period 1 (presurgery) and in 4 of 11 subjects during period 2 (surgery). In the subjects given ephedrine, the median (range) numbers of doses in periods 1 and 2 were 2 (1–4) and 1 (1–2), respectively.

Performance of the Controller

The data on the controller performance in the two study periods are summarized in tables 4 and 5. Between intubation and incision and between incision and closure, the controller was in the control mode 98.9 (1.5) and 95.5 (4.3)% of the time. The reason to change from control to manual mode was an unreliable MAP due to artifacts. In one patient, an additional bolus of alfentanil was given in the manual mode because of a massive blood pressure response to skin incision. The predicted Cp Alf of every subject is presented in figure 4A, and the MAP values are presented in figure 4B.

The reference MAP, which was first set at 70 mmHg in every patient, was changed between 70 and 90 mmHg...

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**Fig. 2.** The performance error (PE, %) of the predicted compared with the measured plasma alfentanil concentrations is depicted related to the time after the start of the alfentanil infusion. The horizontal line represents the median performance error in the study population.

**Fig. 3.** The end-tidal isoflurane concentration (vol%; A) and the Bispectral Index (B) of every subject are depicted. The Bispectral Index values are averaged for the graphical representation with a moving average filter of 1-min length. The dashed vertical line at time zero indicates skin incision.
by the attending anesthesiologist in 8 of 11 patients (fig. 4C). In these subjects, the median (range) number of changes was 3 (1–5). In the remaining 3 subjects, the Cp Alf ref was changed instead (fig. 4D), with a median (range) number of changes of 1 (1–2).

The alfentanil infusion rate and the predicted Cp Alf in a typical subject are presented in figure 5 to illustrate the controller performance.

Post Hoc Simulation

The offline simulation results are summarized in table 6 and figure 6. The predicted Cp Alf values from the DISO simulation were similar to those recorded from the clinical study (fig. 4A). With the SISO simulation, ignoring Cp Alf ref, the cumulative alfentanil dose and the mean (SD) Cp Alf were substantially higher than with the DISO simulation.

Discussion

Mean arterial blood pressure has only rarely been used as an input variable for closed-loop control of anesthesia and analgesia. \textsuperscript{21,22} Our controller mimicked the dosing rules applied by many anesthesiologists in clinical practice and clinical studies\textsuperscript{17,23}; increasing the opioid concentration by administering an intravenous bolus or increasing the infusion rate if the patient shows a hemodynamic response to surgical stimulation, and decreasing the opioid concentration in case the patient does not respond and to avoid excessive opioid concentrations.

The set-point precision of MAP was significantly different in the two study periods (MDPE, table 4) reflecting hypotension observed in the unstimulated patients, most of them needing ephedrine treatment, even though the predicted alfentanil concentration was only 122 (35) ng/ml. The set-point precision of Cp Alf during the preoperative period (MDPE, table 5) was in the same range as the set-point precision of MAP. During surgery, however, it was significantly worse. This reflects the controller tuning where the priority was set to control MAP. Our simulation illustrates the effect of the Cp Alf ref in reducing the alfentanil dose, especially during surgery (fig. 6).

Although this controller may be considered a DISO, it was designed to control only one of the three components of general anesthesia. An ideal anesthesia control system would integrate closed-loop control of hypnosis, analgesia, and neuromuscular blockade (multiple input–multiple output [MIMO]), but this has never been attempted for multiple reasons: the lack of a specific parameter to measure analgesia, the number of confounding factors influencing MAP together with noxious stimulation, and the effect of opioid–hypnotic–anesthetic drug interactions on blood pressure and electroencephalography, which could provoke controller instability and put the patient at risk of severe hypotension or inadequate anesthesia. In this study, the hypnotic component of anesthesia was represented by the BIS, and the end-tidal isoflurane concentration was kept rather constant (table 2 and fig. 3). The mean (SD) BIS values and the mean (SD) isoflurane concentrations were similar to values published by Locher\textsuperscript{1} for their isoflurane BIS controller tested in a similar patient population. In view of the fact that only minimal adjustments of the isoflurane concentration were necessary to keep the BIS in the target range, we presume that in the context of adequate hypnosis, a closed-loop administration of an opioid according to blood pressure results in a similar anesthetic state as closed-loop administration of a hypnotic according to BIS in the context of adequate analgesia. Fixing either the hypnotic or the analgesic component and extending the concept of a SISO controller by using a second input variable to optimize the output variable as in our study may solve the potential problem of controller instability. This controller may thus be a further step toward a future MIMO controller.

There are certain limitations in our study: The mean arterial blood pressure is not specific for the response to noxious stimulation and may be affected by a number of covariates, such as blood loss, heart failure, arrhythmia, manipulation of great blood vessels, and a variety of drugs (e.g., inhalation anesthetics, propofol, β blockers,

<table>
<thead>
<tr>
<th>Table 4. Performance of the Controller (Number of Records, %): MAP</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Control mode, % of time</td>
</tr>
<tr>
<td>Manual mode, % of time</td>
</tr>
<tr>
<td>Passive mode, % of time</td>
</tr>
<tr>
<td>MAP reliable, % of time</td>
</tr>
<tr>
<td>MAD, mmHg</td>
</tr>
<tr>
<td>MDPE, %</td>
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<tr>
<td>MDAPE, %</td>
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<tr>
<td>Wobble, %</td>
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</tbody>
</table>

Data are mean (SD).

MAD = mean absolute difference of mean arterial blood pressure; MAP = mean arterial blood pressure; MDAPE = median absolute performance error; MDPE = median performance error.

<table>
<thead>
<tr>
<th>Table 5. Performance of the Controller (Number of Records, %): Cp Alf</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>MAD, ng/ml</td>
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<tr>
<td>MDPE, %</td>
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<tr>
<td>MDAPE, %</td>
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<tr>
<td>Wobble, %</td>
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</table>

Data are mean (SD).

