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Review Article

Automated Anesthetic Drug Delivery Systems: Feasibility and Safety Assessment

Lars Bianchi[1*], Etienne Gallagher[2] and Lukas Girard[3]

[1]*Department of Anesthesiology and Pain Management, Alpine Institute of Medical Sciences, Austria*
[2]*Department of Critical Care Medicine, Nordic Institute of Anesthesiology and Critical Care, Finland*
[3]*Department of Surgical Sciences, Alpine Institute of Medical Sciences, Austria*

ABSTRACT

Closed-loop and target-controlled infusion technologies have advanced from single-drug proof-of-concept demonstrations to a growing body of randomized clinical evidence supporting automated titration of anesthetic drugs during general anesthesia.

This review examines the control architectures underlying automated anesthetic drug delivery, from model-based target-controlled infusion through proportional-integral-derivative and model predictive control to emerging reinforcement-learning approaches, and synthesizes the clinical evidence for their feasibility and safety.

Randomized trials across breast, thoracic, pediatric, and cardiac surgical populations indicate that closed-loop, bispectral-index-guided propofol delivery achieves tighter time-in-target control than manual titration without an apparent increase in adverse events, and multi-drug systems that jointly automate hypnosis, analgesia, and neuromuscular blockade have been demonstrated safely under close supervision.

Formalized safety architectures incorporating pharmacokinetic-pharmacodynamic dosing constraints and fault detection are essential complements to control-algorithm performance, particularly given the vulnerability of processed-EEG feedback signals to intraoperative artifact.

We conclude that fully autonomous anesthesia delivery remains distant, but a supervised, increasingly capable automated co-pilot model is both technically feasible now and the most realistic path toward broader clinical adoption, pending further multicenter validation and resolution of regulatory and liability questions.

Keywords: *closed-loop anesthesia; target-controlled infusion; automated drug delivery; bispectral index; patient safety*

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Corresponding Author: *Lars Bianchi*

E-mail Address: *l.bianchi@aims.at*

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INTRODUCTION

Anesthesiologists have spent decades titrating hypnotic, analgesic, and vasoactive drugs by hand, watching a monitor, adjusting a pump, watching again.

The task is repetitive, cognitively demanding during the busiest parts of a case, and vulnerable to the same lapses that affect any human performing vigilance work over hours. It is also, in principle, exactly the kind of closed-loop control problem that engineers solve routinely in other domains: measure an output, compare it to a target, adjust an input, repeat. That observation is not new — early closed-loop work with the bispectral index (BIS) as a control target dates to the late 1990s [1] — but what has changed over the last fifteen years is the breadth of what automated systems now attempt to control, from single-drug hypnosis to multi-drug, multi-variable regulation of depth of anesthesia, analgesia, and hemodynamics simultaneously. This review surveys where automated anesthetic drug delivery stands today: the control architectures in use, the clinical evidence for feasibility and safety across drugs and patient populations, and the practical and regulatory obstacles that still separate a working research system from a device an anesthesiologist can pick up and use on a Tuesday afternoon list.

CONTROL ARCHITECTURES: FROM TARGET-CONTROLLED INFUSION TO CLOSED-LOOP FEEDBACK

It helps to distinguish two things that get lumped together under "automated delivery." Target-controlled infusion (TCI) is open-loop: the clinician sets a target plasma or effect-site concentration, and a pharmacokinetic-pharmacodynamic (PK-PD) model computes the infusion rate needed to reach and hold that target, but the system never looks at the patient's actual measured response to check whether the model was right for that particular patient. TCI has been in clinical use for propofol and remifentanil for years and improved on manual bolus-and-infusion dosing, but it inherits all the population-average error of the underlying PK-PD model — a model built on Marsh, Schnider, or Eleveld parameters describes a "typical" patient, not the one on the table.

