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Application of Machine Learning Algorithms in Automatic Anesthetic Drug Delivery Systems

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Abstract

The dynamic advancements in artificial intelligence are enabling the integration of machine learning into medical practice. A significant challenge in modern anesthesiology is the need for precise, continuous adjustment of anesthetic drug doses in response to the patient's rapidly changing physiological state. Traditional manual methods of drug delivery often result in excessive variability in the depth of anesthesia and hemodynamic stability. Utilizing machine learning algorithms represents a modern, promising approach designed to enhance the overall quality and safety of anesthetic care.

Aim of the study: The objective of this study is to review the current state of knowledge concerning machine algorithms in automated anesthetic drug delivery systems and to compare these with conventional administration methods, evaluating the benefits and limitations of each approach.

Materials and methods: A review of selected literature in the PubMed, Google Scholar database was conducted, using the following keywords: “anesthetic drugs”, “machine learning”, “closed-loop system” “artificial intelligence”

Conclusions: The review demonstrates that Machine Learning-driven Closed-Loop Anesthesia Delivery Systems (CLADS) offer superior stability of anesthetic depth and hemodynamic control compared to manual administration. The implementation of AI allows for the personalization of therapy and a significant reduction in drug and gas wastage, supporting the "Green Anesthesia" initiative. Furthermore, automation contributes to better long-term outcomes, such as reduced incidence of postoperative delirium and cognitive dysfunction. However, despite high autonomy, the "human-in-the-loop" paradigm remains essential due to technical artifacts and unforeseen surgical events. Future research should focus on regulatory standardization and the integration of multi-loop systems managing hypnosis, analgesia, and neuromuscular blockade simultaneously.

Key words: anesthesiology, anesthetic drugs, machine learning algorithms, “closed-loop systems”

The rapid advancement of artificial intelligence and machine learning has facilitated the integration of emerging technologies into clinical practice, aiming to optimize patient outcomes and mitigate adverse events **[1, 2]**. In anesthesiology, the precise titration of anesthetic agents—crucial for inducing hypnosis and anterograde amnesia—is paramount. Overdosage carries a heightened risk of neurotoxicity, hypotension, and delayed emergence, whereas underdosage may lead to intraoperative awareness **[3, 4]**. A primary challenge lies in maintaining hemodynamic stability while ensuring an adequate depth of anesthesia within the therapeutic window. Recent studies indicate that machine learning-driven automated anesthesia delivery systems significantly reduce the incidence of complications compared to manual control **[5, 6]**.

A critical issue in anesthetic drug delivery is the temporal variability of the patient's physiological state, necessitating continuous dosage adjustments. Notably, anesthetic requirements are subject to substantial inter-individual variability, influenced by factors such as age, gender, genetics, and comorbidities **[7]**. Furthermore, the "human factor"—encompassing clinician fatigue, cognitive load, and multitasking—poses a significant challenge, potentially resulting in delayed responses to critical changes in the patient's condition **[8, 9]**.

1. The History of Automation in Anesthesiology

1.1 Historical Context and TCI The first clinical application of Target Controlled Infusion (TCI) was performed in Germany in the 1980s **[10]**. At that time, TCI was utilized for the administration of etomidate and alfentanil, enabling the achievement of sufficiently deep anesthesia and a reduction in patient recovery time. This marked the initial step toward automation. Over the years, TCI has become widely adopted globally. However, it is important to note that TCI relies on statistical averages (population-based models), which may not always be adequate due to inter-patient variability **[11]**.

1.2 The Advent of Advanced Systems In 2013, the McSleepy system was introduced **[12]**. McSleepy was based on advanced algorithms and mathematical models designed to mimic the reasoning of an anesthesiologist by integrating multiple variables. More than 40 years after the inception of automation, the advancement of Artificial Intelligence now allows for the optimization of anesthetic delivery through the use of Deep Reinforcement Learning **[13]**.

2. Operational concept

2.1 Monitoring Anesthetic Depth

To control the depth of anesthesia, several parameters are assessed in real-time. These include heart rate, oxygen saturation, arterial blood pressure, the Bispectral Index (BIS) **[14]**, and entropy monitoring **[15]**. Appropriate algorithms implemented in Automated Loop Systems utilize measurements of the aforementioned parameters to adjust the anesthetic dosage and perform necessary corrections in response to the patient's current hemodynamic status.