Cp Alf = predicted plasma alfentanil concentration; MAD = mean absolute difference of the predicted to the reference plasma alfentanil concentration (Cp Alf ref); MDAPE = median absolute performance error; MDPE = median performance error.
vasodilators). Nevertheless, the performance of this controller was similar to the performance of other recently published hypnotic controllers.\textsuperscript{1,3,19} One reason for the good performance may be that we enrolled healthy patients (American Society of Anesthesiologists physical status I or II) undergoing surgery associated with only minimal blood loss. Only one subject had a blood loss more than 500 ml (2,200 ml), which was adequately replaced with colloids. Therefore, we do not have any data on controller stability in situations with larger blood loss; in such cases, continuous and sufficient volume replacement would be essential to preserve stability during closed-loop alfentanil administration. The frequent administration of ephedrine in the presurgery study period reveals that this controller in the context of the isoflurane concentrations necessary to keep the BIS level in the target range is not able to prevent hypotension in periods with limited noxious stimulation. One reason might be the choice of alfentanil instead of remifentanil, which would have allowed a more rapid decrease of the concentration after induction. Alfentanil was selected for better comparability of the results with our previous study.\textsuperscript{1} It was even the purpose of the second control

Fig. 4. The predicted plasma alfentanil concentration (A), the mean arterial pressure (MAP; B), the reference MAP (C), and the reference plasma alfentanil concentration (D) are presented for every subject. The dashed vertical line indicates skin incision; the dashed horizontal line indicates the initial reference values (MAP and plasma alfentanil concentration).

Fig. 5. The difference of the measured mean arterial pressure (MAP) to the reference MAP (= ∆MAP), the reference plasma alfentanil concentration (Cp ref), and the predicted plasma alfentanil concentration (pred Cp) of one typical subject are presented. The zero point of the time axis equals skin incision. The recurrent surgical stimulations were followed by an increase in the alfentanil infusion rate and the plasma alfentanil concentration, so that the difference to the reference Cp also increased. The two peaks of ∆MAP (at −15 and +60 min) represent flushing artifacts due to blood sampling and were detected as artifacts and therefore not followed by an increase of the alfentanil infusion rate.
The anesthesiologist decreased the reference Cp Alf in two subjects to allow rapid emergence. Another potential limitation is the use of the \( k_{e0} \) value of alfentanil for two subjects to allow rapid emergence. Another potential limitation is the use of the \( k_{e0} \) value of alfentanil for electroencephalography effects. Because \( k_{e0} \) of alfentanil to suppress hemodynamic response to noxious stimulation has not been determined, we had to assume that it would not substantially differ from the known \( k_{e0} \) of electroencephalography effect.

The opioid requirement to maintain the MAP within the target range was substantially different among the study population (coefficient of variation, 26–32%). The anesthesiologist in charge had two possibilities to respond to an increased or decreased opioid requirement of the individual subject: decreasing the MAP\(_{\text{ref}}\) or increasing \( C_{\text{p ref}} \) and vice versa. The number of changes of the reference values was limited, however, so that the system remained truly closed loop and was not turned into a “physician closed-loop” system.

We conclude that this model predictive controller has a similar set-point precision as previous electroencephalography-based controllers for hypnotic administration and provides adequate alfentanil dosing during surgery. It may be useful to standardize opioid dosing for research purposes and can be considered a further step toward a future MIMO controller.

### Appendix: Measurement of the Plasma Alfentanil Concentrations

Two to three arterial blood samples were withdrawn in each subject, one before and the other(s) during surgery. The samples were centrifuged at 3,500g for 30 min at 4°C, and the plasma was then stored at −20°C until analysis. Alfentanil plasma concentration was measured by gas chromatography–mass spectrometry\(^{24}\) with a detection limit of 0.4 ng/ml. The capillary column was a DB-XLB (J&W Scientific Inc., Folsom, CA) with 12 m length, 0.2 mm ID, and a film thickness of 0.33 μm. \( \²H₅\text{Alfentanil} \) was used as internal standard (Janssen Pharmaceutica, Beerse, Belgium). Quantification occurred in the selected ion monitoring mode, using the m/z 289 and 294 ion fragments for alfentanil and D₅-alfentanil, respectively with a dwell time of 100 ms each. Plasma samples were extracted with Clean Screen® tubes (United Chemical Technologies Inc., Bristol, PA) with 12 m length, 0.2 mm ID, and a film thickness of 0.33 μm.

### Table 6. Offline Simulation: Impact of the Second Control Variable \( C_{\text{p Alf ref}} \)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DISO Mode</th>
<th>SISO Mode</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil dose, presurgery, μg/kg</td>
<td>31 (16)</td>
<td>46 (30)</td>
<td>0.011</td>
</tr>
<tr>
<td>Alfentanil dose, surgery, μg/kg</td>
<td>127 (22)</td>
<td>218 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma alfentanil, presurgery, ng/ml</td>
<td>120 (37)</td>
<td>187 (78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma alfentanil, surgery, ng/ml</td>
<td>178 (39)</td>
<td>308 (66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effect site alfentanil, presurgery, ng/ml</td>
<td>123 (38)</td>
<td>192 (76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Effect site alfentanil, surgery, ng/ml</td>
<td>177 (38)</td>
<td>304 (65)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean (SD). Double input–single output (DISO) mode: reference mean arterial pressure (MAP\(_{\text{ref}}\)) and reference plasma alfentanil concentration (\( C_{\text{p Alf ref}} \)) considered. Single input–single output (SISO) mode: MAP\(_{\text{ref}}\) considered and \( C_{\text{p Alf ref}} \) ignored.
References