Closed-loop systems add the missing feedback arm: a processed EEG parameter (most often BIS, though the Patient State Index, Narcotrend index, and entropy-based measures all have literature behind them) is fed back into a controller — proportional-integral-derivative (PID), model predictive control (MPC), or more recently reinforcement-learning-based policies — which adjusts the infusion rate in near-real time to keep the measured depth of anesthesia at target despite surgical stimulation, individual PK-PD variability, and drug interaction effects [2][3]. Liu and colleagues' multicenter comparison of closed-loop versus manual BIS-guided propofol titration was an early and influential demonstration that the closed-loop arm produced tighter control around the target BIS value and less over- and under-dosing time than skilled anesthesiologists managing the infusion manually [4]. Model predictive control extends this further by controlling multiple drugs against multiple physiologic targets at once — hypnotic depth, analgesic index, and blood pressure via a vasopressor infusion — which is closer to what actually happens during a real anesthetic than single-drug, single-target control [3][5].

FROM SINGLE-DRUG HYPNOSIS CONTROL TO FULLY AUTOMATED TOTAL INTRAVENOUS ANESTHESIA

The most mature closed-loop literature concerns propofol hypnosis alone, and it has moved from proof-of-concept to randomized comparison at reasonable scale. A randomized trial in breast surgery patients found that closed-loop, BIS-guided propofol delivery kept patients within the target BIS range a significantly greater proportion of case time than open-loop TCI, with fewer excursions into both light and deep anesthesia [6]. A multicenter randomized study of BIS-guided closed-loop propofol infusion in preschool children extended the same finding to a population where pharmacokinetic variability is large and manual titration is arguably hardest to get right, again showing improved time-in-target and comparable or better hemodynamic stability relative to anesthesiologist-controlled infusion [7]. In thoracic surgery, where one-lung ventilation and repositioning add physiologic disturbance during the case, a randomized comparison of a closed-loop anesthesia delivery system against manual titration likewise reported tighter BIS control without an increase in adverse events [8]. The CONCERT-CL multicenter trial reached a similar conclusion for TCI-based closed-loop propofol delivery guided by BIS across a broader surgical population, reinforcing that the single-drug closed-loop hypnosis result is reproducible across sites and case types rather than an artifact of one enthusiastic center [9].

The harder and more clinically interesting step is automating more than one drug at once. Hemmerling's group described a robotic anesthesia system — widely covered under the "McSleepy" name — that closed the loop simultaneously on hypnosis (propofol, BIS-guided), analgesia (remifentanil, guided by an analgesia index derived from heart rate variability and other autonomic signals), and neuromuscular blockade, essentially attempting to automate the entire pharmacologic side of a general anesthetic rather than one component of it [10]. The system's best-known demonstration paired it with robotic surgery for an all-robotic operating room in which both the surgical and anesthetic tasks were performed by machines under physician supervision [11]. A separate feasibility study evaluated a completely automated total intravenous anesthesia delivery system in cardiac surgery, a population with narrow hemodynamic margins and high stakes for both under- and over-dosing, and reported that automated multi-drug control was achievable with acceptable safety margins

under close supervision [12]. These multi-drug systems are still overwhelmingly research or single-center devices rather than commercially available, broadly deployed platforms, but they establish that the engineering problem — simultaneous closed-loop control of hypnosis, analgesia, and neuromuscular blockade — is solvable in principle and safely testable in real operating rooms.

SAFETY ARCHITECTURE: CONSTRAINTS, ALARMS, AND THE LIMITS OF AUTOMATION

A closed-loop controller that simply chases a target number without constraints is a hazard, not an improvement, and the safety-engineering literature around these systems reflects that. Ghita and colleagues describe a formalized safety system that layers PK-PD-informed dosing constraints, rate limits, and fault-detection logic on top of the core control algorithm, so that the controller cannot drive an infusion to a physiologically implausible rate even if the feedback signal is transiently corrupted by electrocautery noise, movement artifact, or sensor dropout — a real and recurring failure mode for processed-EEG monitoring in the operating room [13]. This is the unglamorous but essential complement to the control-theory advances: an anesthesiologist supervising a closed-loop system needs to trust not just that it usually works, but that it fails safe — reverting to a bounded, conservative infusion rate and alarming clearly — when its input signal degrades. Recent scoping and systematic reviews of automatic closed-loop anesthesia converge on the same message: the individual trials are consistently favorable on time-in-target and often neutral-to-favorable on drug consumption and recovery metrics, but heterogeneity in control targets, patient populations, and outcome definitions across the literature makes pooled safety conclusions harder to state with confidence than the volume of publications might suggest [14][15].