2.2 Control Mechanisms

In contrast to manual dose adjustment by a clinician, the decision-making unit in an Automated Loop System is the system's algorithm. The AI model is trained on clinical data encompassing the perioperative period, allowing for more accurate prediction of anesthesia-related adverse events and a faster response to changes in the patient's physiological state. It is crucial to emphasize that the algorithm is not an autonomous entity; it remains subject to the supervision of the anesthesiologist **[16]**. Consequently, the role of the anesthesiologist remains indispensable in the application of closed-loop systems, as the purpose of the algorithm is to support the physician's work, not to replace it entirely **[17]**.

2.3 The Effector

The effector—the executor of the decisions made by the AI algorithm—consists of infusion pumps in the case of intravenous anesthesia, or vaporizers in the case of inhalational (gas) anesthesia.

3.Classes of algorithms

3.1 PID (Proportional-Integral-Derivative) algorithms

Within the CLAD system architecture, the control object (the "plant") is the patient, characterized by complex and nonlinear pharmacokinetic and pharmacodynamic profiles. **[18,19]** The controlled variable (output) is a measurable physiological parameter, such as the Bispectral Index (BIS) for the depth of hypnosis or the Train-of-Four (TOF) ratio for neuromuscular blockade.**[20]** The manipulated variable (input) is the infusion rate of the

anesthetic agent administered via a syringe pump. The primary challenge in anesthesia control lies in the immense inter-patient and intra-patient variability.**[18,21,22]** A propofol dose sufficient to induce adequate anesthesia in one subject may precipitate hemodynamic collapse in another. Furthermore, surgical stimuli—such as skin incision, intubation, or visceral manipulation—act as stochastic disturbances that the controller must effectively reject without driving the system into instability.**[19,23]** The PID controller addresses these challenges through three fundamental components:

• Proportional Term (P): Responds to the current error (the difference between the setpoint and the measured depth of anesthesia). In the context of anesthesia, a high proportional gain allows for a rapid response to sudden nociceptive stimuli; however, it carries the risk of overshoot and oscillations, which are clinically hazardous.**[18,21,24]**

• Integral Term (I): Accumulates past errors to eliminate steady-state error. In anesthesiology, where continuous drug metabolism and redistribution create a constant "load" on the system, the integral term is crucial for maintaining the setpoint. However, it introduces the risk of "integral windup" (saturation) when the infusion pump reaches its physical performance limits.**[18,24]**

• Derivative Term (D): Predicts future error based on the rate of change. It functions as a damping element, which is critical during the rapid induction phase of anesthesia to prevent precipitous drops in arterial blood pressure.**[18,21,24]**

3.2. **Fuzzy Logic Control (FLC)**

Fuzzy Logic in anesthesiology facilitates the translation of expert clinical knowledge into control algorithms.**[25,26]** Unlike binary logic, which relies on discrete truth values, FLC operates on degrees of truth, thereby mimicking the heuristic decision-making process of an anesthesiologist.**[25]** Mechanism of Action: A Fuzzy Logic-based CLAD system typically operates in three stages:**[25,26]**

- Fuzzification: Deterministic input variables (e.g., BIS error, derivative of Mean Arterial Pressure) are mapped onto linguistic sets (e.g., "Small Error," "Rapid Drop") using membership functions.

- Inference: The controller processes these inputs based on a rule base derived from clinical expertise (e.g., "IF BIS is Too Low AND Blood Pressure is Decreasing, THEN Significantly Reduce propofol infusion").
- Defuzzification: The resulting linguistic value is converted back into a crisp numerical control signal (e.g., infusion rate in ml/h) to drive the syringe pump.

Clinical Application: Recent studies highlight the efficacy of hybrid Fuzzy-PID architectures.**[26,28]** In these systems, fuzzy logic dynamically tunes the PID gains in real-time, differentiating between anesthesia phases (induction vs. maintenance). This hybridization has been shown to minimize overshoot and reduce recovery time compared to fixed-gain controllers.**[26]**

3.3. Artificial Neural Networks (ANN):

Artificial Neural Networks are utilized in CLAD systems primarily for their universal approximation capabilities and ability to learn from data, allowing for the modeling of the "patient as a black box" [29,30,31].

3.3.1. Mechanism of Action:

Model Predictive Control (MPC): Neural networks, particularly Recurrent Neural Networks (RNN), are employed to learn patient dynamics from intraoperative data. The network predicts future physiological states (e.g., BIS values) in response to drug administration. The controller uses this prediction to optimize the infusion profile before a deviation from the setpoint occurs **[32,33,34]**.

Reinforcement Learning (RL): Emerging research explores Deep Reinforcement Learning, where the ANN learns an optimal control policy through interaction with the patient (or a simulator). The system receives a "reward" for maintaining stability and a "penalty" for adverse events such as hypotension or intraoperative awareness **[13,33]**.

Application: ANNs demonstrate superiority in therapy personalization. Through online learning, the network can adapt the pharmacodynamic model to the individual patient in real time, compensating for inter-patient variability that standard population models (e.g., Marsh or Schnider) may fail to predict **[37,38]**.

3.4 Model Predictive Control (MPC)

Model Predictive Control (MPC) represents a sophisticated control paradigm that has gained significant traction in automated anesthesia delivery due to its superior handling of system time delays and constraints compared to classical PID algorithms **[41,42,43]**.

Mechanism of Action: Unlike reactive controllers (PID), MPC is proactive. It relies on an explicit internal model of the patient (typically a PK/PD model) to predict the future evolution of the physiological variable (e.g., BIS or MAP) over a defined prediction horizon. At each sampling instant, the controller solves an online optimization problem to compute a sequence of future infusion rates that will minimize the difference between the predicted output and the target setpoint, while minimizing drug consumption **[44,45,46]**. Only the first step of this optimized sequence is implemented, and the process repeats in a "receding horizon" fashion **[44,43,45,47]**.

4.Clinical Efficacy and Safety

The quality of anesthesia delivery is often measured by the ability to maintain the patient within a narrow therapeutic window—deep enough to prevent awareness and trauma, yet shallow enough to avoid toxicity and cardiovascular depression.**[46,48]**

4.1 Analysis of Time in Therapeutic Range

Numerous clinical studies unequivocally indicate the superiority of Closed-Loop Anesthesia Delivery Systems (CLADS) over manual control regarding the stability of the Bispectral Index (BIS). The BIS range of 40–60 is widely accepted as the target for general anesthesia. Comparative studies have demonstrated that CLADS maintain the BIS index within the target range for a significantly higher percentage of the procedure duration than manually controlling anesthesiologists.**[46-48]**

In a multicenter study conducted in India, the time spent in the optimal range (BIS ±10 from target) was 81.4% for the CLADS group compared to 55.34% for the manual group.**[47]**Randomized Controlled Trial (RCT) indicates a difference of 15.8 percentage points in favor of automation (75.24% vs 59.5%).**[47]**

4.2. Clinical Significance of MDAPE and Wobble Indices

Engineering metrics such as MDAPE (Median Absolute Performance Error) and Wobble have direct implications for brain physiology.**[49]** Lower Wobble scores in CLADS groups indicate that the patient's brain is not subjected to rapid changes in drug concentrations (the "rollercoaster" effect).**[48]** A smooth anesthesia course minimizes the risk of sudden lightening (and awakening) in response to strong nociceptive stimuli, as CLADS make adjustments much more frequently than humans. In one study, the automated system performed an average of 31.55 adjustments per hour, whereas the clinician in the manual group performed only 6.84.**[47]** This "micro-titration" is impossible for a human to replicate without dedicating undivided attention to a single task.**[47,48]**

It is worth clarifying that while MDAPE is a measure of system accuracy (determining how close the patient is to the setpoint on average), Wobble defines control stability (measuring the amplitude of oscillation around the mean error). In clinical practice, a low MDAPE value guarantees that the patient is neither too lightly nor too deeply anesthetized, while low Wobble ensures the absence of rapid fluctuations in anesthetic depth, which are most taxing on the autonomic nervous system.**[51]**

4.3. Avoidance of Burst Suppression

A particularly critical aspect is avoiding states of excessively deep anesthesia, manifesting in EEG as "burst suppression" (periods of electrical silence). These events are strongly correlated with the incidence of postoperative delirium and Postoperative Cognitive Dysfunction (POCD).**[50]** Studies indicate that patients in CLADS groups spend significantly less time with BIS values < 40.**[51]** Automated systems, free from the psychological mechanism of risk aversion (which inclines physicians to deepen anesthesia "just in case"), reduce infusion immediately when parameters indicate excessive depth of sleep.**[48,53]**

4.4. Hemodynamic Stability: Organ Protection

Anesthetic drugs, particularly propofol, are potent cardiovascular depressants, causing vasodilation and decreased cardiac contractility. Manual drug administration often leads to so-called "bolus-induced hypotension," where rapid drug administration to deepen anesthesia

results in sudden hypotension.

4.5. Reduction of Hypotension Episodes and MAP Variance

Comparative studies, especially those involving high-risk patients (ASA III-IV), provide evidence that CLADS exert a cardioprotective effect by stabilizing perfusion pressure. In a prospective study involving patients undergoing major abdominal and thoracic surgeries, the mean number of hypotension episodes per patient was dramatically lower in the CLADS group (2.1 ± 1.4) compared to the manual group (5.7 ± 2.3).**[46]** Furthermore, the deviation of Mean Arterial Pressure (MAP) from baseline values was nearly half as large in the automated group (8.5 mmHg vs. 15.4 mmHg).**[46]** This indicates that CLADS not only prevent pressure drops below alarm thresholds but also maintain the patient closer to their physiological norm throughout the procedure. This is crucial for preserving cerebral and renal blood flow autoregulation.