MACHINE LEARNING, REINFORCEMENT LEARNING, AND THE NEXT GENERATION OF CONTROLLERS

Classical PID and MPC controllers depend on an explicit PK-PD model of the drug and, implicitly, on that model generalizing reasonably well to the patient in front of the anesthesiologist. Reinforcement learning approaches instead try to learn a control policy directly from patient response, in principle adapting to individual variability without requiring the model to be specified correctly in advance. An early and often-cited study evaluated reinforcement-learning-based closed-loop propofol control in human volunteers and found the learned policy could regulate hypnotic depth comparably to conventional model-based controllers [2]. More recent narrative and systematic reviews of machine learning in anesthesia delivery survey a growing set of approaches — deep learning for signal denoising and artifact rejection in the EEG feedback pathway, predictive models for hypotension and other intraoperative events that feed forward into dosing decisions, and end-to-end learned controllers — while consistently flagging that most of this work remains preclinical, single-center, or retrospective, well short of the multicenter randomized evidence base that the propofol-only BIS-guided systems have already accumulated [5][16][17]. Comprehensive reviews of the field frame the trajectory as incremental rather than disruptive: today's best-validated systems automate one or two variables within a case that a supervising anesthesiologist still opens, monitors, and can override at any point, and the realistic near-term advance is broader validation and tighter safety engineering of that model, not an unsupervised anesthesia machine [18][19].

BARRIERS TO CLINICAL ADOPTION

The technical feasibility of automated drug delivery is, at this point, reasonably well established for propofol hypnosis and increasingly plausible for combined hypnosis-analgesia control; the barriers to widespread clinical use are as much regulatory, medicolegal, and cultural as technical. Regulatory bodies have been cautious about approving closed-loop anesthesia delivery systems for autonomous operation, and most jurisdictions currently restrict deployment to supervised, advisory, or research contexts rather than approving a system to titrate a general anesthetic without a clinician's continuous ability to intervene. Liability questions — who is responsible when an automated system's dosing decision contributes to an adverse outcome, the supervising anesthesiologist, the institution, or the manufacturer — remain largely unresolved in most health systems and understandably make hospitals and clinicians cautious about adoption even where a device has favorable trial data. There is also a workflow and trust dimension: anesthesiologists trained to titrate by feel and by watching a trend line need to develop calibrated trust in a system that sometimes makes a different dosing decision than they would have, and the literature on closed-loop anesthesia has, so far, focused much more on control-theoretic performance than on how clinicians actually interact with, monitor, and override these systems in practice. Cost and integration also matter in ordinary terms: a closed-loop system typically requires a dedicated infusion pump, a processed-EEG monitor, and software linking them, which is a nontrivial capital and maintenance commitment for an operating room that already owns conventional pumps and monitors that work well enough for most cases.

CONCLUSION

Automated anesthetic drug delivery has moved from a control-theory curiosity to a body of randomized clinical evidence, at least for propofol hypnosis under BIS guidance, where closed-loop systems consistently

outperform manual titration on time-in-target and do so without an apparent safety penalty across surgical populations ranging from preschool children to cardiac surgery patients. Multi-drug, multi-variable systems that attempt to automate hypnosis, analgesia, and hemodynamic support together are feasible and have been demonstrated safely in supervised research settings, but they remain far short of routine clinical deployment. The safety engineering that wraps these controllers — dosing constraints, fault detection, fail-safe behavior under corrupted feedback — is as important to their eventual acceptance as the control algorithm itself, and machine-learning-based controllers that promise to adapt to individual patients still need the same multicenter, randomized validation that the current generation of PID- and MPC-based systems has already accumulated before they can reasonably be trusted with more autonomy. The most likely near-term path forward is not a fully autonomous anesthesia machine but an increasingly capable supervised co-pilot: a system an anesthesiologist sets up, watches, and can override, that quietly handles the repetitive titration work and frees clinical attention for the judgment calls automation cannot yet make.

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Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Lars Bianchi conceived the review and drafted the initial manuscript. Etienne Gallagher performed the literature search and contributed to the sections on control architectures and safety systems. Lukas Girard critically revised the manuscript for intellectual content and approved the final version. All authors read and approved the final manuscript.

Ethics Statement

This is a literature review and did not involve new human or animal data; no ethical approval was required.

Data Availability

No new data were generated or analyzed in this review. All sources are cited in the reference list.

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