4.6 Integration of Vasopressors and Fluid Therapy

Modern closed-loop systems are evolving towards multi-controller systems that manage not only hypnosis but also hemodynamics in parallel. It has been demonstrated that automated vasopressor delivery (e.g., phenylephrine or ephedrine) during spinal anesthesia for Caesarean section—a clinical situation known for rapid hemodynamic instability—is significantly more effective than manual boluses. These systems reduce the incidence of maternal nausea (associated with hypotension) and decrease total vasopressor consumption by nearly 50% (12.6 mg vs. 24.2 mg in the manual group).**[52]**

5.Pharmacology and Drug Consumption: Clinical and Economic Aspects

The impact of CLADS on total drug consumption is a complex issue, with results depending on the phase of anesthesia and the adopted control strategy.**[53]**

5.1. Induction Phase: Precision Over Excess

In the induction phase, CLADS consistently demonstrate a reduction in propofol requirements. Manual induction often relies on rigid weight-based dosing (e.g., 2 mg/kg), which leads to relative overdosing in elderly patients or those with compromised hemodynamics. CLADS

titrate the drug based on real-time EEG response, stopping the infusion precisely at the moment of loss of consciousness. Meta-analyses confirm a significant reduction in the induction dose, which translates into reduced circulatory depression during this critical period.**[53,55]**

5.2. Maintenance Phase: Quality vs. Quantity

In the maintenance phase, results are inconclusive. Some studies indicate a reduction in propofol consumption in CLADS groups, while others report higher consumption compared to the manual group.**[53]** This apparent contradiction stems from the fact that in manual groups, anesthesiologists may unconsciously (or intentionally) maintain patients at a lighter depth of anesthesia (higher BIS) than the protocol specifies, which decreases drug consumption but increases the risk of intraoperative awareness.**[48,55]** In contrast to manual control, CLADS rigorously aim to maintain the target setpoint (e.g., BIS 50). The algorithm precisely adjusts drug delivery to the required pharmacodynamic effect, which, in patients exhibiting individual resistance to anesthetics, may result in a higher cumulative dose than in the control group. However, this consumption is justified by the clinically superior quality of anesthesia (lower BIS deviations).**[55]**

5.3.New Drugs: The Case of Ciprofol

An interesting area is the adaptation of CLADS to new molecules, such as ciprofol—a propofol analog with higher potency and less circulatory depression. Comparative studies of ciprofol and propofol in sedation procedures (e.g., bronchoscopy) demonstrate that ciprofol provides superior hemodynamic stability.**[54]** In the context of automation, the introduction of new drugs poses a challenge for classical TCI (Target Controlled Infusion) models, which require years of population studies. Conversely, systems based on Machine Learning (ML) and pure feedback loops can potentially adapt more rapidly to the distinct pharmacodynamics of new substances, controlling them based on the target effect rather than a rigid model.**[57,31]**

5.4. "Green Anesthesia": Reduction of Greenhouse Gases A distinct category comprises closed-loop systems for volatile anesthetics (e.g., Et Control systems). Here, the savings are substantial. Manual control of Fresh Gas Flow (FGF) is often inefficient—clinicians frequently set high flows for "safety margins." Automated systems allow for safe operation in minimal flow mode (flows in the range of 0.5–1 l/min), precisely dosing oxygen and the anesthetic agent.

Studies indicate that Et Control automation allows for a reduction in sevoflurane consumption by approximately 45% and a decrease in CO2 equivalent emissions by hundreds of kilograms per operating room annually. On the scale of a large hospital, this translates to massive emission reductions and significant financial savings.**[56]**

5.5. Long-term Outcomes: CNS Regeneration and Cognitive Functions Modern anesthesiology extends beyond the operating room, focusing on the Quality of Recovery (QoR).

5.6. Faster Emergence and Extubation The precision of CLADS control results in a faster return of consciousness. Because the system avoids drug accumulation ("stacking") toward the end of the procedure and can precisely predict the optimal moment to cease infusion, patients wake up faster. The mean time to extubation in CLADS groups is shorter by 1.5 to over 6 minutes compared to manual groups.**[46,55]** This is significant from the perspective of operating theater logistics—faster patient turnover increases throughput.

5.7. Neuroprotection and Prevention of POCD The most critical long-term benefit may be brain protection. Postoperative Cognitive Dysfunction (POCD) and delirium affect a significant percentage of elderly patients. Research suggests that avoiding excessively deep anesthesia (controlled by CLADS) may reduce these complications.**[50]** In a study involving patients aged 60+, a group managed with a "triple-loop" system (depth, hemodynamics, ventilation) demonstrated better scores in cognitive tests during the first postoperative week.**[17]** This mechanism is linked to the elimination of periods of deep electroencephalographic suppression, which is prognostically unfavorable for the aging brain.**[31,50]**

6.The Human Factor: Trust, Ergonomics, and System Safety The introduction of machine autonomy into medicine raises questions regarding the role of the human operator.

6.1. Reduction of Cognitive Load During critical moments of a procedure, the anesthesiologist must process hundreds of data points. Manual pump control is a repetitive task that consumes attentional resources. CLADS systems take over this burden ("cognitive offloading"), allowing the physician to focus on supervision, diagnosis of atypical problems, and communication with

the surgical team. Studies show that automated systems are not subject to the phenomenon of vigilance decrement, which is a natural characteristic of the human brain during prolonged monitoring tasks.**[57]**

6.2. Fail-safe Modes and Reasons for Manual Intervention

Despite their sophistication, CLADS are not 100% autonomous. Studies indicate that approximately 10–12% of cases require a takeover by manual control.**[17]** The main causes include:

- **Technical Artifacts:** Loss of BIS signal (e.g., electrode detachment) or interference from electrosurgery (diathermy), which may generate signal artifacts leading to erroneous algorithm decisions.
- **Hardware Communication Errors:** Cases of communication cable failure between the monitor and the control unit have been described, leading to a halt in automated infusion.
- **Surgical Events:** Sudden hemorrhage or surgical manipulations triggering reactions with dynamics that exceed the algorithm's safety parameters.

Therefore, the "Human-in-the-loop" concept remains a key safety element—a clinician capable of recognizing when the machine is acting on erroneous data and taking manual control of the infusion.**[31,57]**

7.1. Pharmacoeconomic Analysis and Drug Wastage

The economic dimension of anesthesia encompasses not only the price of drugs used but also waste disposal costs and process efficiency.

7.2.Drug Wastage

In manual systems, drug wastage often occurs due to medications prepared "just in case" (e.g., syringes with propofol or ephedrine) that are not used and must be discarded. Studies indicate that propofol is the most frequently wasted intravenous drug, generating financial losses and environmental burdens.**[56]** Automated systems, thanks to precise dosing and the potential use of larger reservoirs (in the future) or pre-filled systems, can limit this phenomenon.

In the case of Et Control systems, savings are direct and measurable. Reduced gas flows mean fewer purchases of expensive volatile anesthetics. Savings of 16,000 USD per 100 hospital beds

annually, combined with the reduction of greenhouse gas emissions, make this technology highly cost-effective.**[56]**

7.3 Cost of Complications

However, the greatest potential savings lie in the reduction of complications. The cost of treating a single case of postoperative delirium, stroke, or Acute Kidney Injury (AKI)—which are consequences of hemodynamic instability and deep anesthesia—exceeds the cost of purchasing a CLADS system many times over.**[17,50]** Although large-scale cost-benefit analyses accounting for these indirect costs are still lacking, clinical data (reduced hypotension, better cognitive functions) suggest strong savings potential over a long time horizon.

Conclusions: A review of the current scientific literature indicates that Closed-Loop Anesthesia Delivery Systems (CLADS) demonstrate a significant superiority over manual administration methods and open-loop Target Controlled Infusion (TCI) systems. These systems offer superior precision in maintaining the targeted depth of anesthesia (BIS) and hemodynamic stability (MAP), thereby directly optimizing the patient safety profile. Process automation minimizes the risk of adverse events such as burst suppression and severe hypotension, contributing to faster emergence times and potentially preserving cognitive function. It must be emphasized that the implementation of CLADS does not replace the clinician but rather redefines their role from operator to supervisor; this transition reduces cognitive load while simultaneously requiring new competencies in the oversight of autonomous systems. Furthermore, the application of closed-loop systems yields measurable economic and ecological benefits, aligning with strategies to reduce the carbon footprint of anesthesiology through the minimization of drug wastage. In light of the available evidence, the integration of machine learning algorithms with drug delivery systems represents a natural evolutionary trajectory for anesthesiology, signifying a paradigm shift from reactive, symptomatic treatment to predictive, personalized precision therapy.

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Declaration of Generative AI and AI-Assisted Technologies
During the preparation of this work, the authors used Gemini 3 Pro (Google) to improve grammar and language clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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